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Cerebrovascular Disorders (D Jamieson, Section Editor)

Sleep Disorders and Stroke: Does Treatment of Obstructive Sleep Apnea Decrease Risk of Ischemic Stroke?

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Abstract

Purpose of review This review aims to support obstructive sleep apnea (OSA) as a risk factor for ischemic stroke, review treatment strategies for OSA, provide a comprehensive review of clinical data on OSA treatment and ischemic stroke risk, and to critically assess if treatment of OSA decreases the risk of ischemic stroke and if treatment improves outcomes and subsequent ischemic stroke risk in post-stroke patients.

Recent findings Several observational studies, randomized controlled trials (RCTs), and meta-analyses have examined the risk of ischemic stroke and cardiovascular events in patients with OSA and have also examined continuous positive airway pressure (CPAP) treatment in these patients. Observational studies have shown an increased risk of ischemic stroke in patients with untreated OSA when compared with patients treated with CPAP; however, results are not statistically significant. RCTs and meta-analyses have shown no significant ischemic stroke risk reduction in CPAP treated patients with OSA. Several studies have shown improved outcomes in post-stroke patients with OSA treated with CPAP; however, few data is available for subsequent ischemic stroke risk reduction. Further research is needed for surgical treatment of OSA and assessment of ischemic stroke risk.

Summary OSA is associated with increased risk of ischemic stroke, and OSA should be treated with the appropriate therapy. While the current data is promising, more studies are necessary to state whether treatment of OSA reduces ischemic stroke risk and subsequent ischemic stroke risk. A practical approach to the sleep disorder evaluation and treatment of patients with cerebrovascular disease is outlined.

Introduction

Studies have shown an association between obstructive sleep apnea (OSA), a type of treatable sleep-disordered breathing (SDB), and ischemic stroke [1, 2]. OSA is characterized by multiple apneic and hypopneic events during sleep due to recurrent upper airway obstruction. The estimated prevalence of OSA in the general population is approximately 26% [3]. OSA increases the risk of hypertension, obesity, atrial fibrillation, coronary artery disease, heart failure, and ischemic stroke [4–8]. Furthermore, untreated OSA has been significantly associated with an increase in cardiovascular and cerebrovascular mortality [9, 10]. It is postulated that recurrent hypoxic events in OSA lead to increased inflammation, sympathetic activation, and the formation of free radicals, which induce endothelial dysfunction, platelet aggregation, and changes in cerebral blood flow [11–13]. Several observational and cross-sectional studies have shown that OSA increases risk of ischemic stroke [1, 4, 5, 8]. Unfortunately, these studies were not adjusted and could be interpreted as OSA indirectly increasing ischemic stroke risk given the common vascular risk factors shared. A landmark study by Yaggi et al. demonstrated that OSA is an independent risk factor for stroke after adjusting for shared vascular risk factors [14]. Other sleep disorders such as snoring, central sleep apnea (CSA), obesity hypoventilation syndrome (OHS), parasomnias, sleep-related movement disorders (SRMD), and excessive daytime sleepiness (EDS) have been shown to have some association with increased ischemic stroke risk [15••, 16–20]. Additionally, there is an increased prevalence of OSA and other sleep disorders after incident ischemic stroke and/or transient ischemic attacks (TIAs), since insults to the central nervous system result in changes in breathing patterns or possibly unmask previously undiagnosed pre-stroke OSA or other sleep disorders in the post-stroke period [15••, 16–21]. The prevalence of OSA in patients with history of stroke was determined to be 61.9% [22•]. Several researchers have demonstrated an association between OSA and an increased incidence of wake-up ischemic strokes [23–26]. The diagnosis of OSA in post-stroke patients is associated with an increased risk of recurrent ischemic stroke and worse outcomes [27, 28]. Several case reports have suggested that OSA is associated with hemorrhagic events such as intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral micro-hemorrhages; however, higher quality studies are needed to establish a correlation [29, 30].

This review aims to establish OSA as a risk factor for ischemic stroke, review treatment strategies for OSA, provide the most recent evidence to critically assess if treatment of OSA reduces risk of ischemic stroke, and assess if treatment of OSA in the post-stroke period improves outcomes. Additionally, a practical approach to the sleep disorder evaluation and management and treatment of patients with OSA and stroke are outlined.

