Dissociation of Obstructive Sleep Apnea From Hypersomnolence and Obesity in Patients With Stroke

Michael Arzt, MD; Terry Young, PhD; Paul E. Peppard, PhD; Laurel Finn, MS; Clodagh M. Ryan, MD; Mark Bayley, MD; T. Douglas Bradley, MD

Background and Purpose—Obstructive sleep apnea (OSA) is seldom considered in the diagnostic investigation in the poststroke period although it is a stroke risk factor and has adverse prognostic implications after stroke. One reason might be that widely used clinical criteria for detection of OSA in the general community are not applicable in patients with stroke. We hypothesized that patients with stroke report less sleepiness and are less obese than subjects from a community sample with the same severity of OSA.

Methods—We performed polysomnography in 96 consecutive patients with stroke admitted to a stroke rehabilitation unit and in a community sample of 1093 subjects without a history of stroke. We compared the degrees of subjective sleepiness assessed by the Epworth Sleepiness Scale and body mass index between the 2 samples according to OSA categories assessed by the frequency of apneas and hypopneas per hour of sleep (<5, no OSA; 5 to <15 mild OSA; and ≥15, moderate to severe OSA).

Results—Compared with the community sample, patients with stroke with OSA had significantly lower Epworth Sleepiness Scale scores and body mass index for mild OSA (Epworth Sleepiness Scale 9.3±0.3 versus 5.6±0.5, P<0.001 and body mass index 33.1±0.5 versus 28.5±1.1, P<0.048) and for moderate to severe OSA (Epworth Sleepiness Scale 9.7±0.4 versus 7.1±0.9, P=0.043 and body mass index 36.4±0.8 versus 27.2±0.8 kg/m², P<0.025).

Conclusions—For a given severity of OSA, patients with stroke had less daytime sleepiness and lower body mass index than subjects without stroke. These factors may make the diagnosis of OSA elusive in the poststroke period and preclude many such patients from the potential benefits of OSA therapy. (Stroke. 2010;41:e129-e134.)

Key Words: apnea ■ obesity ■ rehabilitation ■ sleep disorders

There is strong evidence from large epidemiological studies that obstructive sleep apnea (OSA) contributes to the development of stroke, partly through the aggravation of known risk factors for stroke such as hypertension and diabetes. After stroke, severe OSA increases risk of stroke recurrence and mortality. OSA is also associated with worse functional impairment as well as longer time for and poorer functional outcome from rehabilitation. OSA is present in 44% to 72% of poststroke patients and probably promotes this functional impairment through intermittent nocturnal hypoxia, reduced cerebral perfusion, and fragmented sleep.

Treatment of OSA by continuous positive airway pressure may therefore have the potential to prevent stroke recurrence, reduce mortality, and improve quality of life. For example, in hypertensive patients, treatment of coexisting OSA lowers both nocturnal and diurnal blood pressure and may reduce the risk of stroke recurrence. In an observational study, mortality risk was greater in patients with stroke with OSA than in those without, whereas mortality risk of patients with OSA treated with continuous positive airway pressure was similar to that in patients without OSA. In addition, it has been reported that treatment of OSA in patients with stroke improves subjective well-being and symptoms of depression.

OSA is seldom considered during the poststroke period despite evidence that managing OSA, when present, may benefit patients with stroke. Two key clinical diagnostic criteria, excessive daytime sleepiness (EDS) and obesity, do not appear to be prevalent in patients poststroke. For example, Bassetti and coworkers studied patients with ischemic strokes; despite having severe OSA, such patients were not obese and generally did not have EDS. Kaneko et al made similar observations. Because subjective sleepiness in association with obesity is frequently the reason for referral for assessment of possible OSA in patients without cardiovascular disease, our results suggest that other factors than EDS and obesity may make the diagnosis of OSA elusive in the poststroke period.
lar disease,17 the absence of these diagnostic criteria may prevent physicians from considering investigation of possible OSA after stroke.

