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## Independent Association Between Obstructive Sleep Apnea and Subclinical Coronary Artery Disease

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### Abstract

**Background**—Obstructive sleep apnea (OSA) is associated with coronary risk factors, but it is unknown if OSA is associated with development of coronary disease. We evaluated the association between OSA and the presence of subclinical coronary disease assessed by coronary artery calcification (CAC).

**Methods**—Consecutive patients with no history of coronary disease, who underwent electron-beam computed tomography within 3 years of polysomnography between March 1991 and December 2003, were included. OSA was defined by an apnea-hypopnea index (AHI)  $\geq 5$ , and patients were grouped by quartiles of AHI severity. Logistic regression modeled the association between OSA severity and presence of CAC.

**Results**—There were 202 patients (70% male, median age 50, mean body mass index 32, 8% diabetic, 9% current smokers, 60% hypercholesterolemic, and 47% hypertensive). OSA was present in 76%. CAC was present in 67% of OSA patients and 31% of non-OSA patients ( $p < 0.001$ ). The median CAC score (Agatston Units) was 9 in OSA patients and 0 in non-OSA patients ( $p < 0.001$ ). The median CAC score was higher as OSA severity increased ( $p$  for trend by AHI quartile  $< 0.001$ ). With multivariate adjustment, the odds ratio for CAC increased with OSA severity. Using the first AHI quartile as reference, the adjusted odds ratio for the second, third, and fourth quartiles were 2.1 ( $p = 0.12$ ), 2.4 ( $p = 0.06$ ), and 3.3 ( $p = 0.03$ ) respectively.

**Conclusions**—In patients without clinical coronary disease, the presence and severity of OSA is independently associated with the presence and extent of CAC. OSA identifies patients at risk for coronary disease and may represent a highly prevalent modifiable risk factor.

### Keywords

Calcium; Coronary artery disease; Obstructive sleep apnea; Risk factors

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## Introduction

Obstructive sleep apnea (OSA) is a common medical condition, with an estimated prevalence of 20% middle-aged adults having at least mild OSA and 4 to 9% having OSA symptoms. The prevalence of OSA and its cardiovascular consequences are becoming increasingly recognized.<sup>1,2</sup>

OSA causes repetitive acute hypoxemic episodes and sleep deprivation, leading to abnormalities in cardiovascular regulation. Apneic spells lead to sympathetic activation, increased blood pressure, and endothelial dysfunction.<sup>3, 4</sup> A proinflammatory state is also present in patients with OSA, evidenced by increased C-reactive protein levels.<sup>5, 6</sup> In addition, OSA is associated with metabolic dysregulation, including insulin resistance and elevated leptin levels,<sup>7, 8</sup> as well as diabetes, and obesity.<sup>9-11</sup>

OSA may cause systemic hypertension,<sup>12-19</sup> and is associated with a higher incidence of myocardial infarction and cardiovascular mortality.<sup>20, 21</sup> While OSA has been linked to subclinical carotid atherosclerosis, no previous studies have directly evaluated the relationship between OSA and measures of subclinical coronary atherosclerotic disease.<sup>22, 23</sup> Electron beam computed tomography (EBCT) is an effective tool to quantify the magnitude of coronary artery calcification, which is a marker of coronary atherosclerotic burden,<sup>24</sup> and associated with coronary events and asymptomatic myocardial ischemia.<sup>25-32</sup> Coronary artery calcification has also shown to predict coronary artery stenoses as defined by angiography, intracoronary ultrasound, and histology.<sup>33-36</sup> The goal of the present study was to determine the presence and magnitude of any association between OSA and subclinical coronary disease, as measured by coronary artery calcification.

## Materials and Methods

### Subjects

We performed a historical cross-sectional study of consecutive patients at our institution who underwent polysomnography from March 1, 1991 to December 31, 2003, and who also underwent EBCT for coronary artery calcification quantification within 36 months of polysomnography. Using administrative records, we identified patients that were referred by their caring physicians to the Mayo Clinic Sleep Disorders Clinic and underwent polysomnography for clinically suspected sleep disorders and were also referred for EBCT for coronary artery disease risk stratification. Patients were asymptomatic for coronary artery disease prior to EBCT. For patients with multiple EBCTs or polysomnograms, the first such study was used for analysis. We excluded patients who prior to EBCT or polysomnography had documented coronary artery disease by angiography, prior coronary artery bypass, or history of myocardial infarction. Patients were also excluded if the EBCT report did not quantify the amount of coronary artery calcification, if any, in Agatston units. Diabetes was defined as a fasting blood glucose level >126 mg/dL and/or use of antidiabetic medication. Hypercholesterolemia was defined as total cholesterol >240 mg/dL and/or use of a lipid-lowering medication. Hypertension was defined as systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, or use of an antihypertensive medication.

