Stroke Risk and Sleep Apnea
James B. Lewis, PhD

Obstructive sleep apnea has been associated with cardiovascular diseases in general and with hypertension, coronary artery disease, and heart failure. It is also strongly associated with stroke. Because stroke is the number three killer in the US and a leading cause of long-term disability\(^1\), untreated obstructive sleep apnea can have major public health implications.

**Association between obstructive sleep apnea and stroke**

Based on earlier reports that obstructive sleep apnea might be a risk factor for stroke, a study\(^2\) compared twenty-four recent stroke patients and twenty-seven age and sex-matched controls with no major medical problems. Study subjects were assessed for obstructive sleep apnea using overnight polysomnography in a sleep center, and information was collected concerning known risk factors for both stroke and sleep apnea. Respiratory events recorded by polysomnography were classified as apneas or as hypopneas if airflow was respectively absent or reduced by more than 50 percent. Apneas were classified as obstructive if respiratory effort continued, and central if respiratory effort was absent. An individual with ten or more obstructive events per hour was diagnosed with obstructive sleep apnea. A statistical analysis was performed to assess the association between stroke and the presence of obstructive sleep apnea and other known risk factors.

Central sleep apnea was not found among either stroke or control subjects. Obstructive sleep apnea was found in 77 percent of male stroke subjects and 23 percent of male control subjects, and in 64 percent of female stroke subjects and 14 percent of female control subjects. The mean (average) number of events per hour for men with stroke was 21.5, while for male control subjects it was 4.8. For women, the mean number of events per hour was 31.6 for stroke patients and 2.9 for control subjects. The median (middle value of the range) number of events per hour was 16.8 for male stroke patients, 1.4 for male controls, 38.4 for female stroke patients, and 0 for female controls. During a four-year follow-up period, only stroke patients with obstructive sleep apnea died. The mean number of events per hour for the five patients who died was 41.3, while for the stroke patients who did not die the mean was 22.1 events per hour. The authors conclude that patients with stroke have a high incidence of sleep apnea compared to age- and sex-matched normal controls.

In another study\(^3\), fifty-nine patients with either transient ischemic attack (TIA) or stroke were assessed for sleep apnea and compared with nineteen age and gender-matched controls. From among patients admitted to a hospital during a sixteen-week period for either acute TIA or stroke, fifty-nine were eligible for the study and were evaluated for obstructive sleep apnea by questionnaire concerning habitual snoring and daytime sleepiness. Of these, thirty-six patients were further evaluated by overnight polysomnography, as were the nineteen normal controls. The twenty-three patients not evaluated by polysomnography did not differ significantly from the thirty-six who were evaluated in terms of age, gender, body mass index, cerebrovascular risk factors, stroke severity, habitual snoring, or daytime sleepiness. Sleep apnea was found in 69

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percent of patients versus 15 percent of normal controls. Controls and patients were similar in age, body mass index, and gender, but differed in the prevalence of habitual snoring and in the average number of respiratory events per hour. The thirteen patients with TIA and the twenty-three patients with stroke were similar in age, gender, body mass index, most cerebrovascular risk factors, sleep history, and polysomnography results, except that there was a trend toward more events per hour in those with stroke. Thus, clinically significant sleep apnea is present in many patients with stroke and acute TIA, and does not differ significantly in prevalence between stroke and TIA patients. Based on these results, the authors conclude that sleep apnea precedes the stroke and is a probable risk factor for stroke.

Sleep apnea and the risk of developing stroke

To determine whether the association between obstructive sleep apnea and stroke arises because sleep apnea increases the risk of stroke, a large group of state employees in Wisconsin was assessed by polysomnography and other tests at the beginning of the study and then again after four, eight, and twelve years. Of the 1,475 participants at baseline, 76 percent did not have sleep apnea, 17 percent had mild, and 7 percent had moderate to severe sleep apnea. The latter group was predominantly male and had a significantly higher body mass index. Those subjects in the moderate to severe sleep apnea group were about four times more likely to have had a stroke than those without sleep apnea. Similarly, those subjects in the moderate to severe sleep apnea group were about four times more likely to experience a stroke during the following four years than those without sleep apnea. In both cases, the occurrence of stroke in the group with mild sleep apnea did not differ significantly from the group without sleep apnea. This study provides evidence of a significant link between moderate to severe sleep apnea, and both the prevalence of stroke in the general population and an increased probability of suffering a stroke within the next four years, proving that in many cases sleep apnea precedes stroke. These links were independent of obesity. The authors conclude that sleep apnea may contribute to the development of stroke.

To determine if obstructive sleep apnea patients have an increased risk of stroke or death from any cause that is independent of other cerebrovascular risk factors, a cohort of sleep center patients fifty-years-old or older and without a history of stroke were followed for four years for incidence of stroke, transient ischemic attacks, or death. Sleep apnea was defined as five or more events per hour determined by polysomnography; the control group had less than five events per hour. Event-free survival of patients with sleep apnea was compared to that of those without. Among the study participants, 697 of 1,022 had sleep apnea, with a mean of thirty-five events per hour. The 325 controls had a mean of 2.0 events per hour. The sleep apnea patients had higher prevalence of diabetes and hypertension and were more obese than the controls. Among the 842 subjects for whom follow-up data were available, there were 3.48 events per 100 person-years in the sleep apnea group and 1.60 events per 100 person-years in the control group. The association of sleep apnea with TIA, stroke, or death was still statistically significant after adjustment for age, sex, body mass index, diabetes, hypertension, and several other risk factors. Further, the risk of stroke or death increased with the severity of the sleep apnea.