Although previous studies suggested that patients with stroke and OSA frequently did not report EDS and were often nonobese, no studies have compared subjective sleepiness and body habitus between subjects with and without stroke according to OSA status. Therefore, we tested the hypothesis that patients with stroke report less sleepiness and have lower body mass index (BMI) than a sample of subjects from the community with a similar degree of OSA.

Methods

Subjects

Subjects From the Community

In this analysis, participants from the Wisconsin Sleep Cohort study served as a control group (study protocols and written informed consent documentation approved by the University of Wisconsin Health Sciences Institutional Review Board). This cohort consists of a stratified random sample of 1545 state employees in Wisconsin between 30 and 60 years of age. To achieve a wide spectrum of sleep apnea severity within the cohort and to optimize study power, a stratified sampling procedure to include a higher proportion of self-reported snorers was used.16 This sample weighting is accounted for in analyses using SUDAAN software19 where appropriate. Exclusion criteria were: (1) pregnancy; (2) unstable or decompensated cardiopulmonary disease; (3) airway cancers; (4) recent surgery involving the upper airway; (5) central sleep apnea on polysomnography; (6) time in bed of < 4 hours (n = 22); and (7) history of stroke (n = 22). On admission to the stroke rehabilitation unit, demographic characteristics, medical history including risk factors for stroke, BMI, and subjective daytime sleepiness (see subsequently) were assessed. The protocol was approved by the Research Ethics Committee of the Toronto Rehabilitation Institute, and written consent preceded enrollment.

Polysomnography

Attended, in-laboratory polysomnography was performed using the same methods in both centers (Toronto, Ontario, Canada, and Madison, Wis) as previously reported.18 Sleep-wake stages were recorded and scored according to standard methods. Thoracoabdominal movements were recorded by respiratory inductance plethysmography (Inductotrace; Ambulatory Monitoring Inc, Ardsley, NY) and arterial oxyhemoglobin saturation by pulse oximetry. Bedtime and awakening time occurred between 8:30 PM to 12:00 AM and 5:00 AM to 8:00 AM, respectively, at the discretion of each subject.

Apneas were defined as cessation of airflow for at least 10 seconds and hypopneas as a ≥25% decrease in the amplitude in either of the 2 respiratory effort signals, resulting in a decrease of at least 4% in arterial oxyhemoglobin saturation. Apneas were classified as obstructive or central in the presence or absence of thoracoabdominal motion, respectively. Subjects with central sleep apnea defined as an apnea-hypopnea index (number of apneas and hypopneas per hour of sleep [AHI]) ≥ 5 per hour of sleep with > 50% central apneas were excluded from both samples. No OSA was defined as an AHI < 5, mild OSA as an AHI of ≥ 5 to < 15, and moderate to severe OSA as an AHI of ≥ 15.

Daytime Sleepiness, Cognitive Function, and Body Habitus

In both samples, the degree of subjective daytime sleepiness was assessed using the ESS score, a validated questionnaire that asks subjects to rate their likelihood of falling asleep in a variety of common situations.20 Possible scores range from 0 (the least sleepy) to 24 (the sleepiest). In patients with OSA but without stroke, the ESS score correlates positively with the AHI and inversely with sleep onset latency.21,22 ESS was defined as an ESS score of ≥ 11.20 Cognitive function was assessed in the patients with stroke by the Mini-Mental State Examination (MMSE).23 BMI was quantified as weight in kg/height in square meters. Obesity was defined as a BMI ≥ 30 kg/m².

Results

Characteristics of the Subjects

We studied 96 patients with stroke and 1093 subjects from the community. Patients with stroke were significantly older than subjects from the community whether or not they had OSA (P < 0.001; respectively; Table 1). Sex distribution was similar comparing both samples across all AHI categories (P > 0.05 for all comparisons). With increasing severity of OSA, there was a gradual increase in the proportion of men in both samples. Within each OSA category, the AHIs of the patients with stroke were similar to those of the community sample, except that among those with no OSA, the AHIs of patients with stroke was slightly higher (P = 0.013; Table 1). MMSE scores were in the range of mild cognitive impairment. There was no significant difference in MMSE scores between patients with stroke with no and mild OSA (P = 0.412); those with moderate to severe OSA had significantly lower MMSE scores than patients with stroke without OSA (P = 0.016).

