Sleep-Disordered Breathing and Acute Ischemic Stroke
Diagnosis, Risk Factors, Treatment, Evolution, and Long-Term Clinical Outcome

Claudio L. Bassetti, MD; Milena Milanova, MD; Matthias Gugger, MD

Background and Purpose—Sleep-disordered breathing (SDB) is frequent in stroke patients. Risk factors, treatment response, short-term and long-term outcome of SDB in stroke patients are poorly known.

Methods—We prospectively studied 152 patients (mean age 56±13 years) with acute ischemic stroke. Cardiovascular risk factors, Epworth sleepiness score (ESS), stroke severity/etiology, and time of stroke onset were assessed. The apnea-hypopnea index (AHI) was determined 3±2 days after stroke onset and 6 months later (subacute phase). Continuous positive airway pressure (CPAP) treatment was started acutely in patients with SDB (AHI ≥15 or AHI ≥10+ESS >10). CPAP compliance, incidence of vascular events, and stroke outcome were assessed 60±16 months later (chronic phase).

Results—Initial AHI was 18±16 (≥10 in 58%, ≥30 in 17% of patients) and decreased in the subacute phase (P<0.001). Age, diabetes, and nighttime stroke onset were independent predictors of AHI (r²=0.34). In patients with AHI ≥30, age, male gender, body mass index, diabetes, hypertension, coronary heart disease, ESS, and macroangiopathic etiology of stroke were significantly higher/more common than in patients with AHI <10. Long-term incidence of vascular events and stroke outcome were similar in both groups. CPAP was started in 51% and continued chronically in 15% of SDB pts. Long-term stroke mortality was associated with initial AHI, age, hypertension, diabetes, and coronary heart disease.

Conclusions—SDB is common particularly in elderly stroke male patients with diabetes, nighttime stroke onset, and macroangiopathy as cause of stroke; it improves after the acute phase, is associated with an increased poststroke mortality, and can be treated with CPAP in a small percentage of patients. (Stroke. 2006;37:967-972.)

Key Words: diabetes mellitus ■ hypertension ■ outcome ■ sleep apnea syndromes ■ stroke

Several studies suggest a strong link between sleep-disordered breathing (SDB) and stroke. Epidemiological studies have shown that loud/frequent (habitual) snoring and other symptoms suggestive of obstructive sleep apnea are independent risk factors for stroke. A cross-sectional study of >6000 subjects in the general population reported a modest but significant association of SDB with stroke. Untreated severe SDB (apnea-hypopnea index [AHI] >30) was shown, even after adjustment for potential confounders, to increase significantly the risk of fatal and nonfatal cardiovascular events. Moderate–severe SDB (AHI ≥20) was found to be associated in 1189 subjects in the general population with an increased 4-year risk of suffering a first-ever stroke, even after adjustment for confounding factors. On the other hand, SDB is very frequent (44% to 72% of patients have an AHI ≥10) in acute ischemic stroke. The observation of a similar frequency of SDB in patients with stroke and transient ischemic attacks (TIAs) suggests that SDB may in some cases precede stroke. In accord with this hypothesis, severity of white matter disease and computed tomography (CT) evidence of cerebrovascular disease were found to be associated with SDB after stroke. The mechanisms linking SDB with stroke are complex and include hemodynamic, neural, metabolic, endothelial, coagulatory, and inflammatory changes secondary to respiratory events and recurrent hypoxemia. However, stroke may also aggravate or even cause SDB “de novo.” This hypothesis is supported by the observation in a few studies of an improvement of SDB after the acute phase of stroke. Only limited data are available on short-term and long-term effect of SDB on stroke outcome and mortality.

The aim of this study was to address the following 5 questions that are unclear at this point: (1) In which stroke patients SDB should be suspected? (2) Is conventional polysomnography necessary for diagnosing? (3) How often and to what extent can SDB improve after the acute phase? (4) What is the short-term and long-term compliance of stroke patients for continuous positive airway pressure (CPAP) treatment? (5) What are the short-term and long-term...
Effects of SDB on stroke outcome, recurrence rate, and mortality?

Patients and Methods

We assessed a consecutive series of 152 patients admitted with a CT- or MRI-proven acute ischemic stroke. Patients admitted >1 week after stroke onset and patients with sopor/coma, cardiac, or respiratory insufficiency were excluded. Patients already on a CPAP treatment were also not included in this series. The study was approved by the local ethical committee, and subjects gave informed consent.

