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JCSM
Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

The Diagnostic Yield of Exercise Stress Testing as a Screening Tool for Subclinical Coronary Artery Disease in Patients with Moderate to Severe Obstructive Sleep Apnea

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Study Objective: To address the yield of routine exercise stress testing as a screening tool for subclinical coronary artery disease (CAD) in patients with moderate to severe obstructive sleep apnea (OSA).

Design and Setting: A cross-sectional study in a university hospital.

Participants: Of 380 consecutive patients with OSA, data from 206 subjects (mean apnea-hypopnea index [AHI] 41 ± 21 events/h) were studied; data from 78 with a history of CAD and 96 with mild OSA (AHI 5-15 events/h) were excluded.

Measurements: Routine exercise stress testing.

Results: Six subjects could not reach maximal exercise capacity. Of the remaining 200 patients, the results of exercise stress testing were normal in 189. Three had a positive stress test, with coronary angiography confirming the diagnosis of CAD. Eight patients had suspected positive findings on the stress test, but the results of the myocardial perfusion study were negative.

Conclusion: The prevalence of subclinical CAD in this selected population with OSA was 1.5%, which is not higher than that in a general population. Our results do not support the routine use of exercise stress testing in patients with moderate to severe OSA who do not have symptoms of CAD.

Keywords: Coronary artery disease, exercise stress testing, obstructive sleep apnea

Citation: Cilli A; Batmaz F; Demir I; Boz A; Toprak E; Ozdemir T; Peker Y. The diagnostic yield of exercise stress testing as a screening tool for subclinical coronary artery disease in patients with moderate to severe obstructive sleep apnea. *J Clin Sleep Med* 2011;7(1):25-29.

Obstructive sleep apnea (OSA) is a common condition in the middle-aged population.[1] There is growing evidence that OSA is a potential risk factor for cardiovascular diseases, including hypertension, coronary artery disease (CAD), and stroke.[2] Epidemiologic data suggest that OSA is overrepresented in patients with CAD,[3] and long-term outcome is poor in these patients.[4] Moreover, people with OSA seem to have a peak in sudden death from cardiac causes during the sleeping hours, compared with the nadir of sudden death from cardiac causes during this period in people without OSA and in the general population.[5,6]

When looking at the issue from the opposite perspective, i.e., the rate of CAD in patients with OSA, Maekawa et al.[7] examined patients with OSA to determine the prevalence of CAD and found that patients with moderate to severe OSA had a higher prevalence of CAD, as compared with patients without OSA or who had mild disease. In a smaller cohort of patients with OSA without a history of CAD, ST-segment depression on electrocardiography (ECG) was found in 30%, and these changes were eliminated by the use of continuous positive airway pressure.[8] An even higher prevalence (68%) was reported in a slightly larger study of unselected patients with OSA.[9] Furthermore, Marin et al. showed that the risk of fatal and nonfatal cardiovascular events was significantly increased in patients with severe untreated OSA, as compared with healthy control subjects.[10] More recently, a retrospective evaluation of more than 200 patients who underwent electron-beam computed tomography within 3 years of having had an overnight sleep recording addressed the occurrence of subclinical coronary artery calcification.[11] In this study, with multivariate adjustment, the odds ratio for having subclinical coronary artery calcification was 3.3 in the quartile with the most severe apnea-hypopnea index (mean AHI, 63.4/h). Thus, OSA has been identified not only in patients with clinical CAD, but also in those with subclinical CAD.

Current guidelines suggest that exercise stress testing, which is inexpensive, noninvasive, and safe and provides accurate results,[12] may be of clinical value when conducted in patients who

BRIEF SUMMARY

Current Knowledge/Study Rationale: Current guidelines suggest that exercise stress testing may be of clinical value when conducted in patients with estimated intermediate risk of developing coronary artery disease (CAD). Obstructive sleep apnea (OSA) is a potential risk factor for CAD. The diagnostic yield of exercise stress testing as a screening tool for subclinical CAD in patients with moderate to severe OSA is uncertain.

