Snoring as a Risk Factor for Sleep-Related Brain Infarction

Heikki Palomäki, MD, Markku Partinen, MD, Seppo Juvela, MD, and Markku Kaste, MD

We studied 177 consecutive male patients aged 16–60 years with brain infarction verified by neuroradiology and analyzed the time of onset of stroke symptoms related to sleep and the role of possible or known risk factors for brain infarction. Brain infarction occurred relatively more often during the first 30 minutes after awakening than at any other time. In multiple stepwise logistic regression analyses, snoring was the only independent risk factor differentiating stroke occurring during sleep and stroke occurring either during sleep or during the first 30 minutes after awakening from stroke occurring at other times of the day. The risk ratios were 2.65 (95% confidence interval 1.32–5.29, p<0.005) and 3.16 (95% confidence interval 1.61–6.22, p<0.001), respectively. Other factors tested were age, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, and body mass index. Arterial hypertension seemed to have an additive effect on the independent risk caused by snoring. (Stroke 1989;20:1311–1315)

There is a relation between the onset of stroke symptoms and the time of day,1–7 which may relate to the underlying pathophysiology of stroke type. Intracerebral hemorrhage, subarachnoid hemorrhage, and embolic infarction often occur during daily activities, whereas atherothrombotic brain infarctions often have their onset during sleep or the early morning hours.1,2

Habitual snoring has been associated with arterial hypertension and angina pectoris.8–11 Snoring has also been suggested as a risk factor for brain infarction.11,12 Heavy snoring is almost always present in obstructive sleep apnea, and obstructive sleep apnea syndrome has many harmful effects on the cardiovascular system.13–16

We studied the association between diurnal variations in ischemic brain infarction and potential risk factors for stroke, including the history of snoring and sleep apnea.

Subjects and Methods

We studied 177 consecutive male patients aged 16–60 years admitted to the Meilahti University Hospital, Helsinki; we excluded from further study 10 patients whose sleeping habits could not be obtained or in whom the time of stroke onset could not be determined. Brain infarction was diagnosed by a neurologist in the 167 patients and was verified in 165 (98.8%) by computed tomography, nuclear magnetic resonance imaging, single-photon emission computed tomography, or radioisotope planar scintigraphy. In many patients, more than one neuroradiologic method was used. When the clinical presentation indicated brainstem infarction, auditory evoked potentials were also recorded. We determined the occurrence of arterial hypertension (previous arterial hypertension with treatment or blood pressure ≥150/100 mm Hg on admission and follow-up), coronary heart disease (previous myocardial infarction and/or clear signs of angina pectoris requiring medication), and diabetes mellitus (previous antidiabetic medication and/or special diet because of impaired glucose tolerance) from hospital charts and by clinical and laboratory examinations during follow-up.

Smoking and drinking habits were established using a standardized questionnaire. The frequency of alcohol consumption was categorized as never or occasionally, 1–3 times/month, 1–3 times/week, and daily or almost daily. In 150 patients (89.8%), it was possible to estimate the quantity of alcohol consumed in grams per week. However, we chose frequency as the variable for alcohol consumption because the data were more complete. Body mass index (BMI) in kilograms per square meter was also calculated.

All patients or their cohabiting relatives were interviewed using a standardized questionnaire for
the patients’ sleeping habits, possible respiratory pauses when sleeping, and snoring frequency (always or almost always, often, occasionally, or never). Snorers were defined as those who snored always, almost always, or often; those who snored occasionally or never were defined as non-snorers. We had previously conducted whole-night sleep recordings with simultaneous microphone monitoring of breathing sounds to validate our questionnaire. All reported habitual snorers snored during the recording; approximately 13% of the reported non-snorers snored.\(^\text{17}\) Accordingly, obtaining snoring history by questionnaire seems to be valid.

We determined the time of onset of stroke symptoms and its relation to sleeping and awakening by using the same standardized questionnaire. If the stroke was progressing, onset of the first symptom was defined as the time of the infarction. Mechanisms that precipitate stroke during sleep may also have some influence soon after awakening. Therefore, a sleep-related stroke was defined two ways. By Definition A, a sleep-related stroke was only one occurring during sleep and noticed immediately on awakening; by Definition B, sleep-related stroke also included those with an onset of symptoms during the first 30 minutes after awakening. Accordingly, we had two groups of sleep-unrelated strokes.