Stroke workup included assessment of cardiovascular risk factors, time of stroke onset, and estimation of stroke severity (National Institutes of Health Stroke Scale [NIHSS] and Scandinavian Stroke Scale). Etiology of stroke was classified according to the Trial of Org 10172 in Acute Treatment (TOAST) study in macroangiopathy, microangiopathy, cardiembolism, other causes, and unknown etiology.

Sleep workup included a standard questionnaire assessing history of habitual snoring, witnessed apneas, and Epworth sleepiness score (ESS) preceding stroke onset, as well as body mass index (BMI). An ESS >10 indicates the presence of excessive daytime sleepiness (EDS). Sleep breathing was assessed in all patients using a portable automatic CPAP device (AutoSet, diagnostic mode, ResMed) that has been validated in our sleep laboratory. The respiratory sleep study was performed in the ward a mean of 3 ± 2 days (range 0 to 9 days) after stroke onset. The AHI was calculated by taking into account the time spent with the automatic CPAP device. The CT₉₀ (ie, the percentage of nighttime below 90% saturation) was obtained automatically.

In the first consecutive 31 patients, sleep breathing was assessed the same night with standard polysomnography and automatic CPAP device. Both recordings were scored independently. Scoring of respiratory events during standard polysomnography was performed according to international criteria.

In the first consecutive 33 SDB patients, respiratory recordings were repeated in the subacute phase of stroke (after a mean interval of 6 months, subacute phase). In patients treated with CPAP, treatment was discontinued ≥4 days before the follow-up recording.

In all patients with AHI >15 or AHI >10 and EDS, CPAP titration was attempted during acute hospitalization using an automatic CPAP device (Autoset, treatment mode, software version 3.0). After hospital discharge, the patients were treated with a fixed pressure conventional CPAP similarly to our regular SDB patients. Regular clinical visits occurred usually 1 to 2 times per year.

Stroke outcome was assessed by the Barthel index (BI) and the modified Rankin Score (mRS) at discharge from hospital. Stroke outcome (mRS), mortality, and occurrence of new vascular events (TIA, stroke, or myocardial infarction) were assessed by a structured telephone interview in 132 (86%) of 152 patients 60 months after stroke (chronic phase, long-term follow-up).

Data are expressed as means ±SD. For nominal variables, we used the χ² test or the Fisher exact test. For ordinal variables and abnormally distributed parametric variables, group comparisons were performed with the Mann–Whitney test. The Blandman and Altman test of concordance was used to analyze the concordance between respiratory events (AHI) as assessed by standard (conventional) polysomnography and by automatic CPAP. Multiple linear regression analyses were used to analyze if any variable found on an univariate analysis to be associated (P<0.05 or at least P<0.2) with AHI (1. analysis) or long-term mortality (2. analysis) were also independent predictors of AHI (1. analysis) or long-term mortality (2. analysis). All analyses were performed with Excel (Microsoft) and the Statistical Package for the Social Sciences (SPSS).

Results

There were 49 women and 104 men with a mean age of 55 ± 13 years and a mean NIHSS of 7 ± 5. Onset of stroke was between 9:01 PM and 6:00 AM in 25% of patients and between 6:01 AM and 9:00 PM in the remaining 75%. At hospital discharge, the mean BI was 87 ± 27. Habitual snoring was reported by 47% patients. The mean AHI was 18 ± 16, the mean apnea index was 8 ± 13, and the mean CT₉₀ was 7 ± 16. The AHI was ≤10 in 42%, ≥10 in 58%, ≥20 in 31%, and ≥30 in 17% of patients. SDB was found in 46% of patients (Figure 1). These and other results are summarized in Table 1.

Significant differences between patients with AHI <10 and AHI ≥30 were found in age, BMI, history of hypertension, smoking, hypercholesterolemia, history of habitual snoring, ESS, and NIHSS. A macroangiopathic etiology of stroke was significantly more common in patients with AHI ≥30, whereas cardiembolic strokes were significantly more common in patients with AHI <10 (P<0.0001; Table 2). In a multivariate analysis, age, diabetes, and nighttime onset of stroke (between 9:01 PM and 6:00 AM) were independently associated with SDB (Table 6).

A good correlation (r²=0.75) was found between the AHI as estimated by polysomnography and automatic CPAP in 1 week after stroke (chronic phase, long-term follow-up).