Sleep Structure

Sleep structure is shown in Table 2. After adjusting for age, BMI, and sex distribution between the stroke and the com-
munity sample, differences in sleep structure were not statistically significant ($P>0.05$ for all comparisons).

### Subjective Sleepiness

The patients with stroke presented with significantly lower ESS scores than subjects from the community in all OSA categories indicating less subjective sleepiness (no OSA, $P<0.001$; mild OSA, $P<0.001$; moderate to severe OSA; $P=0.043$, probability values are adjusted for age, sex, and BMI; Table 3; Figure 1).

In the community sample, ESS scores increased significantly with increasing severity of OSA (no versus mild OSA, $P=0.018$; no versus moderate to severe OSA $\geq 15$, $P=0.001$; Figure 1). In contrast, in patients with OSA, ESS scores did not increase significantly from no to mild OSA ($P=0.566$). However, ESS did increase significantly from no to moderate to severe OSA ($P=0.050$; Figure 1). When the overall relationship between OSA categories and ESS was compared between the stroke and the community sample (testing for an interaction), there were no statistically significant differences, indicating that the overall relationship between OSA categories and ESS did not differ between the stroke and community samples. Within the patients with stroke, there was no significant relationship between MMSE scores and ESS scores ($r=-0.17$, $P=0.116$).

In the community sample, the presence of subjective EDS (ie, ESS $\geq 11$) was associated with a significantly increased OR of having OSA (ie, AHI $\geq 5$; OR [95% CI] 1.5 [1.1 to 2.0], $P=0.016$). In patients with stroke, the presence of EDS was also associated with increased OR of having OSA (2.4 [0.4 to 13.6], $P=0.305$). However, this association was not significant owing to the high variability of the measurement. Patients with stroke with OSA reported significantly less frequent EDS than subjects from the community sample with OSA (frequency [95% CI]: 10% [4 to 22] versus 38%, [32 to 44], $P<0.001$; Figure 2).

### Body Mass Index

BMI was significantly lower in patients with stroke than in the community sample with no OSA ($P=0.007$) and mild OSA ($P=0.048$), and moderate to severe OSA ($P<0.001$, probability values are adjusted for age, sex, and BMI; Table 3; Figure 2). In the community sample, an increase of OSA severity from no to mild and to moderate was associated with a progressive increase in BMI ($P<0.001$ compared with no OSA for both comparisons, respectively). In contrast, in the stroke sample, no significant association between a rise in OSA severity and an increase in BMI was observed ($P>0.5$ for all comparisons). When the overall relationship between OSA categories and BMI was compared between the stroke and the community sample (testing for an interaction), there were statistically significant differences ($P<0.0001$), indicating that the overall relationship between OSA categories and BMI differed significantly between the stroke and community samples as described previously.

In the community sample, the OR of having OSA associated with obesity (BMI $\geq 30$ kg/m$^2$) was significantly increased at 4.7 (3.4 to 6.2, $P<0.001$), but there was no such association between obesity and OSA in the stroke sample (1.1 [0.4 to 2.9], $P=0.814$). Patients with stroke with OSA (AHI $\geq 5$) were significantly less often obese than subjects from the community sample with OSA (frequency [95% CI] 26% [16 to 40] versus 70% [65 to 76], respectively, $P<0.001$; Figure 3).