### Polysomnography

Polysomnography was performed using the standard clinical protocol at the Mayo Clinic Sleep Disorders Center, which utilized a digital polygraph (NCI, Wisconsin) that measured three electroencephalograms, two electro-oculograms, submental and tibialis electromyograms, rib cage and abdominal respiratory inductance plethysmography (RIP, Ambulatory Monitoring, Inc., New York), nasal pressure transducer (PTAF Pressure Transduce, Pro-Tech Inc.,

Washington), pulse oximetry (Ohmeda 3740, Wisconsin), sonography via decibel meter (Tandy Corp, Texas), and body position measurements. Sleep staging and arousals were scored using 30-s epochs with criteria by Rechtschaffen, Kales, and the American Sleep Disorders Association.<sup>37</sup> 38 OSA was diagnosed by standard criteria, requiring an apnea-hypopnea index (AHI)  $\geq 5$  events per hour.<sup>37</sup>

### Electron Beam Computed Tomography

EBCT imaging was performed using a GE Imatron-150 with contiguous 3-mm slice thickness and 100 msec scanning time, with a total of 40 slices extending from carina to diaphragm. Tomographic imaging was triggered through three-lead electrocardiography at 80% of the R-to-R interval during end-inspiration to minimize artifact. The degree of coronary artery calcification was determined using a standard protocol. An automated system was utilized to score the tomograms after scan acquisition. Lesion area in square millimeters was obtained, and the peak CT scan density of each lesion was calculated. Lesion area was defined as a plaque of 4 consecutive pixels (area of 1.0 mm<sup>2</sup>) with a density of  $>130$  Hounsfield units. A score for each lesion was generated by multiplying the measured area of any lesion  $>1.0$  mm<sup>2</sup> by an attenuation coefficient based on its peak CT number. The summation of the scores for each lesion in each vessel was used to determine the overall calcium score, and a percentile score adjusted for age and gender, according to the Agatston quantification algorithm.<sup>24</sup>

Informed consent was obtained from all study participants, and this study was approved by the Mayo Foundation Institutional Review Board.

### Statistical Analysis

OSA was defined by an AHI  $\geq 5$ . The severity of OSA was determined using quartiles of the AHI distribution. Patients were classified as having subclinical coronary disease if the coronary artery calcification score was  $> 0$ . Chi-square and independent-sample t-test were used to compare demographics and clinical characteristics. We compared the median value of coronary artery calcification among patients with increasing severity of OSA, based on AHI quartiles, with the non-parametric Kruskal-Wallis test because of the non-Gaussian distribution of coronary calcification scores. We compared the mean percentile coronary calcification among AHI quartiles using one-way ANOVA. Step-wise logistic regression models tested the independent association between measures of obstructive sleep apnea and the presence of coronary calcification after adjusting for sex, body-mass index, current smoking status, hypertension, diabetes mellitus and dyslipidemia. OSA was used as a categorical variable and the second, third and highest quartiles were compared to the first quartile. Different measures of OSA (AHI, lowest overnight oxygen saturation and average overnight oxygen saturation) were included in the models separately. Statistical significance was defined as a p-value  $< 0.05$  for all analyses.

## RESULTS

The study sample comprised 202 patients. The average time between EBCT and polysomnography was 16 months (0 to 35.5 months). Of the 103 OSA patients having EBCT after polysomnography, 38 patients initiated CPAP therapy for an average of 18 months. Tables 1 and 2 provide a comparison of characteristics for patients with and without OSA and when grouped by OSA severity, respectively. Patients with OSA were more likely to be older, male, obese, and had more traditional risk factors than non-OSA patients except for active smoking status. Coronary artery calcification was present in 67% of OSA patients and 31% of non-OSA patients ( $p<0.001$ ). The median coronary artery calcification score was significantly greater in OSA (9 Agatston units) compared to non-OSA patients (0 Agatston units,  $p<0.001$ ). The mean amount of coronary artery calcification was significantly higher in patients with OSA (144

