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COMMENTARY

Wake-up Call to Identify Obstructive Sleep Apnea in Patients with Ischemic Strokes

Commentary on Aaronson et al. Effects of continuous positive airway pressure on cognitive and functional outcome of stroke patients with obstructive sleep apnea: a randomized controlled trial. *J Clin Sleep Med* 2016;12(4):533–541, and Šiarnik et al. Association of sleep disordered breathing with wake-up acute ischemic stroke: a full polysomnographic study. *J Clin Sleep Med* 2016;12(4):549–554.

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In this issue of the *Journal of Clinical Sleep Medicine,* two articles examine the important bidirectional relationships between acute ischemic stroke, stroke outcome, continuous positive airway pressure (CPAP) therapy, and wake-up strokes. More than 50% to 70% of patients with acute ischemic stroke or transient ischemic attack (TIA) have obstructive sleep apnea (OSA).[1] A 2012 meta-analysis of 29 case-control studies found 72% of 2,343 patients with stroke or TIA had an apnea-hypopnea index (AHI) ≥ 5 per hour in 72%, AHI > 20 in 38%, AHI > 30 in 29%, and AHI > 40 in 14%.[1] As many as 70% to 80% of patients with sleep apnea are neither diagnosed nor treated.[1] One of the major barriers to diagnosing and treating OSA is lack of provider awareness. A recent questionnaire-based survey found only 13% of health care professionals and medical students identified OSA as an independent risk factor for stroke.[2]

Several large, well-designed, general population-based prospective studies have established that OSA is an independent risk factor for incident stroke.[3–7] An observational study found an AHI ≥ 5/h in 1,022 community-dwelling adults independently increased the risk for stroke or death by 1.97 times even after adjusting for multiple confounders.[5] An AHI ≥ 30/h was associated with a 2.5-fold higher risk for stroke within ≤ 6 years in 394 community-dwelling elders.[8] The Sleep Heart Health Study followed 5,422 participants for a median of 8.7 years who were without a history of stroke at baseline examination and untreated for sleep apnea.[4] Men with an obstructive AHI ≥ 20 had a 2.9-fold higher risk for incident stroke compared to those with AHI < 5/h. In women, increased risk for stroke was observed in those with an obstructive AHI > 25.

Stroke patients who have OSA have worse cognitive functioning, worse functional capacity, reduced motility, greater impairment in activities of daily living (ADL), and longer stays in inpatient rehabilitation than those without OSA.[9–12] A recent case-control study compared cognitive and functional status upon admission in 80 stroke patients with OSA and 67 without OSA.[12] The OSA patients performed worse on tests of attention, executive functioning, visual perception, psychomotor ability, and intelligence than those without OSA. A prospective study with 10-year follow-up found the long-term risk of death was 1.8 times higher in stroke patients admitted to stroke rehabilitation with OSA (AHI ≥ 15) than those without OSA and independent of multiple cofounders.[3]

In 2014, the American Heart Association/American Stroke Association (AHA/ASA) published guidelines which for the first time recommended a sleep study be considered for patients with ischemic stroke or TIA on the basis of the very high prevalence of sleep apnea in this population and the strength of the evidence that the treatment of sleep apnea improves outcomes in the general population.[13] They further recommended considering treatment with CPAP for patients with acute ischemic stroke or TIA and OSA given emerging evidence in support of improved outcomes and reducing the risk for recurrent stroke.[13] However, this has not trickled down to those who need to know this. OSA remains the largely neglected stepchild of independent risk factors for stroke. Too often, diagnosis, let alone treatment, of OSA in acute stroke is not even thought of, attributing the stroke to other comorbidities.

Recent studies suggest that OSA may be the only independent variable predisposing to so-called wake-up strokes (WUS).[14–16] Most ischemic strokes (myocardial infarcts and sudden cardiac death) occur awake between 6 am and noon, and the lowest risk between midnight and 6 am.[17] A 2006 study found OSA (AHI ≥ 15) was an independent predictor of nocturnal stroke in 152 patients with acute ischemic stroke.[18] Severe OSA has been shown to predispose to sudden cardiac death during sleep. The risk for sudden cardiac death during sleep was 2.6 times greater in patients with AHI ≥ 40 compared to those with AHI 5–39/h, and far greater than would be predicted in the general population or even by chance.[19] Recent studies suggest that OSA may be the only independent variable predisposing to so-called wake-up strokes (WUS).[14–16]

In this issue, Siarnik et al. compared clinical, polysomnographic and metabolic findings in 88 subjects with acute ischemic stroke: 16 (18%) were WUS, 82% non-WUS. Using binary logistic regression, they found patients with WUS had

significantly higher AHI (25 vs. 8/h), desaturation index (27 vs. 9/h), and arousal index (23 vs 14/h) than those with non-WUS.[15] They further found significantly higher frequency of moderate-to-severe OSA among the WUS population (69% vs. 29%). Other diagnostic tests which characterized the WUS group were significantly higher diastolic blood pressure and serum triglyceride levels. The blood pressure pattern of diastolic hypertension (and loss of nocturnal dipping) is characteristic of early OSA. Elevated triglyceride levels in patients with WUS may be related to metabolic syndrome, also common in patients with OSA.

