Increased Risk of Stroke in Patients With Coronary Artery Disease and Sleep Apnea
A 10-Year Follow-Up

Fredrik Valham, MD; Thomas Mooe, MD, PhD; Terje Rabben, MD; Hans Stenlund, PhD; Urban Wiklund, PhD; Karl A. Franklin, MD, PhD

Background—The effect of sleep apnea on mortality and cardiovascular morbidity is mainly unknown. We aimed to study whether sleep apnea is related to stroke, death, or myocardial infarction in patients with symptomatic coronary artery disease.

Methods and Results—A total of 392 men and women with coronary artery disease referred for coronary angiography were examined by use of overnight sleep apnea recordings. Sleep apnea, defined as an apnea-hypopnea index ≥5, was recorded in 54% of the patients. All patients were followed up prospectively for 10 years, and no one was lost to follow-up. Stroke occurred in 47 (12%) of 392 patients during follow-up. Sleep apnea was associated with an increased risk of stroke, with an adjusted hazard ratio of 2.89 (95% confidence interval 1.37 to 6.09, \( P = 0.005 \)), independent of age, body mass index, left ventricular function, diabetes mellitus, gender, intervention, hypertension, atrial fibrillation, a previous stroke or transient ischemic attack, and smoking. Patients with an apnea-hypopnea index of 5 to 15 and patients with an apnea-hypopnea index ≥15 had a 2.44 (95% confidence interval 1.08 to 5.52) and 3.56 (95% confidence interval 1.56 to 8.16) times increased risk of stroke, respectively, than patients without sleep apnea, independent of confounders (\( P \) for trend = 0.011). Death and myocardial infarction were not related to sleep apnea. Intervention in the form of coronary artery bypass grafting or percutaneous coronary intervention was related to a longer survival but did not affect the incidence of stroke.

Conclusions—Sleep apnea is significantly associated with the risk of stroke among patients with coronary artery disease who are being evaluated for coronary intervention. (Circulation. 2008;118:955-960.)

Key Words: sleep apnea syndromes • coronary disease • stroke • prognosis • risk factors • myocardial infarction

Obstructive sleep apnea is characterized by repeated obstructions of the upper airway during sleep, which result in oxygen desaturations and alterations in blood pressure and cerebral blood flow.1 Sleep apnea is associated with cardiovascular disease and hypertension.2–6 Yaggi and colleagues4 recently reported that sleep apnea was related to the combined end point of stroke and death among men ≥50 years of age who were referred because of a suspicion of sleep apnea.

Clinical Perspective p 960

Sleep apnea is common among patients with coronary artery disease, regardless of snoring and daytime sleepiness,7–13 but the effect of sleep apnea on cardiovascular morbidity is mainly unknown, and the results regarding death rates are conflicting. Peker and colleagues12 reported an increase in mortality rates among 62 patients with coronary artery disease during 5 years of follow-up. On the other hand, Hagenah and colleagues14 reported no increase in death rates related to sleep apnea among 50 patients with coronary artery disease. We have previously reported an increased risk of the combined end point of death, myocardial infarction, stroke, and transient ischemic attack at an oxygen desaturation index of 5 or more.15 We performed the present study after a long follow-up with considerably more end-point events and thereby greater power to study the effect of sleep apnea on single major end points. We aimed to study the effect of sleep apnea on stroke, death, and myocardial infarction in patients with symptomatic coronary artery disease who were being evaluated for coronary intervention.