Study Impact: The prevalence of subclinical CAD in this selected OSA cohort was not higher than that in a general population. Our results do not support routine screening by exercise stress testing in OSA patients who do not have symptoms of CAD.

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have an estimated intermediate risk of developing CAD[13] and in patients with diabetes mellitus; however, there is insufficient evidence to support using this test as a routine screening tool in asymptomatic adults. Whether screening for the detection of CAD should be undertaken in patients with OSA without a history of CAD is unclear. In the current study, we sought to identify the prevalence of subclinical CAD using exercise stress testing in patients with moderate to severe OSA to determine whether screening in this population is merited.

MATERIALS AND METHODS

Patients

We prospectively studied consecutive patients with moderate to severe OSA who underwent polysomnography from May 2004 to September 2007. Data on demographic characteristics, sleep and medical history, and medication use were obtained with the use of a standardized questionnaire before the overnight polysomnogram. The sleep questionnaire included history of snoring and the relationship of snoring with position, choking, witnessed apnea, sleep fragmentation, nocturia, night sweating, morning tiredness, and headache. Each patient's height and weight were recorded at the time of the polysomnogram, and the body mass index was calculated. The Epworth Sleepiness Scale in Turkish[15] was used to report subjective daytime sleepiness. Data regarding risk factors for CAD included a history of hypertension, diabetes mellitus, or hyperlipidemia reported by the patient on the baseline medical questionnaire, noted in the file, or both. Smoking habit was also documented on the routine baseline questionnaire. The detailed physical examination included measurement of neck circumference.

A routine, resting, 12-lead ECG, as well as echocardiography, was performed in all patients to exclude subjects with signs of a former myocardial infarction or significant myocardial, pericardial, or valvular abnormalities.

Study Design

All patients fulfilling the inclusion criteria were recruited and underwent the exercise stress testing according to the Bruce protocol[16] utilizing Quinton Q5000 (Cardiac Science, Corp., Bothell WA). The results of exercise stress testing were interpreted by an experienced cardiologist as negative, positive, or suspected positive, with positive results being defined as the patient having developed any combination of the following: significant ST-segment depression (> 2-mm horizontal or downsloping depression in frontal derivations, > 1 mm in precordial derivations, or both) ST-segment elevation (> 1 mm), ventricular tachycardia, or onset of left bundle branch block. The results from patients with upsloping ST-segment depression or T-wave changes and those with right bundle branch block or supraventricular tachycardia were regarded as suspected positive. The test results were considered negative for CAD when the patient reached 85% of the predicted maximal heart rate without the above-noted ECG changes occurring.

Patients with a positive treadmill result were regarded as the high-risk group, and they subsequently underwent coronary angiography to confirm the diagnosis of CAD. The patients with medium or low risk whose results of exercise stress testing were suspected positive were referred for a myocardial perfusion study. These patients underwent a 2-day exercise/rest Tc-99m hexakis-methoxy-isobutyl-isonitrile (MIBI) single-photon emission computed tomography (SPECT) myocardial perfusion scintigram. For stress SPECT imaging, patients underwent a symptom-limited maximal treadmill exercise test using the Bruce protocol. The patients received 720 MBq Tc-99m MIBI intravenously and continued to exercise for 1 additional minute; heart rate and blood pressure were measured every 2 minutes, and ECG was monitored continuously. On the second day, 720 MBq Tc-99m MIBI was injected for the resting SPECT imaging. SPECT imaging for both the stress and rest periods were acquired 1 hour after injections by a gamma camera (Sopha DST-XLi, Twinsburg, OH) with a low-energy high-resolution collimator. During image analysis, the myocardium was divided into 3 segments: apical, mid, and basal. A reversible myocardial perfusion defect found in at least 1 myocardial segment was defined as an ischemic event in the respective coronary vascular region. Both exercise and resting SPECT images were evaluated by an experienced nuclear medicine physician.