The differences in potential risk factors for brain infarction between patients with sleep-related or sleep-unrelated stroke were tabulated and analyzed using BMDP. Univariate risk ratios (RRs) with 95% confidence intervals (CIs) were computed for 2x2 tables.\(^\text{18}\) If the lower limit of the CI is 1, the respective probability value is 0.05; a lower limit of <1 indicates a nonsignificant difference (\(p>0.05\)). Multiple stepwise logistic regression analysis was carried out with age, arterial hypertension, diabetes mellitus, smoking, alcohol consumption, BMI, and snoring as the independent variables and sleep-related stroke by Definitions A and B as the dependent variables. Moreover, univariate RRs between snoring and sleep-related stroke were also computed for certain subgroups of patients. To obtain individual RRs from the 2x2 tables and the logistic regression analyses, the independent variables were dichotomized as age: >45 versus ≤45 years, arterial hypertension: yes versus no, diabetes mellitus: yes versus no, smoking: >10 versus ≤10 cigarettes/day (including nonsmokers), alcohol consumption: >1–3 versus ≤1–3 times/month (including abstainers), BMI: >27.0 versus ≤27.0 kg/m\(^2\), and snoring: snorers versus non-snorers.

### Results

The mean age of the 167 patients was 49.2 (SD 9.3, median 52, range 16–60) years; 45 patients (26.9%) were aged <45 years. The occurrence of previous brain infarction, arterial hypertension, coronary heart disease, and diabetes mellitus are presented in Table 1. The drinking habits of four patients were not known; of the remaining 163 patients, 38 (23.3%) consumed alcohol never or occasionally, 54 (33.1%) 1–3 times/month, 48 (29.5%) 1–3 times/week, and 23 (14.1%) daily or almost daily. The estimated mean consumption of alcohol in 150 patients was 109.5 (median 40, range 0–1,225) g/week. The smoking habits of six patients were not known; of the remaining 161 patients, 70 (43.5%) had never smoked or had stopped smoking, 20 (12.4%) smoked ≤10 cigarettes/day, and 71 (44.1%) smoked >10 cigarettes/day. The mean BMI of 165 patients was 26.2 (SD 4.1, median 25.7, range 14.4–39.9) kg/m\(^2\). The occurrence of snoring among all 167 patients is also given in Table 1.

Sixteen of the 167 patients (9.6%) were suspected of having embolic infarction of cardiogenic origin because of a recent myocardial infarction and/or a detectable mural thrombus, atrial fibrillation, or endocarditis. The brain infarction was in the carotid artery territory in 126 patients (75.4%) and in the vertebrobasilar territory in the remaining 41 patients (24.6%).

By Definition A, 59 of the 167 patients (35.3%) had sleep-related stroke; by Definition B, 70 patients (41.9%) did so (Figure 1). One patient was napping when he suffered infarction; in the other 69 patients, the onset of sleep-related stroke occurred during nocturnal sleep or during the 30 minutes after awakening. In 11 patients (6.6%), infarction occurred during the first 30 minutes after awakening; if brain infarctions had been evenly distributed, only 2.1% would have occurred during this period. Therefore, there was an overrepresentation of brain infarctions during these 30 minutes.

### Table 1. Occurrence of Snoring and Other Risk Factors in 167 Male Patients With Brain Infarction

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Snoring</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Always, almost always, often</td>
<td>88</td>
<td>52.7</td>
</tr>
<tr>
<td>Occasionally, never</td>
<td>79</td>
<td>47.3</td>
</tr>
<tr>
<td>Previous brain infarction</td>
<td>16</td>
<td>9.6</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>59</td>
<td>35.3</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>47</td>
<td>28.1</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>30</td>
<td>18.0</td>
</tr>
</tbody>
</table>

### FIGURE 1. Bar graphs of sleep-related brain infarction by definition. Definition A, infarction during sleep noticed immediately on awakening; Definition B, infarction during sleep or during first 30 minutes after awakening.
### TABLE 2. Occurrence of Snoring and Other Possible or Known Risk Factors in 167 Male Patients With Sleep-Related or Sleep-Unrelated Brain Infarction

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Timing of stroke</th>
<th>Analysis</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sleep-related</td>
<td>Sleep-unrelated</td>
<td>Univariate RR 95% CI</td>
<td>Multivariate RR 95% CI p</td>
</tr>
<tr>
<td>Snoring</td>
<td>(n=59)</td>
<td>(n=108)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;45 yr</td>
<td>40</td>
<td>48</td>
<td>2.63 1.37–5.07</td>
<td>2.65 1.32–5.29 &lt;0.005</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>23</td>
<td>36</td>
<td>1.70 0.82–3.53</td>
<td>1.36 0.61–3.04 NS</td>
</tr>
<tr>
<td>Body mass index &gt;27.0 kg/m²*</td>
<td>25</td>
<td>39</td>
<td>1.28 0.66–2.47</td>
<td>1.25 0.60–2.59 NS</td>
</tr>
<tr>
<td>Smoking &gt;10 cigarettes/day†</td>
<td>26</td>
<td>45</td>
<td>1.26 0.66–2.42</td>
<td>1.28 0.63–2.60 NS</td>
</tr>
<tr>
<td>Alcohol consumption &gt;1–3 times/month‡</td>
<td>25</td>
<td>60</td>
<td>1.05 0.55–1.98</td>
<td>0.99 0.50–1.98 NS</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>10</td>
<td>20</td>
<td>1.02 0.52–2.00</td>
<td>1.02 0.51–2.03 NS</td>
</tr>
</tbody>
</table>

Sleep-related stroke (Definition A), infarction during sleep noticed immediately on awakening; RR, risk ratio; CI, confidence interval; NS, not significant.