Agatston units) compared to patients without OSA (26 Agatston units,  $p=0.001$ ) and OSA patients had higher percentile coronary artery calcification scores than non-OSA patients, 46<sup>th</sup> versus 20<sup>th</sup> percentile ( $p<0.001$ ) respectively. Coronary artery calcification had a strong direct correlation with the severity of OSA, based on the AHI (Table 3). The median and mean score of coronary artery calcification as well as the percentile score increased as OSA worsened (all with a  $p<0.001$ ). The strength of the association remained essentially unchanged after adjustment for age and sex and after multivariate adjustment for traditional coronary risk factors (Figure 1). Coronary calcification was not associated with lowest or average overnight oxygen saturation.

## DISCUSSION

The novel finding of the present study is that OSA is associated with subclinical coronary artery disease, independent of traditional coronary risk factors. Not only was coronary artery calcification more likely to be present in patients with OSA, but the amount of coronary artery calcification increased with increasing severity of OSA.

Similar to previous studies that have shown OSA to be associated with coronary risk factors, our patients with OSA had more comorbidities than the non-OSA group.<sup>9–19, 39</sup> While associations between OSA and coronary events have been reported,<sup>20, 21</sup> no prior study has identified a relationship between OSA and subclinical coronary disease in patients without established coronary artery disease. Prior studies have shown an association of OSA and atherosclerosis in mice and patients with known symptomatic CAD by angiography have been evaluated for sleep disordered breathing.<sup>40,41</sup> The present findings may represent an intermediate step from the pathophysiology of OSA to the development of clinical outcomes.

Our findings highlight not only an association between coronary artery calcification and increasing OSA severity, but also suggest a high prevalence of subclinical coronary artery disease in patients with OSA. Detection of subclinical coronary artery calcification is important for risk stratification and treatment decisions. Traditional cardiac risk factors have been shown to correlate with the severity of coronary artery calcification.<sup>42–44</sup> However, several studies have pointed out that Framingham risk scores may under-recognize patients with subclinical coronary artery calcification who are at higher risk.<sup>45–47</sup> In one study, patients with diabetes had the same survival rate as non-diabetics if no calcification was present but had increased mortality if any calcification was present.<sup>48</sup> Coronary artery calcification is associated with silent ischemia and coronary events.<sup>25–32</sup> Our data further show that an AHI >15 is associated with a mean coronary artery calcification score of 162 Agatston Units that is suggestive of significant coronary lesions or extensive atherosclerotic heart disease, and increased risk of ischemia and coronary events.<sup>20, 21, 28, 32, 49–53</sup>

Our findings are strengthened by the use of the gold standard test, polysomnography, to diagnose OSA, and inclusion of patients without prior polysomnography, thereby eliminating the possibility of prior OSA therapy. Also, patients had no clinical history of coronary disease, and data used were from each patient's first EBCT. All EBCT and polysomnograms were performed under standardized protocols at a single facility minimizing variability of methodology and interpretation of these measures.

Our findings confirm and extend the results of other studies assessing the potential interaction between OSA and coronary artery disease. The AHI, which can be considered a composite measure of hypoxia severity and apneic episode frequency, correlated to the coronary atherosclerosis present.<sup>40–41</sup> The magnitude of the association between OSA and coronary artery calcification we identified is similar to that shown in two longitudinal studies that

reported associations between OSA and incidental cardiovascular disease, stroke, and death.<sup>20, 21</sup>

Interestingly, the amount of coronary calcification did not correlate to the average overnight oxygen saturation or with the lowest overnight oxygen desaturation. Potential explanations for this include the possibility that mechanisms linking CAD and OSA relate more to the hyperadrenergic state generated by apneic episodes, more than to the hypoxia itself. Other studies have suggested different stresses and disease mechanisms for different comorbidities linked to OSA. These various stresses include hypoxia, but also carbon dioxide retention, sleep disruption, truncated total sleep time, and strenuous respiratory efforts. The effect of these stressors is manifested through the neuro-humoral, vascular, and endocrine responses, but the individual or collective contribution of these in OSA is unknown. One study showed that the frequency of respiratory related arousals most strongly correlated with higher blood pressure, more so than nocturnal hypoxemia in OSA patients.<sup>54</sup> Similarly, in a study by Norman the treatment of OSA with CPAP lowers AHI and blood pressure, but treatment with supplemental nocturnal oxygen did not affect blood pressure despite improved oxyhemoglobin saturation.<sup>55</sup>