Diagnostic evaluation

Screening for OSA can be accomplished with ease in the office setting. The signs and symptoms of OSA are excessive daytime sleepiness, habitual snoring, nocturnal choking/gasping, and morning headaches. Patients with OSA usually have a wide neck (> 17 inches in men and > 16 inches in women) and/or physical features that suggest a narrowed upper airway, such as, obesity, enlarged tonsils and uvula, nasal obstruction, micrognathia, and/or retrognathia. Screening questionnaires are administered to patients where the signs and symptoms and physical exam for OSA are uncertain. The most common screening questionnaires used are the Berlin questionnaire (BQ), STOP-BANG questionnaire (SBQ), and Epworth sleepiness scale (ESS). Of these screening tools, STOP-BANG seems to have the highest sensitivity but poor specificity for OSA, whereas the ESS seems to have the highest specificity for diagnosis of OSA [31]. The polysomnography (PSG) test is widely considered the gold standard for the diagnosis of OSA. PSG measures apneas and hypopneas during sleep.

The apnea-hypopnea index (AHI) measures the total number of apnea and hypopnea events over the total sleep time hours. The AHI determines the severity of OSA, where an AHI less than 5 per hour is associated with no OSA, 5–14 per hour is mild OSA, 15 to 29 per hour is moderate OSA, and greater than or equal to 30 per hour is considered severe OSA [32••]. Equipment for OSA testing at home can be obtained through a variety of national purveyors or a local sleep center. Home testing includes indicators of OSA such as air flow and oxygenation, and also can detect shifts in body position. The limitation of home testing is a lack of sleep stage data using EEG, limiting insight into sleep disorders other than OSA.

Treatment

The first line treatments for OSA are weight loss, lifestyle changes, and use of continuous positive airway pressure (CPAP) [33, 34]. In a meta-analysis of seven randomized controlled trials (RCTs) assessing the effectiveness of lifestyle interventions in OSA revealed that dieting, physical activity, and dieting plus physical activity, correlated with a significant pooled mean reduction in AHI of 6.04/h [35]. A large body of evidence suggests that CPAP is an effective first line of treatment for OSA and has a high grade of recommendations with a moderate to strong level of evidence in several clinical practice guidelines [33, 34, 36, 37].

OSA increases risk of ischemic stroke and, if untreated, increases risk of mortality. Accordingly, treatment should reduce risk of ischemic stroke. CPAP, the first line treatment for OSA, is the primary treatment modality studied in clinical trials. In a small long-term follow-up study of 168 patients comparing the cardiovascular outcomes, including stroke, in patients with untreated and treated OSA with CPAP therapy revealed higher deaths from cardiovascular causes in the untreated group than the treated group at average follow-up of 7.5 years, supporting a protective effect of CPAP in OSA [38]. In an observational study by Marin et al., the 10-year incidence of fatal vascular events, including ischemic stroke and myocardial infarction, in men with untreated OSA was 1.06 per 100-person years when compared with men with treated severe OSA at 0.35 per 100-person years, suggesting that CPAP treatment reduces ischemic stroke and cardiovascular risk in men [5]. Campos-Rodriguez performed two prospective cohort studies to assess the risk of vascular events, including ischemic stroke and cardiovascular events, in women with OSA and the effect of CPAP treatment. In the first study, it was found that when compared with the control group, women with untreated severe OSA had significant vascular mortality at mean follow-up of 72 months; however, there was a non-significant decrease risk of vascular events in the CPAP-treated group [39]. Similar results were obtained in Campos-Rodriguez's second prospective analysis of a similar cohort: HR for untreated OSA group was 2.76, and the HR of the treated OSA group was 0.91. Interestingly, their analysis revealed a significantly stronger association of incident ischemic stroke than incident coronary heart disease in the untreated OSA group [40].