Table 1. Characteristics of 152 Patients With Ischemic Stroke

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>152 (103 men, 49 women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>55.6 ± 13.2 (18–80)</td>
</tr>
<tr>
<td>BMI</td>
<td>26.3 ± 3.9 (18–38)</td>
</tr>
<tr>
<td>ESS</td>
<td>5.8 ± 4.1 (0–18)</td>
</tr>
<tr>
<td>NIHSS</td>
<td>7.0 ± 4.5 (1–24)</td>
</tr>
<tr>
<td>Scandinavian Stroke Scale</td>
<td>35.9 ± 9.5 (2–52)</td>
</tr>
<tr>
<td>AHI</td>
<td>17.5 ± 15.8 (0–78)</td>
</tr>
<tr>
<td>AHI ≤10 (%)</td>
<td>58%</td>
</tr>
<tr>
<td>AHI ≥20 (%)</td>
<td>31%</td>
</tr>
<tr>
<td>AHI ≥30 (%)</td>
<td>17%</td>
</tr>
<tr>
<td>Apnea index</td>
<td>9.2 ± 13.6 (0–68)</td>
</tr>
<tr>
<td>CT₉₀</td>
<td>7.0 ± 16.4 (0–100)</td>
</tr>
<tr>
<td>TOAST 1/2/3/4/5 (%)</td>
<td>21/15/28/10/26</td>
</tr>
<tr>
<td>BI at hospital discharge</td>
<td>86.5 ± 21.7 (15–100)</td>
</tr>
<tr>
<td>mRS at hospital discharge</td>
<td>1.9 ± 1.3 (0–5)</td>
</tr>
</tbody>
</table>

*Stroke etiology: 1, macroangiopathy; 2, microangiopathy; 3, cardioembolism; 4, others; 5 = unknown.
device (Figure 2). According to Bland and Altman, there was a good concordance among the patients evaluated simultaneously for AHI by both methods with a mean AHI difference of 1.3 (the limits of agreement for the AHI were 15.8 to −18.4).27

In 28 of 33 patients, a significant decrease of AHI (from 32±11 to 16±11; P<0.001) was found in the subacute phase of stroke. Thirteen (40%) of the 33 patients with SDB in the acute stage had an AHI <10 at follow-up.

In 48 (69%) of the initial 70 patients with SDB, CPAP titration within the first week of stroke was successful, and 36 (51%) patients were discharged from the hospital on CPAP. Twenty-six (72%) of these 36 patients were available for long-term follow-up, and 8 (31%) of them were still using CPAP. There were no differences at baseline between patients with and without long-term CPAP use (Table 3).

### TABLE 2. Characteristics of Stroke Patients With Initial AHI <10 and ≥30

<table>
<thead>
<tr>
<th></th>
<th>AHI &lt;10</th>
<th>AHI ≥30</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>64</td>
<td>26</td>
</tr>
<tr>
<td>Age</td>
<td>49.4±14.2</td>
<td>64.4±8.4</td>
</tr>
<tr>
<td>Male gender</td>
<td>53%</td>
<td>89%</td>
</tr>
<tr>
<td>BMI</td>
<td>25.4±4.2</td>
<td>27.9±4.0</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>34%</td>
<td>64%</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>3%</td>
<td>31%</td>
</tr>
<tr>
<td>History of coronary disease</td>
<td>19%</td>
<td>42%</td>
</tr>
<tr>
<td>Smoking (pack/years)</td>
<td>11.2±21.5</td>
<td>13.8±21.0</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>33%</td>
<td>44%</td>
</tr>
<tr>
<td>History of habitual snoring* (before stroke)</td>
<td>24%</td>
<td>44%</td>
</tr>
<tr>
<td>ESS (before stroke)</td>
<td>4.9±4.4</td>
<td>6.8±4.4</td>
</tr>
<tr>
<td>Initial NIHSS</td>
<td>6.9±4.7</td>
<td>8.3±4.8</td>
</tr>
<tr>
<td>Initial Scandinavian Stroke Scale</td>
<td>36.3±9.2</td>
<td>33.8±9.9</td>
</tr>
<tr>
<td>TOAST 1/2/3/4/5** (%)</td>
<td>11/17/44/15/39</td>
<td>39/13/9/0/39</td>
</tr>
</tbody>
</table>

*Snoring every night or almost every night; **stoke etiology: 1, macroangiopathy; 2, microangiopathy; 3, cardioembolism; 4, others; 5, unknown.

A long-term follow-up was possible in 132 patients (84% of patients with AHI<10, 92% of patients AHI 10 to 30, and 88% of patients with AHI ≥30). At final follow-up, the mRS was higher in patients with AHI ≥30 than in patients with AHI <10; this difference was not significant (Table 4).