Potential limitations of the present study include the inherent limitations of a cross-sectional design, which cannot identify causal or temporal relationships between OSA and subclinical coronary artery calcification. Given the established effects of OSA on cardiovascular disease mechanisms, the most plausible explanation is that OSA contributes to coronary atherosclerosis and not vice versa. Another potential limitation is the time between the polysomnography and EBCT, up to 3 years in some cases. The interval was variable since referrals for these studies were unrelated to one another. However, the effects of OSA on vascular health take many years to develop and coronary calcifications scores should not significantly change within 3 years. Furthermore, any bias incorporated by time delay between the studies would be toward the null hypothesis. Selection bias is another limitation, since the study sample was comprised of patients referred for polysomnography and cardiac EBCT. This may have resulted in a study sample with higher risk individuals than the average individual with OSA in the community. However, the number of males in the OSA group fit with prevalence data previously published.<sup>1</sup> Gender is an important factor and possible confounder, and an analysis stratified by gender would be ideal. With our number of patients, however, the statistical power to do this analysis would be very low and the results difficult to interpret. Thus, we cannot say with our current data if the association applies to both sexes or if it is limited to men or women. Our use of multivariate regression analysis included sex as a covariate and therefore most of the potential confounding effect by sex and the other confounders should have been accounted for. However, the results likely are not directly applicable to individuals from the community who would not have been otherwise referred for polysomnography or cardiac risk assessment.<sup>56</sup> But, importantly, our results should be applicable to the large population of patients who are seen in medical clinics who are at risk for sleep disorders or coronary artery disease. A prospective study of individuals from the community was outside the scope of our research. It is not clear if the results in this study can be extended to other ethnic groups, since our study cohort comprised mostly white Caucasian patients.

In conclusion, we found a strong association between OSA and subclinical coronary disease, as measured by coronary artery calcification. This association was independent of traditional risk factors and correlated with the severity of OSA. The presence and severity of OSA should be considered for coronary artery disease risk stratification, and in general, OSA should be an important consideration in the practice of preventive cardiology.

## Abbreviations

AHI            apnea-hypopnea index

CAC	coronary artery calcification
EBCT	electron beam computed tomography
OSA	obstructive sleep apnea

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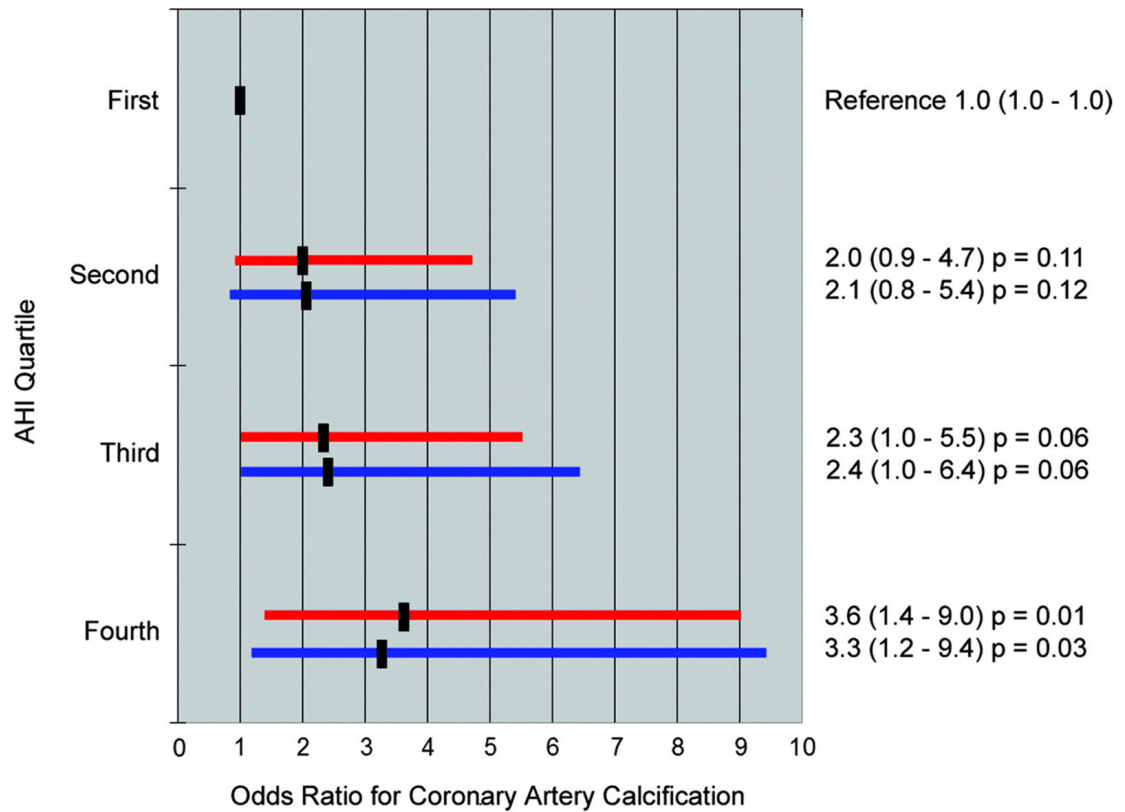
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**Multivariate analysis for the association between OSA severity measured by AHI quartile and CAC.**