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Table 1. Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>All Patients (n=392)</th>
<th>AHI &lt;5 (n=181)</th>
<th>AHI ≥5 (n=211)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>59.9±7.4</td>
<td>59.3±7.8</td>
<td>60.7±7.0</td>
<td>0.026</td>
</tr>
<tr>
<td>Men, %</td>
<td>67</td>
<td>60</td>
<td>73</td>
<td>0.005</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean±SD</td>
<td>27.0±3.5</td>
<td>26.8±3.3</td>
<td>27.3±3.7</td>
<td>0.148</td>
</tr>
<tr>
<td>Arterial hypertension, %</td>
<td>38</td>
<td>34</td>
<td>41</td>
<td>0.156</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>14</td>
<td>11</td>
<td>17</td>
<td>0.090</td>
</tr>
<tr>
<td>Previous stroke/TIA, %</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>0.673</td>
</tr>
<tr>
<td>Atrial fibrillation, %</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>0.806</td>
</tr>
<tr>
<td>Current smoking, %</td>
<td>23</td>
<td>23</td>
<td>22</td>
<td>0.843</td>
</tr>
<tr>
<td>Left ventricular function, %</td>
<td>0.068</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>72</td>
<td>77</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Fair</td>
<td>23</td>
<td>21</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>4</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Medication, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Blockers</td>
<td>72</td>
<td>71</td>
<td>73</td>
<td>0.785</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>16</td>
<td>14</td>
<td>18</td>
<td>0.330</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>37</td>
<td>36</td>
<td>37</td>
<td>0.754</td>
</tr>
<tr>
<td>Diuretics</td>
<td>17</td>
<td>14</td>
<td>19</td>
<td>0.138</td>
</tr>
<tr>
<td>Digoxin</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>0.202</td>
</tr>
<tr>
<td>Nitrates, long-acting</td>
<td>74</td>
<td>73</td>
<td>76</td>
<td>0.511</td>
</tr>
</tbody>
</table>

AHI indicates apnea-hypopnea index; TIA, transient ischemic attack.
*P for difference between patient groups AHI <5 and AHI ≥5.

Methods

Patients

Four hundred twenty-four patients aged 70 years and younger who had been referred to the Department of Cardiology at Umeå University Hospital from March 26, 1992, to June 15, 1995, for coronary angiography because of symptomatic angina pectoris were invited to participate. This unit was the only facility for coronary angiography in the catchment area of northern Sweden, with 900 000 inhabitants during the inclusion period. Coronary disease was verified by coronary angiography and left ventriculography before inclusion, and eligible patients were randomly selected by lot each day for participation with overnight sleep apnea recordings. Sixteen patients refused to participate, and another 16 patients were excluded from the final analysis owing to technical failures in respiratory monitoring. A total of 392 patients were included in the final analysis and were followed up for 10 years after inclusion. There were 264 men and 128 women. All patients had stable angina recorded in 211 (54%) of the patients at the start of the study. Nineteen percent of the patients had 1-vessel disease, 30% had 2-vessel disease, 51% had 3-vessel disease, and 14% had a left main stem stenosis. Patient characteristics at baseline are given in Table 1. Approval for the study was obtained from the Medical Ethics Committee at Umeå University, and all patients provided written informed consent.

Baseline Investigations

Overnight cardiorespiratory sleep apnea recordings were made in the hospital. They included continuous recordings of oronasal flow (Nihon Kohden ZE-7323A, Tokyo, Japan), blood oxygen saturation, and heart rate by pulse oximetry with a finger transducer (Ohmeda Biox 3700, Louisville, Colo); respiratory and body movements with a pressure-sensitive bed (polyvinylidene fluoride foil, Apnomat, Duorek Ltd, Raisio, Finland); and sleep position with a body-position indicator (Vitalog Monitoring Inc, Redwood City, Calif).

All the recordings were scored manually, and the duration of sleep was estimated from the recordings by a specialist experienced in polysomnographic scoring. An apnea episode was defined as a cessation in air flow that lasted at least 10 seconds and a hypopnea episode as a 50% reduction in air flow compared with baseline in combination with oxygen desaturation ≥3%. Sleep apnea was defined as a mean of 5 apnea and hypopnea events per hour of sleep or more, ie, an apnea-hypopnea index ≥5. The oxygen desaturation index was defined as the mean number of oxygen desaturations of 4% or more per hour of sleep. More details regarding the recording and data analysis have been described previously.

Left ventricular function was assessed visually from left ventriculograms and scored as good, fair, and poor, which correspond to an ejection fraction of >0.5, 0.35 to 0.5, and <0.35, respectively. Body mass index was defined as the weight in kilograms divided by the square of height in meters. Arterial hypertension was defined as a previous doctor’s diagnosis of arterial hypertension.