### Table 1. Characteristics of the Subjects According to OSA Status

<table>
<thead>
<tr>
<th>AHI &lt;5</th>
<th>5 ≤ AHI &lt; 15</th>
<th>AHI ≥ 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Sample</td>
<td>Stroke</td>
<td>$P$</td>
</tr>
<tr>
<td>Subjects, no.</td>
<td>784</td>
<td>46</td>
</tr>
<tr>
<td>Age, years</td>
<td>49.7±0.3</td>
<td>66.5±2.1</td>
</tr>
<tr>
<td>Male, %</td>
<td>40.7</td>
<td>43.5</td>
</tr>
<tr>
<td>AH1, no. per hour of sleep</td>
<td>1.2±0.1</td>
<td>1.8±0.2</td>
</tr>
<tr>
<td>MMSE*</td>
<td>23.8±3.1</td>
<td>23.1±3.2</td>
</tr>
</tbody>
</table>

Values shown are means±SE or proportions. $P$ values represent comparisons with the community sample after adjusting for differences in age, sex, and BMI.

### Table 2. Sleep Structure of the Subjects According to OSA Status

<table>
<thead>
<tr>
<th>AHI &lt;5</th>
<th>5 ≤ AHI &lt; 15</th>
<th>AHI ≥ 15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Sample</td>
<td>Stroke</td>
<td>$P$</td>
</tr>
<tr>
<td>Sleep onset latency, minutes</td>
<td>13.0±0.6</td>
<td>20.7±3.0</td>
</tr>
<tr>
<td>Time in bed, minutes</td>
<td>456±2</td>
<td>465±8</td>
</tr>
<tr>
<td>Total sleep time, minutes</td>
<td>384±2</td>
<td>354±12</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>84.3±0.4</td>
<td>76.0±2.0</td>
</tr>
<tr>
<td>Slow wave sleep, %</td>
<td>14.5±0.4</td>
<td>12.0±1.4</td>
</tr>
<tr>
<td>Rapid eye movement sleep, %</td>
<td>19.2±0.2</td>
<td>16.9±1.1</td>
</tr>
</tbody>
</table>

Values shown are unadjusted means±SE or proportions. $P$ values represent comparisons with the community sample after adjusting for differences in age, sex, and BMI.
Discussion

The present study provides several novel observations regarding differences in factors associated with OSA in unselected patients with stroke undergoing rehabilitation and a random sample from the community without a history of stroke. First, patients with stroke reported significantly less EDS than individuals from the community sample for any given severity of OSA. Second, patients with stroke with mild and moderate to severe OSA had significantly lower BMI compared with the community sample with the corresponding severity of OSA. Third, the expected association between BMI and the severity of OSA observed in the community sample was absent in patients with stroke. Finally, subjective EDS and obesity were significantly less frequent in patients with stroke with OSA than in the community sample in the same AHI category.

Our study confirms, in a case-controlled design, observations from previous uncontrolled case series of patients with stroke that, even in the presence of severe OSA, such patients generally do not have EDS and are often not obese. One reason for this variability in prevalence is probably that different scoring rules for apneas and hypopneas were used in different studies. In the present study, sleep stages and respiratory events were scored according to identical criteria both in patients with stroke and the community sample. This enabled us to perform valid comparisons of subjective EDS and body habitus between these 2 groups according to the OSA severity. In addition, we were able to analyze mean differences in EDS and BMI after controlling for potential confounding factors (age, sex, and BMI when appropriate). Accordingly, we demonstrated that the 3.7 and 2.7 lower ESS scores and the 4.6 and 9.2 kg/m² lower BMI in patients with stroke compared with the community sample with mild and moderate to severe OSA, respectively, cannot be explained by differences in the severity of OSA, age, sex distribution, or BMI. In addition, control subjects with OSA were 3.8 times more likely to have EDS and 2.7 times more likely to be obese than the patients with stroke after controlling for potential confounding fac-

Table 3. Adjusted Mean Differences in ESS Score and BMI Between the Community Sample and the Patients With Stroke

<table>
<thead>
<tr>
<th>AHI ≤5</th>
<th>Community Sample Versus Stroke</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ESS score*</td>
<td>3.39</td>
</tr>
<tr>
<td></td>
<td>BMI, kg/m²†</td>
<td>2.68</td>
</tr>
<tr>
<td>AHI 5–15</td>
<td>ESS score*</td>
<td>2.98</td>
</tr>
<tr>
<td></td>
<td>BMI, kg/m²†</td>
<td>3.08</td>
</tr>
<tr>
<td>AHI ≥15</td>
<td>ESS score*</td>
<td>2.45</td>
</tr>
<tr>
<td></td>
<td>BMI, kg/m²†</td>
<td>4.23</td>
</tr>
</tbody>
</table>