All participants underwent a full-night in-hospital polysomnogram using the Embla system (Medcare Flaga, Reykjavik, Iceland). The polysomnographic recordings included 4-channel electroencephalography, 2-channel electrooculography, 1-channel submental electromyography, O_2 saturation via an oximeter probe, respiratory movements via chest and abdominal belts, nasal pressure via pressure sensor, ECG, and leg movements via tibial surface electrodes. Apnea was defined as a complete cessation of airflow ≥ 10 sec. Hypopnea was defined as a reduction in airflow of at least 30% accompanied by ≥ 4% desaturation in the preceding 30 sec and a reduction in chest wall movement or an arousal. The AHI included the average number of apneas and hypopneas/h of sleep. The patients were classified as have mild OSA (AHI 5.0-14.9/h), moderate OSA (AHI 15.0-29.9/h), or severe OSA (AHI ≥ 30/h). Sleep stages were scored according to the system described by Rechtschaffen and Kales.[17]

All patients provided written informed consent to participate in the study, and the local ethics committee approved the study.

Data Analysis

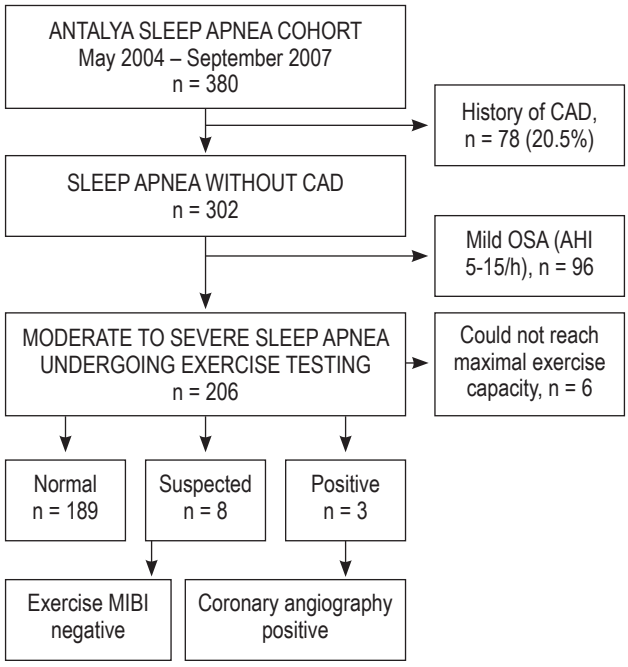
The results are presented as mean (SD) values and as percentages. Descriptive analysis was carried out using SPSS version 11.5 (SPSS, Inc., Chicago, IL).

RESULTS

As illustrated in **Figure 1**, 380 consecutive patients with OSA were initially recruited for the study. After excluding the patients with a history of CAD (n = 78), as well as the subjects with mild OSA (n = 96), 206 individuals with moderate (n = 74) to severe OSA (n = 132) were identified as the final study population. None of the participants had signs of myocardial infarction on the resting ECG or significant myocardial, pericardial, or valvular abnormalities on the echocardiogram. Six patients could not complete the exercise stress testing due to morbid obesity. Two hundred patients with OSA (181 men and 19 women) fully completed the exercise stress testing protocol and reached the maximal exercise capacity. Demographic and

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Figure 1—Patient log demonstrating the study cohort and the different subgroups



CAD refers to coronary artery disease; OSA, obstructive sleep apnea.

Table 1—Demographic and cardiac risk profiles of the 200 patients in this study

Variable	Values
Age, y	48.1 ± 9.9
BMI, kg/m^2	32.2 ± 5.3
AHI, events/h	41.1 ± 21.4
Neck circumference, cm	41.8 ± 2.9
ESS, score	11.1 ± 5.1
Diabetes mellitus	25 (12.5)
Current smoker	92 (46)
Ex-smoker	72 (36)
Hyperlipidemia	54 (27)
Family history of CAD	55 (27.5)
Systemic hypertension	57 (28.5)
Currently taking antihypertensive medication	
Any	52 (26.0)
Diuretic	14 (24.6)
β-adrenergic receptor-blocking agent	10 (17.5)
Calcium-channel antagonist	9 (15.8)
ACE inhibitor	12 (21.1)
Angiotensin II antagonist	26 (45.6)
Combination drugs	18 (31.6)