**Figure 1.** Multivariate Analysis for the Association Between Obstructive Sleep Apnea Severity Measured by AHI Quartile and Coronary Artery Calcification  
 ■ Adjusted for age and gender  
 ■ Adjusted for age, gender and traditional risk factors  
 Traditional risk factors = diabetes mellitus, hypercholesterolemia, active smoking, hypertension, and body mass index

**Table 1**

Comparison of Baseline Characteristics Between Patients With and Without Obstructive Sleep Apnea

Variables	Patients with OSA * (n=154)	Patients without OSA (n=48)	P-value
Age, y	51	46	<0.001
Male sex, %	72	63	0.21
Diabetes mellitus, %	9	4	0.46
Hypercholesterolemia, %	64	48	0.03
Hypertension, %	49	40	0.44
Active smoking, %	8	15	0.07
Past smoking, %	48	46	0.20
Body Mass Index mean, kg/m <sup>2</sup>	35	31	0.15
Fasting blood glucose mean, mg/dL	105	97	0.01
LDL mean, mg/dL	132	131	0.83
Systolic blood pressure mean, mmHg	132	126	0.02
Diastolic blood pressure mean, mmHg	82	79	0.03
Presence of coronary artery calcification	67	31	<0.001

\* OSA = obstructive sleep apnea

**Table 2**  
 Comparison of Baseline Characteristics Between Patients With Increasing Obstructive Sleep Apnea Severity Measured by AHI\* Quartile

Variables	First Quartile (n=53)	Second Quartile (n=50)	Third Quartile (n=49)	Fourth Quartile (n=50)	P-value
Age, y	46	51	51	52	0.001
Male sex, %	64	58	76	82	0.04
Diabetes mellitus, %	4	8	16	4	0.12
Hypercholesterolemia, %	49	66	65	62	0.39
Hypertension, %	40	36	49	62	0.09
Active smoking, %	13	10	4	10	0.48
Past smoking, %	47	52	35	56	0.24
Body Mass Index mean, kg/m <sup>2</sup>	30	32	33	40	0.03
Fasting blood glucose mean, mg/dL	97	106	108	104	0.22
LDL mean, mg/dL	131	129	131	137	0.67
Systolic blood pressure mean, mmHg	127	130	131	134	0.11
Diastolic blood pressure mean, mmHg	80	82	80	84	0.13

\* AHI = apnea hypopnea index

**Table 3**  
 Mean AHI\* and Coronary Artery Calcification Score by Obstructive Sleep Apnea Severity Measured by AHI Quartile

Variable	First AHI Quartile	Second AHI Quartile	Third AHI Quartile	Fourth AHI Quartile	P-value for trend
Mean AHI (Range)	2.2 (0-5)	8.9 (6-13)	20.5 (14-32)	63.4 (≥33)	<0.001
Presence of Coronary Artery Calcification, %	36	58	65	76	<0.001
Median Coronary Artery Calcification Score, Agatston Units (Range)	0 (0-500)	4 (0-2300)	6 (0-245)	44 (0-2196)	<0.001
Mean Coronary Artery Calcification Score, Agatston Units (Standard deviation)	32 (97)	109 (340)	38 (60)	286 (569)	<0.001
Mean Coronary Artery Calcification Percentile for age and sex (Standard deviation)	22 (33)	43 (41)	41 (35)	54 (38)	<0.001

\* AHI = apnea hypopnea index