Values are shown as means [95% CI].
*Adjusted for age, sex, and BMI.
†Adjusted for age and sex.

score of 6.8 and BMI of 27.9 kg/m² indicated that they were generally neither subjectively sleepy nor obese. Similarly, Wessendorf and colleagues observed that in 105 patients with stroke with moderate to severe OSA (AHI ≥15), the mean ESS score was 7.2 and mean BMI was 28.7 kg/m².

The reported prevalence of OSA in patients with stroke ranges from 44% to 72%. One reason for this variability in prevalence is probably that different scoring rules for apneas and hypopneas were used in different studies. In the present study, sleep stages and respiratory events were scored according to identical criteria both in patients with stroke and the community sample. This enabled us to perform valid comparisons of subjective EDS and body habitus between these 2 groups according to the OSA severity. In addition, we were able to analyze mean differences in EDS and BMI after controlling for potential confounding factors (age, sex, and BMI when appropriate). Accordingly, we demonstrated that the 3.7 and 2.7 lower ESS scores and the 4.6 and 9.2 kg/m² lower BMI in patients with stroke compared with the community sample with mild and moderate to severe OSA, respectively, cannot be explained by differences in the severity of OSA, age, sex distribution, or BMI. In addition, control subjects with OSA were 3.8 times more likely to have EDS and 2.7 times more likely to be obese than the patients with stroke after controlling for potential confounding fac-

Figure 1. Patients with stroke (solid line) had significantly lower ESS scores in all AHI categories compared to the community sample (dashed line) with no history of stroke indicating less subjective sleepiness (mean ± SE: 5.2 ± 0.3 versus 8.4 ± 0.2, 5.6 ± 0.5 versus 9.3 ± 0.3, and 7.1 ± 0.9 versus 9.7 ± 0.4, probability values are adjusted for age, sex, and BMI). In the community sample, ESS scores increased significantly with increasing AHI category. In contrast, there was no significant difference in ESS scores between patients with stroke with an AHI <5 and those with an AHI ≥5 to <15. However, patients with stroke with an AHI ≥15 had a significantly higher ESS score compared with those with an AHI <5.

Figure 2. In the AHI ≥5 to <15 and AHI ≥15 categories, patients with stroke (solid line) had significantly lower BMI than the community sample (dashed line, probability values are adjusted for age and sex). In the community sample, AHI category increased significantly in association with increasing BMI (28.8 ± 0.2, 33.1 ± 0.5, and 36.4 ± 0.8 kg/m², respectively). In contrast, there was no significant increase in AHI category with increasing BMI in patients with stroke (27.3 ± 0.8, 28.5 ± 1.1, and 27.2 ± 0.8 kg/m², respectively).

Table 3. Adjusted Mean Differences in ESS Score and BMI Between the Community Sample and the Patients With Stroke
resistance such as the multiple sleep latency test\(^2\) and the significantly, with the AHI as we observed in our community subjects without stroke, the ESS correlates modestly, but and 26 \([16 \text{ to } 40]\) versus 71 \([65 \text{ to } 76]\) \% respectively).\(^{\text{[16 to 44]}}\)

There have been no Oxford Sleep Resistance Test.\(^{\text{[24]}}\) However, there have been no studies in patients with stroke examining the relationship between ESS and objective measures of sleepiness. It is possible that in patients with stroke, ESS is not as sensitive a marker of hypersomnolence as it is in the control subjects. Stroke-related cognitive impairment was probably not the reason for the lack of reported daytime sleepiness in patients with stroke, because cognitive function was only mildly impaired and because there was no significant relationship between MMSE and ESS scores.