New, nonfatal vascular events were reported in 7 (14%) of 49 survivors with AHI <10, in 6 (11%) of 56 survivors with AHI 10 to 30, and in 3 (15%) of 18 survivors with AHI ≥30. Eighteen (14%) of these 132 patients died during the observational period (in 10 of them, myocardial infarction or stroke was the cause of death). Of these 18 patients, 5 had an AHI <10 (mortality 5 of 64; 8%), 8 an AHI of 10 to 30 (10 of 61; 16%), and 5 an AHI ≥30 (5 of 23; 22%). Age, history of hypertension, history of diabetes, and AHI differed significantly between survivors and nonsurvivors (Table 5). However, a logistic regression analysis identified only age as
TABLE 6. Independent Predictors of AHI

<table>
<thead>
<tr>
<th></th>
<th>Wald’s Statistic</th>
<th>P Value</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>14.722</td>
<td>0.000</td>
<td>1.069</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6.056</td>
<td>0.014</td>
<td>4.269</td>
</tr>
<tr>
<td>Nighttime onset of stroke*</td>
<td>4.367</td>
<td>0.037</td>
<td>2.641</td>
</tr>
</tbody>
</table>

Logistic regression analysis, dependent variable: AHI. Nagelkerke $r^2=0.295$.

*Onset of stroke between 9:01 AM and 6:00 AM, 25%; between 6:01 AM and 9:00 PM, 75%.

independent predictor of mortality with an odds ratio of 1.102 (95% CI, 1.033 to 1.156).

The overall incidence of fatal and nonfatal vascular events in our population was of 39 per 1000 person years.

Diabetes, Sleep-Related Stroke, and Macroangiopathy Predict SDB in Stroke Patients

In most studies in which the cardiovascular risk profile has been assessed, stroke patients with SDB were found to be older, more often males, and to have a higher frequency of cardiovascular risk factors. This study is the second in which diabetes was found to be an independent predictor of AHI in acute stroke patients. Several publications have suggested that SDB is independently associated with impaired glucose tolerance and insulin resistance, and that these effects can be reversed by CPAP treatment.

We confirm that stroke severity or topography do not predict presence or severity of SDB. This observation supports the hypothesis that SDB often precedes stroke. The high frequency of SDB in TIA patients further supports this hypothesis.

We found an association between sleep-related stroke onset and SDB, as reported previously by Iranzo et al. These results are in line with the recent observation of a peak in sudden death from cardiac causes during sleep in patients with SDB. Several changes occurring with respiratory events including hypoxemia, reduction of cerebral blood flow, decreased cardiac output, cardiac arrhythmias, blood pressure swings, increased sympathetic activity, baroreceptor dysfunction, endothelial dysfunction, inflammatory changes, decreased fibrinolytic activity, and increased platelet aggregability may be responsible for onset or rapid progression of stroke during sleep in patients with SDB.

In the present study, an association between SDB after stroke and macroangiopathy as cause of stroke was observed for the first time. However, based on indirect evidence, 2 previous studies suggested an association between SDB after stroke and macroangiopathy. Harbison et al reported that in 8 patients with lacunar strokes, SDB was significantly worse than in 53 patients with nonlacunar stroke. In a second study, the same group found an association between CT evidence of prestroke white matter disease and severity of SDB after acute stroke. The association between macroangiopathy and SDB after stroke fits to the recent suggestion of an association between SDB and the so-called metabolic syndrome.

Diagnosis of SDB in Acute Stroke Can Be Made With Automatic CPAP

Standard polysomnography is cumbersome, expensive, and often not available in stroke units. This is, to our best knowledge, the first study proving a similar accuracy of a portable, automatic CPAP device to conventional polysomnography in this clinical setting; others have also reported the use of similar systems previously.

SDB Improves After the Acute Phase of Stroke

After the acute phase of stroke, we found an improvement of SDB in most patients, with a normalization of the AHI in 40% of them. Similar observations were made by Parra et al (AHI from 22 to 17 within the first 3 months) and Harbison et al (AHI from 30 to 24 within the first 6 weeks). Our study does not allow to identify the nature and the cause of SDB improvement. Parra et al observed a preferential improvement of central sleep apnea. Reduction in brain damage, improvement in lung/chest function, decrease in sleep time spent in the supine position, and recovery from acute stroke-associated complications (eg, aspiration pneumonia, cardiac arrhythmias) may play a role.
Treatment of SDB Is Possible on a Long-Term in About 15% of Stroke Patients