In a nationally representative cohort study of 3 million US veterans, it was found that when compared with OSA negative patients, there was 3.5 times higher risk of incident ischemic stroke for untreated and treated OSA. Notably, the OSA-treated group was not associated with a lower risk of incident ischemic

stroke when compared with untreated OSA patients [41]. In another prospective cohort study comparing the impact of CPAP therapy for OSA and risk of ischemic stroke and other vascular events by Schipper et al., it was found that untreated OSA patients had significantly more vascular events compared with OSA patients treated with CPAP [42•]. A prospective cohort study of elderly patients with OSA (> 65 years of age) found an increased risk of vascular mortality for untreated patients and a nonsignificant reduction of these risks in patients treated with CPAP [43]. In another study examining the risk of ischemic stroke in the elderly population with OSA and the effect of treatment with CPAP, the adjusted HR ratio for the incidence of stroke were 3.42, 1.02, and 1.76 for the untreated severe OSA group, CPAP-treated group, and untreated mild-moderate OSA group, respectively, when compared with the reference group, which suggests that there is an increased risk of ischemic stroke in this population and CPAP may reduce this risk [44•]. These prospective cohort studies fortify the association of increased risk of stroke and cardiovascular events in patients with OSA. Additionally, these studies also show an association of reduced risk of ischemic stroke and other vascular events with CPAP treatment.

Three RCTs have been published that assessed the effect of CPAP treatment and vascular outcomes, including ischemic stroke [45••, 46••, 47••]. Barbé et al. sought to investigate the effects of CPAP treatment and the incidence of hypertension and cardiovascular events, including cardiac and cerebrovascular events, in nonsleepy (asymptomatic) patients with OSA [45••]. This trial was a multicenter trial that included 723 patients who were randomized to a CPAP treatment group and no active treatment group with mean follow-up of 4 years. In the treatment group, there were 68 patients with new diagnosis of hypertension and 28 patients with vascular events (3 patients with ischemic stroke and 2 with TIAs), and in the control group, there were 79 patients with new diagnosis of hypertension and 31 patients with vascular events (2 patients with ischemic stroke and 5 with TIAs); the event incidence density ratios (IDR) were 9.20 per 100 per-years and 11.02 per 100 per-years, respectively, and when compared, the IDR was 0.83 [45••]. In a sub-analysis for CPAP adherence in the treatment group, it was noted that the IDR was significantly lower in the CPAP group with adherence of > 4 h per night when compared with < 4 h per night [45••]. Barbé et al's RCT results suggested that CPAP treatment in nonsleepy patients with OSA does not significantly reduce hypertension and vascular events when compared with patients with untreated OSA; however, their study did show a statistically significant reduction in hypertension and vascular events in patients with CPAP compliance of > 4 h per night [45••].

The Randomized Intervention with Continuous Positive Airway Pressure in Coronary Artery Disease (CAD) and OSA (RICCADSA) RCT by Peker et al. also investigated the effects of CPAP on long-term cardiovascular outcome risk, including ischemic stroke in nonsleepy patients with OSA [46••]. This trial was a single center study involving 244 patients with asymptomatic OSA who were divided evenly to a CPAP treatment group and no treatment group with mean follow-up of 57 months and primary endpoint of first event of repeat revascularization, myocardial infarction, ischemic stroke, or cardiovascular mortality [46••]. The incidence of the primary endpoint did not significantly differ in the CPAP treatment group and non-treatment group [46••]. Additionally, subgroup analysis of the treatment group did reveal a significant decrease in the primary

endpoint in patients who received CPAP > 4 h per night when compared with those who received CPAP < 4 h per night [46••]. The results of the RICCADSA RCT were similar to Barbé et al's RCT [45••, 46••]. The Sleep Apnea Cardiovascular Endpoint (SAVE) trial was a secondary prevention trial designed to evaluate CPAP effect in reducing the rate of vascular events in patients with OSA and coronary and cerebrovascular disease [47••]. The SAVE trial was a multicentered, international, blinded RCT, that included 2717 patients with moderate-severe OSA with coronary and/or cerebrovascular disease, of which 1346 were randomly assigned to the CPAP group and 1341 were assigned to the usual care group with the primary endpoint of composite death from any vascular cause (myocardial infarction, ischemic stroke, or hospitalization for heart failure, acute coronary syndrome, or TIAs) [47••]. Results were non-significant; after mean follow-up of 3.7 years, primary endpoint events had occurred in 229 patients in the CPAP group (17.0%) and in 207 patients in the usual-care group (15.4%). The SAVE trial revealed that treatment with CPAP in patients with OSA and cardiovascular and cerebrovascular disease did not reduce subsequent vascular events when compared with usual care, suggesting that CPAP has low utility in secondary prevention [47••]. Interestingly, participants in the treatment group adhered to CPAP approximately 3.3 h per night. The prior trials revealed that compliance with CPAP of > 4 h per night resulted in a significant decrease in cardiovascular events, which could explain the negative result for the SAVE trial [45••, 46••].