Another potential explanation for the lack of subjective sleepiness in patients with stroke compared with the community sample is that owing to their physical disability, they have a relatively low level of physical activity. This does not tax them physically, so they may be less likely to feel sleepy. For example, aside from the 1 to 2 hours of physio- or occupational therapy they receive per day while in the hospital, most of their physical needs (eg, bathing, cooking and serving food, and washing up afterward) is met by hospital personnel. Therefore, they were most likely exposed to lower levels of physical activity than the working community sample, which might affect subjective daytime sleepiness. A third possibility is that drugs commonly used in patients with stroke, but rarely in the community sample such as \(\beta\) receptor antagonists, diuretics, statins, thrombocyte aggregation inhibitors, and antiarrhythmic drugs may have reduced perception of daytime sleepiness through a central nervous system stimulating effect. However, none of these drugs is known to have such central stimulating effects, and none have been reported to reduce perceptions of sleepiness.\(^{\text{[25]}}\)

Therefore, it is unlikely that prescribed drug use could explain lower levels of daytime sleepiness in the patients with stroke than in the community sample. There are a number of other conditions that may contribute to the finding that for a given severity of OSA, patients with stroke had less daytime sleepiness and lower BMI than subjects without stroke (eg, occupation, socioeconomic status, and depression). However, regardless of the underlying mechanisms, these factors may make the diagnosis OSA elusive in the poststroke period and preclude many such patients from the potential benefits of OSA therapy. Interestingly, these findings in patients with stroke correspond to those we previously described in patients with heart failure who also had lower ESS scores at any given AHI than control subjects from the community.\(^{\text{[26]}\)}\)

This may reflect a lack of awareness of sleepiness due to the stroke-related brain injury itself; however, others have also reported a general lack of subjective sleepiness in patients with heart failure.\(^{\text{[26,27]}}\)

These findings raise the intriguing possibility that in patients with cardiac and cerebrovascular diseases, subjective daytime sleepiness is not common in general and, in particular, is not a common feature of OSA. This lack of reported sleepiness may often elude clinical suspicion and thereby prevent detection of OSA in such patients.

Another striking finding of our study was the lack of an association between BMI and the severity of OSA in our patients with stroke that contrasts with the well-established relationship between rising BMI and increasing severity of OSA in patients without stroke.\(^{\text{[28,29]}}\)

Therefore, OSA may often elude clinical suspicion and thereby prevent detection in patients with stroke. In view of the potential benefits on prognosis and functional outcome of patients with stroke when coexisting OSA is treated,\(^{\text{[26-34]}}\)

Brain damage might also predispose to OSA in the poststroke period. However, the observation that the presence of OSA is not related to the type, location, or severity of stroke in the poststroke period does not favor this possibility.\(^{\text{[8,16]}}\)

Based on our findings, we conclude that in patients with stroke, neither the presence of subjective EDS nor obesity is a sensitive or reliable marker to identify those with OSA. Therefore, OSA may often elude clinical suspicion and detection in patients with stroke. In view of the potential benefits on prognosis and functional outcome of patients with stroke when coexisting OSA is treated,\(^{\text{[26-34]}}\)

indications for polysomnography to diagnose OSA in the stroke population may differ from those in the nonstroke population. Further research will be required to determine what factors contribute to the pathogenesis of OSA in patients with stroke and whether treating OSA in patients with stroke, particularly in those without subjective daytime sleepiness, leads to improved outcomes.

**Sources of Funding**

The study was supported by operating grants from the National Institutes of Health (HL62252, AG14124, 1UL1RR025011, 24473R01).
RR03186), the Canadian Institutes of Health Research (MOP 11607), and the Medical Research Service of the Department of Veterans Affairs. M.A. was supported by a Research Fellowship from the German Research Foundation (AR 459/1-1) and by a Heart and Stroke Foundation of Canada CIHR AstraZeneca Canada Research Fellowship.

Disclosures

None.

References


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Stroke. 2010;41:e129-e134; originally published online January 14, 2010;
doi: 10.1161/STROKEAHA.109.566463
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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