Other recent studies provide support for OSA, especially when severe, predisposing to WUS. The SLEEP TIGHT (Sleep Apnea in Transient Ischemic Attack and Stroke) study recently reported WUS in 30.3% of 164 patients with acute ischemic strokes.[14] Men with WUS had significantly higher rates of severe OSA (AHI > 30, 45% vs. 18%). Another study found WUS in 26 (37%) of 71 patients with acute ischemic strokes and mean AHI were significantly higher in subjects with WUS compared those with non-WUS (mean 23 ± 19/h vs. 13 ± 12).[16] The only independent variable associated with WUS was an AHI ≥ 30/h (OR 6.1).

Far more evidence is needed to show treating OSA in patients with ischemic stroke reduces the risk of recurrent stroke, improves stroke outcome, and reduces mortality in patients with acute ischemic stroke and OSA. A prospective observational study followed 967 women and found those with untreated OSA (AHI ≥ 10) had a 6.4-fold higher risk for incident stroke over the median 6.8 years of follow-up.[20] The hazard ratio was 0.9 for the CPAP-treated OSA compared to controls without OSA.

Only a few randomized control trials (RCT) have studied the effect of continuous positive airway pressure (CPAP) on adverse events in stroke and TIA patients with OSA. One study found CPAP only improved symptoms of depression in 29 patients with stroke patients admitted to a stroke rehab unit compared to 30 controls, but poor compliance was present in many.[21] Another study of 152 ischemic stroke patients started CPAP in 70 within 3 ± 2 days after stroke onset.[18] CPAP did not affect outcome in patients with stroke and OSA, but only 8 (11%) of 70 had adequate CPAP compliance, limiting their ability to assess the effect of CPAP. Another RCT found no benefit from CPAP use in 33 patients with AHI ≥ 30 but CPAP use was poor (only 1.4 h/night).[22] Prescribing (not necessarily compliant use) of CPAP did not reduce subsequent incidence of cardiovascular events including stroke in a RCT of 725 consecutive patients who had an AHI ≥ 20/h TST and an Epworth Sleepiness Scale score of ≤ 10 (non-sleepy) followed for a median of 4 years.[23]

However, one longitudinal RCT still ongoing has reported favorable outcome data on the use of CPAP in 140 patients with acute ischemic infarcts and moderate-to-severe OSA (AHI ≥ 20/h): 71 were treated with CPAP, 69 served as controls.[24,25] The percentage of patients with neurological improvement at 1 month after stroke was significantly higher (Rankin scale 91% vs. 56%) in patients who started CPAP within 3–6 days following acute ischemic strokes,[24] and patients with first-ever ischemic stroke an AHI ≥ 20/h treated with CPAP had better long-term survival (100% vs. 90%, p = 0.015).[25]

In this issue, Aaronson et al. performed a well-designed RCT on the effectiveness of CPAP in stroke patients during inpatient rehabilitation using a comprehensive battery of neuropsychological and neurological tests and ADL scales.[26] Beginning with 449 eligible stroke patients, 206 agreed to level III studies, which identified 80 as having OSA (AHI ≥ 15). Still others were excluded such that the final study groups were only 20 patients with mild-to-moderate OSA (AHI ≥ 15 but < 60/h) treated with CPAP for 4 weeks, and 16 other patients with OSA who were not initially offered CPAP.

Although the number of patients studied was small, the strength of this RCT was how they performed comprehensive testing with nine neuropsychological tests assessing cognitive function, two evaluating neurological status and functional independence, and yet others validated measures of activity of daily life (ADL), functional independence, sleepiness, fatigue, anxiety and depression, and subjective sleep quality. Investigators allowed patients initially in the control group to try CPAP after 4 weeks; 16 of the control group used CPAP beginning at 4 weeks. They compared results of CPAP on outcome in the OSA patients to 44 stroke patients without OSA (AHI < 15/h). After 4 weeks of CPAP, the CPAP group showed moderate to large improvements in attention and executive functioning compared to OSA controls not initially treated with CPAP. A recent meta-analysis showed that patients with OSA exhibit medium to very large impairments in executive function.[27] The selective improvement in executive function in the stroke patients with OSA shown in this study supports benefit of compliant use of CPAP in stroke patients with OSA. The weaknesses of their study like so many others evaluating CPAP use in stroke are small sample size and only fair CPAP compliance. Average CPAP compliance was 2.5 h/night. Of the 36 patients who used CPAP, only 7 (19%) used it > 4 h/day ≥ 5 days/week.

Treating OSA in acute ischemic stroke remains a challenge.[11] Stroke patients with OSA as a group do not report lower levels of sleep quality or higher levels of sleepiness, fatigue, and depressed mood than stroke patients without OSA.[12] They have poor tolerance of CPAP interfaces, and difficulty putting masks back on during the night. Recruitment of patients for CPAP trials is difficult,[28] further complicated by ethical issues.[29] Large RCT of CPAP use in stroke are underway which hopefully will provide sufficient evidence to support effectiveness of CPAP. Efforts need to be made by sleep specialists and organizations to raise awareness among clinicians and the general public of the role of OSA in stroke or TIA, stroke outcome, and recurrent stroke. Different treatment strategies for OSA in CPAP-intolerant stroke patients need to be studied including patient education and behavioral therapies,[30] positional therapy,[31–33] nasotracheal suction mechanical ventilation,[34] oral appliances, high-flow humidity, oxygen, hypoglossal nerve stimulation, and weight loss.[11]

CITATION

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DISCLOSURE STATEMENT

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