Outcome Measurements

The vital status and the dates and causes of death were obtained from the Causes of Death Register at the Swedish National Board of Health and Welfare. Onset of stroke and acute myocardial infarction that corresponded to ICD-9 (International Classification of Diseases, 9th Revision) codes 410, 430 to 434, and 436 and ICD-10 (International Classification of Diseases, 10th Revision) codes I21, I22, I60, I61, I63, and I64 were obtained from the Swedish Hospital Discharge Register at the Swedish National Board of Health and Welfare. Hospital records were obtained for all patients for source documentation of end points. Death certificates and autopsy reports, if available, were obtained for any patients who died during follow-up. The World Health Organization definition of stroke was used: rapidly developing clinical signs of focal (or global) disturbance of cerebral function that lasted for ≥24 hours with no apparent cause other than a vascular origin. End-point classification was made without any knowledge of sleep study results.

Statistical Analysis

Baseline data are presented as means and SDs or as proportions. Cox proportional hazards regression was used to analyze the impact of sleep apnea on time to death, stroke, and myocardial infarction, with adjustments for age, gender, body mass index, current smoking, hypertension, previous stroke/transient ischemic attack, atrial fibrillation, diabetes mellitus, coronary artery intervention, and left ventricular function at baseline. Hazard ratios (HRs) were regarded as significant when the 95% CI did not include the value of 1, corresponding to a probability value of <0.05. All statistical calculations were made with the Statistical Package for the Social Sciences (SPSS version 15.0, SPSS Inc, Chicago, Ill).

The authors had full access to the data and take full responsibility for its integrity. All the authors have read and agree to the manuscript as written.

Results

All 392 included patients were followed up prospectively for 10 years after inclusion, and no one was lost to follow-up. Sleep apnea with an apnea-hypopnea index of 5 or more was recorded in 211 (54%) of the patients at the start of the study. Patients with sleep apnea were slightly older and more frequently male (Table 1). A coronary intervention in the form of coronary artery bypass grafting or percutaneous coronary intervention was performed in 77% of the patients.

Stroke occurred in 47 (12%) of 392 patients during the follow-up. There were 6 hemorrhagic strokes and 41 infarctions. Patients with sleep apnea ran an increased risk of stroke compared with patients without sleep apnea in the unadjusted analysis, with an HR of 3.92 (95% CI 1.90 to 8.11, P<0.001; Tables 2 and 3; Figure). Sleep apnea remained as a significant
risk factor for stroke in the multivariate analysis, with an adjusted HR of 2.89 (95% CI 1.37 to 6.09, \( P = 0.005 \)), independent of age, body mass index, gender, left ventricular function, coronary artery intervention, diabetes mellitus, hypertension, previous stroke/transient ischemic attack, atrial fibrillation, and smoking (Table 3). There was a dose-response relationship between an increasing apnea-hypopnea index and stroke occurrence (\( P < 0.001 \) in unadjusted analysis and \( P = 0.011 \) in adjusted analysis). HRs for the occurrence of stroke during follow-up according to the apnea-hypopnea index at baseline are given in Table 4.

An oxygen desaturation index \( \geq 5 \) was recorded in 148 patients; these patients had an adjusted HR of 2.27 (95% CI 1.21 to 4.23, \( P = 0.01 \)) for stroke compared with patients with an oxygen desaturation index \( < 5 \). Death was recorded in 80 (20%) of 392 patients at follow-up, and 36 of them died of a cardiovascular event. Death due to any cause or death due to a cardiovascular cause was not related to sleep apnea or to an oxygen desaturation index \( \geq 5 \) (Table 5). Acute myocardial infarction occurred in 75 (19%) of 392 patients during the follow-up. Myocardial infarction was not related to sleep apnea or to an oxygen desaturation index \( \geq 5 \).