Several systematic reviews and meta-analyses have pooled data from observational studies and RCTs on CPAP treatment in OSA and ischemic stroke risk. Kim et al. performed a meta-analysis to examine if treatment of OSA with CPAP reduces risk of ischemic stroke [48•]. In their meta-analysis of three cohort studies, the relative risk (RR) of ischemic stroke with CPAP treatment was reduced, but results were insignificant [48•]. Abuzaid et al. performed a meta-analysis on four RCTs comparing CPAP treatment versus medical treatment in patients with OSA and reported vascular outcomes, including cardiac, ischemic stroke, and TIA [49•]. In their meta-analysis, CPAP use was not associated with reduced risk of major adverse cardiac events, however, in the subgroup meta-analysis of patients who used CPAP > 4 h per night, there was a significant decrease in cardiac events [49•]. In their subgroup analysis, CPAP treatment was also not associated with reduced risk of ischemic stroke and TIAs [49•]. In a recent meta-analysis involving nine RCTs aimed to assess the effects of CPAP in survival and secondary prevention of major vascular events in patients with OSA and cardiovascular disease, the pooled RR for ischemic stroke was 0.77 (0.46-1.28, l2 = 16%) which suggest that CPAP nonsignificantly reduces the risk of ischemic stroke in patients with OSA and cardiovascular disease [50••].

OSA has a high incidence and prevalence in the post-stroke population and treatment of OSA in this population should improve outcomes [22•]. In a prospective observational study by Martínez-García et al., PSG was performed on 166 patients 2 months after acute ischemic stroke [51]. Their study revealed 96 of the 166 patients had an AHI of >20/h and were offered CPAP treatment, in which 68 did not tolerate CPAP and 28 tolerated CPAP at 5 years follow-up [51]. Their study showed an increase in mortality in post-stroke patients with OSA who did not tolerate CPAP therapy when compared with those who did [51]. In a RCT by Parra et al., the impact of early CPAP treatment in patients with ischemic stroke with OSA was examined [27]. In their study, patients with

ischemic stroke and AHI >20/h were randomized to early treatment arm with CPAP, 3–6 days after stroke onset, and control group. This study showed that patients with early treatment with CPAP had significant improvement of their modified Rankin score (mRS) at 1 month follow-up and longer mean time to vascular events, including ischemic stroke, at 1 year follow-up when compared with control [27]. At 5-year follow-up, the CPAP treatment group had significantly higher cardiovascular and cerebrovascular survival than the control group [52••]. Parra et al. showed that early use of CPAP accelerates neurological recovery in patients with OSA and ischemic stroke, delays subsequent vascular events, and decreases mortality when compared with untreated patients [27, 52••]. Hsu et al. showed no benefit of CPAP treatment in patients with ischemic stroke and OSA when compared with controls at 3 month follow-up; however, results were not significant, and compliance with CPAP was poor [53]. In a RCT of 70 patients with ischemic stroke and OSA at a single center in India, CPAP treatment resulted in a non-significant reduction in vascular events and improved mRS when compared with the untreated patients at 1 year follow-up, suggesting that CPAP treatment is associated with reduced subsequent events and better stroke outcomes [54••].

Several RCTs have examined CPAP treatment in patients with ischemic stroke and OSA to assess functional, neurocognitive, and motor outcomes and all studies have shown a trend toward positive results in treatment groups when compared with controls [55, 56]. In a recent meta-analysis of ten RCTs examining the effectiveness of CPAP treatment in post-stroke patients with OSA, Brill et al. revealed that CPAP treatment in patients with ischemic stroke and OSA showed an overall significant neurofunctional improvement; however, it also showed significant drop out of CPAP use in all studies [57••]. This meta-analysis suggests that CPAP might be beneficial for neurologic recovery; however, there was a significant CPAP dropout among participants [57••]. Although CPAP treatment in post-stroke OSA patients is feasible, compliance remains an issue and may impair potential improvement in functional, motor, and cognitive outcomes [58, 59]. Colelli et al. investigated predictors of CPAP adherence in patients who had an ischemic stroke or TIA and found that patients with greater post-stroke functional capacity and less daytime fatigue were associated with greater compliance [60•]. Compliance with CPAP therapy may lead to improved neurofunctional outcomes and improved stroke outcomes.