* n=59 for sleep-related, n=106 for sleep-unrelated.
† n=58 for sleep-related, n=103 for sleep-unrelated.
‡ n=57 for sleep-related, n=106 for sleep-unrelated.

Of the 167 patients, 88 (52.7%) had a history of snoring (Table 1). Of those with sleep-related stroke, 40 of 59 (67.8%) according to Definition A and 48 of 70 (68.6%) according to Definition B were snorers.

The respective proportions of snorers among those with sleep-unrelated stroke were 48 of 108 (44.4%) and 40 of 97 (41.2%). The differences in potential risk factors for brain infarction between patients with sleep-related or sleep-unrelated stroke (separately for Definitions A and B), together with RRs, 95% CIs, and p values, are presented in Tables 2 and 3. Snoring was the only independent risk factor explaining the diurnal variation in timing of stroke.

The univariate RRs of snoring for sleep-related stroke by territory are presented in Table 4. There were few brainstem infarctions; thus the CIs of the RRs are large.

Of the 16 cardiogenic strokes, six were sleep-related by Definition A and eight were sleep-related by Definition B.

Of the 151 patients with probable atherothrombotic infarction 53 (35.1%) had sleep-related strokes by Definition A and 62 (41.1%) by Definition B. The RRs for sleep-related atherothrombotic infarction associated with snoring are 2.59 (95% CI 1.31–5.12, p<0.01) and 3.24 (95% CI 1.66–6.33, p<0.001), respectively.

The highest RR of snoring for sleep-related stroke was found among the 59 patients with arterial hypertension. Of the 26 hypertensive patients with sleep-related stroke by Definition B, 20 (76.9%) were snorers; the RR was 6.67 (95% CI 2.18–20.4, p<0.001). Furthermore, all five of these hypertensive patients who suffered sleep-related vertebrobasilar territory infarction also snored, but because of the few hypertensive patients with vertebrobasilar territory infarction (n=18), statistical testing was not applicable.

In addition to snoring, 39 of the 167 patients (23.4%) were reported as having apneic periods during sleep. However, the proportion of such patients was higher among those with sleep-related stroke (19 of 59 [32.2%] and 22 of 70 [31.4%] according to Definitions A and B, respectively) than among patients with sleep-unrelated stroke.

### TABLE 3. Occurrence of Snoring and Other Possible or Known Risk Factors in 167 Male Patients With Sleep-Related or Sleep-Unrelated Brain Infarction

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Timing of stroke</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sleep-related</td>
<td>Sleep-unrelated</td>
</tr>
<tr>
<td>Snoring</td>
<td>(n=70)</td>
<td>(n=97)</td>
</tr>
<tr>
<td>Age &gt;45 yr</td>
<td>48</td>
<td>40</td>
</tr>
<tr>
<td>Smoking &gt;10 cigarettes/day*</td>
<td>55</td>
<td>67</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Alcohol consumption &gt;1–3 times/month†</td>
<td>26</td>
<td>33</td>
</tr>
<tr>
<td>Body mass index &gt;27.0 kg/m²‡</td>
<td>31</td>
<td>40</td>
</tr>
</tbody>
</table>

Sleep-related stroke (Definition B), infarction during sleep or during first 30 minutes after awakening; RR, risk ratio; CI, confidence interval; NS, not significant.

* n=69 for sleep-related, n=92 for sleep-unrelated.
† n=68 for sleep-related, n=95 for sleep-unrelated.
‡ n=70 for sleep-related, n=95 for sleep-unrelated.
those with sleep-unrelated stroke (20 of 108 [18.5%] and 17 of 97 [17.5%], respectively). The RRs of snoring with suspected apnea for sleep-related stroke according to Definitions A and B were 2.09 (95% CI 1.01-4.32, p<0.05) and 2.16 (95% CI 1.04-4.46, p<0.05), respectively. These comparisons were between snorers with suspected apnea and all other patients, many of whom were still snorers.