Patients who had undergone coronary artery intervention in the form of coronary artery bypass grafting or percutaneous coronary intervention ran a reduced risk of death, with an adjusted HR of 0.35 (95% CI 0.20 to 0.59, \( P < 0.001 \)); Table 5). Coronary artery intervention did not affect the occurrence of stroke (Table 3). Nine patients had been treated with continuous positive airway pressure, mandibular repositioning appliances, or surgery for sleep apnea during the study period, and this treatment did not affect outcomes.

### Discussion

This is the first study to provide evidence that sleep apnea is an independent risk factor for stroke among patients with coronary artery disease. Fifty-four percent of the present patients had sleep apnea, with an apnea-hypopnea index of \( \geq 5 \) or more, and they had an almost 3-fold increase in the risk of stroke during a 10-year follow-up, independent of age,
Table 4. HRs for Stroke According to the Apnea-Hypopnea Index at Baseline

<table>
<thead>
<tr>
<th>Apnea-Hypopnea Index (Events/h)</th>
<th>Unadjusted HR (95% CI)</th>
<th>Adjusted HR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to &lt;5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5 to &lt;15</td>
<td>3.28 (1.36–6.74)</td>
<td>2.44 (1.08–5.52)</td>
</tr>
<tr>
<td>≥15</td>
<td>5.34 (2.43–11.7)</td>
<td>3.56 (1.56–8.16)</td>
</tr>
</tbody>
</table>
| *Adjusted for age, body mass index, gender, left ventricular function, coronary artery intervention, diabetes mellitus, hypertension, previous stroke/transient ischemic attack, atrial fibrillation, and current smoking.

Table 5. Predictors of Death

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Unadjusted HR (95% CI)</th>
<th>P</th>
<th>Adjusted HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea-hypopnea index ≤5</td>
<td>1.19 (0.77–1.86)</td>
<td>0.434</td>
<td>0.99 (0.63–1.60)</td>
<td>0.396</td>
</tr>
<tr>
<td>Apnea-hypopnea index ≥5</td>
<td>1.04 (1.00–1.07)</td>
<td>0.026</td>
<td>1.05 (1.01–1.09)</td>
<td>0.007</td>
</tr>
<tr>
<td>Age, y</td>
<td>0.98 (0.92–1.04)</td>
<td>0.431</td>
<td>0.98 (0.91–1.04)</td>
<td>0.460</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>1.42 (0.87–2.34)</td>
<td>0.165</td>
<td>2.02 (1.15–3.53)</td>
<td>0.014</td>
</tr>
<tr>
<td>Male gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left ventricular function</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>3.51 (2.20–5.60)</td>
<td>&lt;0.001</td>
<td>3.64 (2.25–5.88)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Poor</td>
<td>6.02 (2.90–12.5)</td>
<td>&lt;0.001</td>
<td>7.67 (3.48–16.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary artery intervention</td>
<td>0.56 (0.35–0.87)</td>
<td>0.014</td>
<td>0.35 (0.20–0.59)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.80 (1.05–3.08)</td>
<td>0.031</td>
<td>1.70 (0.96–3.02)</td>
<td>0.176</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.23 (0.79–1.92)</td>
<td>0.360</td>
<td>1.53 (0.94–2.50)</td>
<td>0.089</td>
</tr>
<tr>
<td>Previous stroke/TIA</td>
<td>1.23 (0.45–3.36)</td>
<td>0.687</td>
<td>0.95 (0.34–2.68)</td>
<td>0.920</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>1.02 (0.25–4.14)</td>
<td>0.982</td>
<td>0.93 (0.22–3.99)</td>
<td>0.923</td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.20 (0.72–1.99)</td>
<td>0.483</td>
<td>1.35 (0.77–2.36)</td>
<td>0.299</td>
</tr>
</tbody>
</table>

*Adjusted for apnea-hypopnea index ≥5, age, body mass index, gender, left ventricular function, coronary artery intervention, diabetes mellitus, hypertension, previous stroke/transient ischemic attack, atrial fibrillation, and current smoking.