With increasing evidence of a link between sleep apnea and stroke in middle-aged populations, another study focused on stroke risk in a general population of elderly individuals since, in

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general, stroke risk is highest in the elderly. Initially ischemic event-free and noninstitutionalized, 394 seventy to one-hundred-year-old subjects were assessed by overnight polysomnography and then followed for up to six years (mean 4.5 years). During this period, twenty ischemic strokes occurred; moreover, these were about 2.5 times more prevalent in those with severe sleep apnea at baseline than in those without or with mild or moderate sleep apnea.

A recent study was large enough to determine in the general population (rather than in patients referred for sleep studies) the effect on the risk of stroke of obstructive sleep apnea, even mild obstructive sleep apnea. Baseline overnight unattended polysomnography was performed between 1995 and 1998 on a total of 5,422 participants (2,462 men and 2,960 women) without a history of stroke and who were untreated for sleep apnea. The participants were followed for a median of 8.7 years for the occurrence of an ischemic stroke. Over this period, 193 ischemic strokes occurred (4.4 per 1,000 person-years in men and 4.5 in women). A baseline classification of moderate to severe obstructive sleep apnea was about 30 percent more common in men and women who subsequently had an ischemic stroke than in those who remained stroke-free. After statistical adjustment for age and other risk factors, men in the highest quartile of sleep apnea (more than nineteen events per hour) had 2.86 times the risk of stroke of men in the lowest quartile (less than 4.05 events per hour). In men, the stroke risk also increases across the lower to middle quartiles, indicating that even relatively mild levels of sleep apnea can put men at increased risk for ischemic stroke. In women, the risk of stroke was not significantly associated with the sleep apnea quartile, but increased risk was observed at more than twenty-five events per hour. The authors conclude that the strong association between obstructive sleep apnea and stroke risk among community-dwelling men indicates that sleep apnea is an appropriate target for future stroke prevention trials. In an NIH News release dated April 8, 2010, National Heart, Lung, and Blood Institute Acting Director Susan B. Shurin, M.D. said “This is the largest study to date to link sleep apnea with an increased risk of stroke. The time is right for researchers to study whether treating sleep apnea could prevent or delay stroke in some individuals.”

Sleep apnea and the clinical outcome of a stroke

Given the prevalence of sleep apnea in stroke patients, does the presence of this potentially treatable condition correlate with greater disability or longer recovery times? Sixty-one consecutive stroke patients not previously diagnosed with sleep apnea or dementia and admitted to a stroke rehabilitation unit were assessed to determine their level of functional and mental disability. Overnight polysomnography was done to determine sleep apnea status, with less than ten respiratory events per hour classified as non-sleep apnea and ten or more as denoting the presence of sleep apnea. The primary outcome to be measured was the length of hospitalization. Of sixty patients admitted to the study, forty-eight had ischemic stroke and twelve had hemorrhagic stroke. Sleep apnea was diagnosed in 72 percent of the patients (obstructive sleep apnea in 60 percent and central sleep apnea in 12 percent). The severity of the stroke did not differ significantly between those patients with and without sleep apnea. There was a tendency for patients with sleep apnea to have fewer of the other stroke risk factors, although only in the

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case of heart failure was this difference statistically significant. This observation provides circumstantial evidence that sleep apnea by itself is a risk factor for stroke.

Stroke patients with sleep apnea spent 40 percent more days in the stroke rehabilitation unit and 30 percent more total days in the hospital than did patients without sleep apnea. Length of hospitalization increased with the number of obstructive sleep apnea events per hour but was not correlated with central sleep apnea events. Patients with sleep apnea showed greater functional impairment than did patients without sleep apnea, both at admission and at discharge. There were also significant correlations between functional impairment and the average number of obstructive sleep apnea events per hour. There was no correlation with central sleep apnea events. These results indicate that not only is sleep apnea very prevalent among patients admitted to a stroke rehabilitation unit, but also that obstructive sleep apnea contributed to functional impairment and the length of rehabilitation. Thus sleep apnea may be increasing the social and financial burden imposed by stroke disability and rehabilitation.

Another study of patients admitted for in-hospital stroke rehabilitation examined the correlation between sleep apnea (both obstructive and central) and survival over a ten-year period. Patients were initially evaluated three weeks after the onset of stroke. Of 151 consecutive patients, 132 who consented to and successfully completed overnight polysomnography in the hospital were included in the study. Sleep apnea was defined as fifteen or more events per hour; those patients with less than fifteen events served as controls. Of the enrolled patients, 11.2 percent had experienced a hemorrhagic stroke and 37.1 percent had experienced two or more strokes. Further, 17.4 percent of the patients had obstructive sleep apnea and 21.2 percent had central sleep apnea. (Two patients with both obstructive and central sleep apnea were excluded from further analysis.) At baseline the mean age of the control, obstructive, and central sleep apnea groups varied from seventy-seven to seventy-nine. At follow-up 87.9 percent of the patients had died, including all of the obstructive sleep apnea patients, 96.4 percent with central apnea and 81 percent of the controls. After statistically correcting for age and other factors, the adjusted risk of dying was not significantly different between the central sleep apnea and control groups, but was 1.76 times as great in the obstructive sleep apnea group compared to the controls. The authors conclude that stroke patients with obstructive sleep apnea face an increased risk of early death.

**Conclusion:** Stroke patients have a very high prevalence of obstructive sleep apnea compared to age- and sex-matched controls. Sleep apnea was found among 69 percent of a population of hospital patients admitted for either transient ischemic attack or stroke, compared to 15 percent of age and gender-matched controls. In studies of the general population, individuals with sleep apnea were more likely to have experienced stroke, and were also more likely to have a stroke within the following years, than were those without sleep apnea—this was two to three times more likely in the case of those with the most severe sleep apnea. Stroke patients with obstructive sleep apnea face longer hospitalization times, greater functional impairment, and an increased risk of early death compared to stroke patients without sleep apnea.