Continuous variables are presented as mean ± SD; others, as number (%). BMI refers to body mass index; AHI, apnea-hypopnea index; ESS, Epworth Sleepiness Scale; CAD, coronary artery disease; ACE, angiotensin converting enzyme.

the traditionally recognized cardiovascular risk factors in the final study population are summarized in **Table 1**.

None of the subjects reported experiencing chest pain during the exercise stress testing. However, 8 patients had suspected CAD, and 3 patients had significant ischemic findings on the ECG. All patients with suspected CAD findings underwent an exercise MIBI and had normal results. The patients with significant ECG changes underwent angiography. In all 3 patients, significant coronary artery stenosis was detected, and the patients were referred for cardiovascular revascularization. The AHIs of these patients were 15.1/h, 22.8/h, and 60.0/h. Thus, the prevalence of subclinical CAD was 0.8 % in the group with severe OSA.

Moreover, 2 of the 3 patients with subclinical CAD had ≥ 3 additional risk factors for CAD. The first patient had hyperlipidemia, a family history of CAD, and a history of smoking. The second patient had hypertension, a family history of CAD, and a history of smoking. The third patient had only a history of smoking as an additional risk factor,

DISCUSSION

This is the first report to address the results of exercise stress testing in detecting subclinical CAD in patients with moderate to severe OSA. Because the prevalence of subclinical CAD in this selected population with OSA was not higher than that in a general population, our results do not support routine screening by this method in patients with OSA who do not have symptoms of CAD.

Although the true prevalence of subclinical CAD in patients with OSA is unknown, available data suggest a high occurrence of symptomatic CAD in patients with OSA,[7,9] as was also shown in our cohort. Moreover, in our previous study of a sleep-clinic population, we showed that OSA was associated with an almost 5-fold increase in the risk of developing CAD, independent of age, sex, hypertension, diabetes, and current smoking at a 7-year follow-up.[18] In an uncontrolled prevalence study that included 386 patients, CAD was present in almost one-fourth of the subjects with OSA, and the percentage of patients with CAD was high among those with moderate to severe OSA.[7] Bauer et al.[9] found a much higher prevalence rate (68%) of CAD among patients with OSA who had chest pain. OSA appears to be common in patients with CAD; in the normal population, the prevalence of OSA is 2% to 4%; whereas, in patients with CAD, it is approximately 30% to 65%.[3]

Because a dose-effect relationship of CAD in patients with OSA had been detected in recent trials,[7,10] we screened only patients with moderate to severe OSA. Marin et al. showed that the risk of fatal (odds ratio: 2.87, 95% confidence interval: 1.17-7.51) and nonfatal (odds ratio: 3.17, 95% confidence interval: 1.12-7.51) cardiovascular events was significantly increased in patients with severe untreated OSA, as compared with in healthy control subjects.[10] However, in a general population, asymptomatic persons are expected to be unlikely to have CAD.[19] One interesting study that has addressed the prevalence of subclinical CAD was conducted in Florence and Rome in 4842 men aged 40 to 59 years who were free from major heart disease, severe illnesses, and chest pain.[20] Using a 3-stage diagnostic procedure, the researchers screened the

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subjects with resting and exercise ECGs, the hyperventilation test, and 24-hour Holter monitoring. The subjects who were suspected of having silent myocardial ischemia or having had a previous silent myocardial infarction at the first stage of the study (n = 439; 9.1%) were entered into the second stage, which included ECG, thallium-201 scintigraphy in conjunction with exercise testing or a dipyridamole test, exercise radionuclide ventriculography, and the ergonovine test. The second stage, which included 387 men, found that 104 of the subjects (2.1%) were suspected of having silent CAD. Sixty-two men participated in the third diagnostic workup, which included coronary angiography. The final diagnosis of silent myocardial ischemia or infarction was reached in 25 patients (0.5%).