Poor left ventricular function with congestive heart failure may be associated with apneas of the central type, without concomitant breathing efforts. We did not distinguish between the different apnea types, but the proportion of patients with poor left ventricular function was low, and none of them had symptoms of congestive heart failure at the time of the sleep study, which indicates a low frequency of central apneas among the present patients.

Possible factors explaining an increased risk of stroke among patients with sleep apnea include apnea-induced hypertension, nocturnal cerebral ischemia, and an increased risk of arteriosclerosis. Hypertension is a well-known risk factor for stroke. Sleep apnea is related to hypertension, and blood pressure may be reduced after treatment of sleep apnea. Cerebral blood flow velocity increases during an obstructive apnea and decreases after apnea termination, concomitant with changes in arterial pressure. Low cerebral blood flow, low arterial pressure, and hypoxemia after apnea termination may predispose to nocturnal cerebral ischemia.

Sleep apnea is associated with sympathetic activation and endothelial dysfunction, including hypercoagulability and inflammatory factors, with improvements after treatment with continuous positive airway pressure. Drager and colleagues observed early signs of arteriosclerosis in obstructive sleep apnea in the form of increased intima-media thickness and diameter changes. Treatment with continuous positive airway pressure for 4 months reduced the thickness of the carotid intima-media layer and reduced C-reactive protein and catecholamine levels. Taken together, these studies support the hypothesis that sleep apnea could promote the development of arteriosclerosis.

All of the patients and their referring physicians were informed about the sleep study result; however, only 9 of the present patients received treatment because of sleep apnea.

The findings are complete, because we obtained complete data from the Swedish National Board of Health and Welfare. Furthermore, the data on stroke, myocardial infarction, and death were verified by hospital records and death certificates. Sweden is somewhat unique in that it is possible to obtain the date and cause of death for every citizen, together with ICD codes for every admission to a hospital, after approval by the ethics committee. This is the reason we were able to retrieve complete follow-up data for every patient.
One explanation was probably unawareness of the effect of sleep apnea on cardiovascular morbidity when the evaluations were performed, as well as the fact that patients were referred because of angina pectoris and not because of sleep apnea. Recent studies indicate that patients with sleep apnea experience improved survival and a reduction in cardiovascular events after the onset of continuous positive airway pressure therapy.3,6,39,40 Patients with coronary artery disease who are evaluated for coronary intervention should therefore be considered for sleep apnea investigations and subsequent treatment.41

In conclusion, sleep apnea is significantly associated with the risk of stroke among patients with coronary artery disease who are being evaluated for coronary intervention. Death and acute myocardial infarction were not associated with sleep apnea among the present patients.

Sources of Funding

The present study was supported by grants from the Swedish Heart Lung Foundation, the Swedish Heart and Lung Association, the Heart Foundation of Northern Sweden, the Medical Faculty at Umeå University, and the Research and Development Unit, Jämtland County Council. The funding source had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; or the preparation, review, or approval of the manuscript.

Disclosures

None.

References

We studied the effect of sleep apnea on incident stroke, acute myocardial infarction, and death among 392 men and women referred for coronary arteriography at the Department of Cardiology, Umeå, Sweden. Sleep apnea, defined as a mean of 5 or more apnea and hypopnea events per hour of sleep, occurred in 54% of the patients at baseline. Stroke occurred in 47 (12%) of the patients during 10 years of follow-up. Sleep apnea was associated with an almost tripled risk of stroke, independent of age, body mass index, left ventricular function, diabetes mellitus, gender, coronary artery intervention, hypertension, atrial fibrillation, a previous stroke or transient ischemic attack, and smoking. There was a dose-dependent relationship, and patients with 5 to 15 apnea and hypopnea events per hour of sleep had a 2.4 times increased risk of stroke, whereas patients with ≥15 apnea and hypopnea events per hour of sleep had a 3.6 times increased risk. Intervention in the form of coronary artery bypass grafting or percutaneous coronary intervention was related to a longer survival but did not affect the incidence of stroke. We conclude that sleep apnea, which is a treatable disorder, is significantly associated with the risk of stroke among patients with coronary artery disease who are being evaluated for coronary intervention.
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