Fifty-one percent of our 70 patients with SDB could be discharged from the hospital with CPAP. Our early compliance data contrast with the 71% rate published by others.34 This discrepancy may be explained by that fact that in the latter study, only patients admitted to a rehabilitation unit after a mean interval of 60 days were considered for treatment. In a series of 34 patients, a Chinese group reported, similarly to us, relatively low compliance rates of 47% in the acute phase and of 11% at 3 months, respectively.11 These high dropout rates may be related to a spontaneous improvement of SDB after the acute phase of stroke (see above). In fact, Hui et al found that the small minority who tolerated CPAP had symptoms suggestive pre-existing SDB.11

Five years later, 31% of the patients discharged with CPAP (that is, ~15% of all stroke patients with SDB in the acute phase) were still on this treatment. Considering the high incidence of stroke in the general population (2 to 3 per 1000 per year), CPAP treatment may represent a new therapeutic approach for up to 36 000 to 56 000 new patients per year in the United States. Long-term data on CPAP treatment have never been reported before. This study proves that long-term CPAP treatment can be achieved even in this difficult subgroup of patients with SDB. Unfortunately, we could not identify any predictors of long-term CPAP use. Noteworthy is that the severity of EDS preceding stroke (as estimated by the ESS) was not a predictor of CPAP use in our series. Others found that aphasia and severity of motor disability were predictors of poor CPAP compliance.34

Based on our data and the literature, it is impossible to prove a benefit of CPAP treatment in stroke patients with SDB. However, several publications suggest that treatment of SDB in stroke patients should have favorable effects. First, CPAP has been shown to reduce the metabolic effects of SDB and to improve blood pressure and glycemic control.28,35,36 Second, stroke patients with SDB and CPAP treatment report an improvement of depressive symptoms and subjective well-being.34,37 Third, a recent study has proven for the first time ever that untreated severe SDB (AHI >30) significantly increases the risk of fatal and nonfatal cardiovascular events.3 It is obvious that a prospective study with a large number of patients and adequate follow-up is needed to assess: (1) the “true” acceptance, and (2) the benefit that a long-term CPAP treatment may have on stroke patients with SDB (with and without daytime symptoms).

SDB Is Associated With an Increased Long-Term Mortality

We found an association between AHI and long-term mortality (although only age was independent predictor on a logistic regression analysis) but neither with recurrence of vascular events nor with stroke outcome. Few other studies suggested an increased long-term mortality in stroke patients with SDB. Dyken et al reported a 4-year mortality rate of 21% in 24 patients with stroke.5 In a series of 161 patients with both TIA and stroke, Parra et al found AHI to be an independent predictor of mortality with a 2-year death rate of 14%.20 In a series of 120 patients, Turkington et al reported an increased 6-month mortality of 37%.38 The variable mortality rate found in these studies reflect differences in the stroke populations studied, including age, initial severity of stroke, and stroke etiology. The particularly low mortality found in our study can be explained also by the initial exclusion of patients with unstable clinical situation.

The absence of an association between SDB and recurrence of vascular events in our study was unexpected considering the higher frequency of cardiovascular risk factors in stroke patients with SDB. In the absence of comparative data in the literature, we believe that this (negative) finding may be because of a type II error, which could be related to the low mean age of our population. Larger series of patients with higher mean age and longer follow-up periods are needed to clarify this issue.

Studies on the relationship between SDB and long-term outcome of stroke are contradictory. Our study as well as 3 other large studies did not find any effect of AHI on functional outcome.9,20,38 However, positive results have also been reported. Turkington et al found an association between minimum oxygen saturation, but not AHI, and BI.38 In a case-control study, those reporting snoring were found to have a worse outcome at 6 months.18 Good et al observed a poorer rehabilitation outcome at 1 year in stroke patients with >5 oxygen desaturations per hour.19 In a study of 61 patients, Kaneko et al found a worse 4- to 6-week functional impairment and a longer hospitalization and rehabilitation time in patients with SDB.13 The discrepancy between these different studies may be attributable to the interval between stroke onset and sleep study, leading to an overestimation of SDB severity in the early phase. In 2 of the 3 studies suggesting a link between SDB and functional outcome, sleep recordings were performed >1 month after the acute event.13,19 It is conceivable, although at this point still unproven, that only SDB persisting beyond the first days/few weeks after acute stroke may have a negative impact on long-term stroke outcome.

The population assessed in this study reflects a certain bias in the referral of stroke patients to our university department as well as the exclusion of medically instable patients. The severity and frequency of SDB as well as other results of this study may have been influenced by the relatively low mean age, BMI, and NIHSS of our patients as well as by the relatively high percentage of males.

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References


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