In the absence of a control group in our study, which is a major limitation, our results regarding the prevalence of subclinical CAD appear to be comparable with the results in this general population studied by Fazzinni et al.[20] However, because the mean age of our study population was 48 years, the results might not be comparable with older or younger populations with moderate to severe OSA. Had we included a larger sample size comprising primarily patients with severe OSA, we likely would have found a higher prevalence of subclinical CAD.

The diagnostic value of the exercise stress testing for subclinical CAD, mainly based on the ST-segment depression in asymptomatic subjects, is difficult to assess because few asymptomatic patients undergo coronary angiography.[12] One large study of a clinical population undergoing coronary angiography independent of the results of exercise stress testing showed a poor sensitivity (< 45%) but higher specificity (> 85%) for standard exercise tests.[21] However, coronary angiography represents an incomplete look at disease within the coronary vessel wall, which does not enable clinicians to determine the physiologic response of a diseased endothelium under conditions of stress. It has also been argued that a noninvasive test that demonstrates stress-induced ischemia may well be associated with a coronary angiogram showing only mild disease.[22] If stress leads to a paradoxical vasoconstriction, then ischemia may be present, despite benign-appearing results of a resting coronary angiogram.[22] On the other hand, of those patients who have negative results of a stress ECG test, it is quite possible that many more cases of CAD would be detected with other testing (e.g., stress imaging, coronary calcium scanning, computed tomographic angiography). Even if the prevalence of CAD is low in a population, it may be that, with a larger sample, CAD may be detected in a sufficient number of subjects who can therefore undergo early intervention and, perhaps, avoid the associated increased morbidity and mortality rates associated with untreated CAD.

The value of exercise stress testing as a screening tool for CAD has been addressed in other populations. One study of middle-aged angina-free men with a history of smoking, hypertension, hypercholesterolemia, or a family history of CAD found that men with any of these risk factors had significantly higher incidences of having had a CAD event if they had 2 or more abnormalities on exercise stress testing, as compared with those who had fewer than 2 abnormalities.[23] The authors concluded that routine screening of asymptomatic men without any of the traditionally recognized cardiovascular risk factors was not warranted. The American Diabetes Association has defined which angina-free diabetics should undergo exercise stress testing[13]: testing only for those individuals who have at least 2 additional risk factors. In our cohort, all patients who were found to have CAD were heavy smokers, and it has been shown that patients with severe OSA who smoke are at a higher risk for having a cardiovascular event, as compared with those patients with OSA who do not smoke.[24] Two of our patients had at least 3 additional risk factors; multiple risk factors in the same patient substantially increase the overall cardiovascular risk.[25] The higher the number of risk factors, the higher the pretest probability is for exercise stress testing.[26] It is likely that a similar approach, limiting cardiac screening to those patients with OSA who have additional risk factors for CAD, might improve the predictive value of a positive exercise testing.

It should be noted that our study cohort was a group of consecutive patients seen at a sleep clinic and that the proportion of women was 9.5% among subjects presenting with an AHI of at least 15, which limits the generalizability of our conclusions. Thus, our results apply to a predominantly male sleep-clinic cohort with moderate to severe OSA. We should also add that our results do not mean that we found no relationship between CAD and OSA: the prevalence of a "known CAD" was 20.5% in this consecutive cohort from a sleep clinic, which is in line with the results of previous studies suggesting an independent association between OSA and established CAD.

In conclusion, the prevalence of subclinical CAD in this selected population with OSA was not higher than that in a general population. Our results do not support routine screening by exercise stress testing in patients with moderate to severe OSA who do not have symptoms of CAD.

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ACKNOWLEDGMENTS

The study was supported by grants from Akdeniz University Scientific Project Unit.

SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December, 2009
Submitted in final revised form August, 2010
Accepted for publication September, 2010
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DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.

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