Discussion

Among 167 male patients with brain infarction, history of snoring was the only significant factor explaining the diurnal variation of stroke onset in our study. Snorers suffered brain infarction during sleep more often than did nonsnorers. It has been suggested that ischemic brain infarctions occur most often during sleep or during the early morning hours.1-3 Tsoumentzis et al4 noticed a peak incidence of ischemic strokes later during the morning, but van der Windt and van Gijn5 did not find any diurnal variation in brain infarction. Cardiac emboli tend to have their peak occurrence during daily activities and/or during physical or emotional stress, whereas sleep-related infarctions are generally supposed to be of atherothrombotic origin.6,7 Myocardial infarctions also tend to occur most frequently in the morning.19,20

In our study, 35.3% of 167 brain infarctions occurred during sleep and were noticed on awakening. This tallies with the proportion of 8 hours’ sleep for a 24-hour day. In addition, 41.9% of the infarctions occurred either during sleep or during the first 30 minutes after awakening, which agrees with earlier findings.1-3 However, the first 30 minutes after awakening seems to be an especially dangerous period because there is an overrepresentation of brain infarctions then. This finding tallies with a similar overrepresentation of myocardial infarctions during the morning hours.3,19,20

Of those with probable cardiogenic and probable atherothrombotic infarction, 62.5% and 64.9%, respectively, occurred during daily activities. This does not support the view that cardiogenic strokes occur more often during the daytime than during sleep.

Snoring has been associated with arterial hypertension and obesity.8-11 Moreover, alcohol consumption can precipitate snoring and induce apneic periods,21 and alcohol intoxication has been suggested to be a risk factor for stroke.22-24 However, in our stepwise multiple logistic regression analyses, snoring was the only factor significantly related to the differences in timing of stroke onset (Tables 2 and 3). Although differences in the consumption of alcohol were not related to the timing of stroke onset, drinking may have had an additive effect on the risk for sleep-related stroke by precipitating snoring and respiratory pauses during sleep.21

Ischemic brain infarction is more common among older people, and occurrence of snoring has been shown to increase up to age 60.25 In our study, patients with sleep-related stroke were usually >45 years old. However, using logistic regression analysis, age did not significantly differentiate sleep-related from sleep-unrelated stroke.

The importance of hypertension as a risk factor for ischemic brain infarction is well documented. Although arterial hypertension was not related to the diurnal variation in stroke onset, the highest RR (6.67) for sleep-related stroke (Definition B) associated with snoring was found among patients with hypertension. In other words, although it did not have any independent significance in the diurnal variation of stroke onset, hypertension seemed to have an additive effect on the independent risk caused by snoring. All hypertensive patients with sleep-related brainstem infarction snored, which supports the idea that snoring and hypertension additively increase the risk of brain infarction.

We found associations between snoring and sleep-related stroke in patients with both carotid artery and vertebrobasilar territory infarctions. The RRs of snoring were highest for vertebrobasilar territory infarction (4.91 or 6.00, depending on the definition of sleep-related stroke). However, the lower limits of the respective 95% CIs were low (Table 4). The most likely reason for this was the relatively few patients with vertebrobasilar territory infarction.

The mechanisms by which snoring may increase the risk of sleep-related stroke are not known. Hypotension during sleep and disturbances of cerebral blood flow (CBF) autoregulation during the early morning hours have been suggested as possible mechanisms provoking brain infarction.1,16
Obstructive sleep apnea as a repetitive trigger for transient vertebrobasilar ischemia has recently been documented; habitual, heavy snoring is the most common symptom of obstructive sleep apnea syndrome, which may have many harmful effects on the cardiovascular system. Marked hemodynamic changes, including cardiac arrhythmias, decreased cardiac index, and hypotension, have been reported to occur during obstructive periods, and each could have a negative effect on the local CBF and energy supply and might therefore be involved in the pathophysiology of sleep-related stroke. Normally, CBF increases during rapid eye movement (REM) sleep. In obstructive sleep apnea syndrome, however, cardiovascular function worsens during REM sleep. Accordingly, the discrepancy between CBF and energy metabolism in patients with obstructive sleep apnea is especially high during REM sleep.

There are some reports of diurnal variation in platelet activation, with peak activity in the morning, which may play some role in the pathogenesis of myocardial ischemia during the early morning hours. Whether the same holds true in brain infarction is not known, but our observation that brain infarction occurred often immediately after awakening supports this possibility. High catecholamine concentrations have been measured in patients with obstructive sleep apnea, which in turn could affect platelet aggregation, possibly together with hypoxemia during the obstructive periods that occur with heavy snoring.

In conclusion, brain infarction seems to occur most commonly during the early morning hours, and snoring seems to be associated with the diurnal variation of brain infarction. However, the mechanism whereby sleep-related brain infarction is more common among snorers than among nonsnorers remains unclear.

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References

Key Words • cerebral infarction • risk factors • snoring
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