Surgical interventions are considered second-line therapies or are employed in patients that have poor compliance with CPAP [34]. Surgical options include upper airway surgery such as nasal reconstruction, uvulopalatopharyngoplasty (UPPP), temperature-controlled radiofrequency tissue ablation (TCRFTA), mandibular advancement, and hypoglossal nerve stimulation (HNS) [61]. Several controlled trials have failed to consistently show that surgical intervention is more effective than CPAP [34, 62–65]. In a retrospective analysis by Anand et al. comparing CPAP and surgical intervention, post-treatment comparative analysis revealed superior cures with CPAP on PSG [62]. A randomized controlled trial comparing TCRFTA and CPAP with sham placebo revealed significant improvement with TCRFTA compared with placebo and CPAP compared with placebo in quality of life and subjective sleepiness; however, significant differences were not seen between TCRFTA and CPAP outcomes [63]. Several trials have shown no significant benefit of UPPP over CPAP [64,

65]. However, in a retrospective cohort study on the survival of veterans with OSA with CPAP versus UPPP, CPAP patients had 31% higher probability of mortality at any time relative to UPPP patients, suggesting that surgical intervention may confer a survival advantage [66]. In a recent study by Lee et al., UPPP was found to significantly reduce the incidence of cardiovascular complications, such as congestive heart failure and atrial fibrillation, when compared with patients with untreated OSA [67]. HNS was the latest surgical intervention for OSA approved by the Food and Drug Administration (FDA) in 2014 [68]. In the Stimulation Therapy for Apnea Reduction (STAR) trial, HNS demonstrated a significant decrease in AHI score at 12 months from 29.3 events per hour to 9.0 events per hour and secondary outcome measures showed a reduction in the effects of sleep apnea and improved quality of life [69]. HNS was found to significantly reduce the mean AHI by 21.1 in a recent meta-analysis by Kompelli et al. [70]. Another recent study comparing UPPP and HNS for treatment of OSA at a single institution revealed that patients who underwent HNS had a significant decrease in mean AHI from 38.9 ± 12.5/h to 4.5 ± 4.8/h when compared with mean AHI decreased from 40.3 ± 12.4/h to 28.8 ± 25/h in the UPPP group, suggesting that HNS is superior and possibly curative when compared to UPPP [71]. Still, evidence on surgical treatment of OSA and cerebrovascular risk and outcomes are lacking and require further investigation.

Discussion

OSA increases risk of ischemic stroke, and it is an independent and potentially modifiable risk factor for ischemic stroke. Additionally, there is an increased prevalence of OSA in post-stroke patients and is typically associated with worse outcome and increased mortality. Several clinical trials and observational studies have assessed whether OSA treatment is associated with reduction of ischemic stroke risk and whether treatment of OSA in the post-stroke population is associated with improved outcomes and reduction of subsequent cerebrovascular events. CPAP remains the primary treatment for OSA. Overall, observational studies have suggested reduced risk of ischemic stroke in patients with CPAP-treated OSA. However, only a few studies yielded statistically significant results. The results from the randomized control trials assessing CPAP treatment and cardiovascular and cerebrovascular events (Barbé et al's RCT, RICCADSA, and SAVE) indicated that while there was a reduction of ischemic stroke and cardiovascular events in the CPAP treatment group, these results were not statistically significant. It is important to note that CPAP tolerance and compliance in patients were poor in these studies. However, subgroup analyses showed that patients with CPAP compliance > 4 h per night showed statistically significant reduction in ischemic stroke and cardiovascular events when compared to users with CPAP < 4 h per night. Additionally, meta-analyses of these observational and RCTs support a nonsignificant reduction in ischemic stroke and cardiovascular events with CPAP treatment in OSA patients. Several RCT were conducted in post-stroke patients with OSA to determine if treatment with CPAP improved outcomes and reduced subsequent ischemic stroke risk. CPAP treatment was determined to be feasible in post-stroke patients, and multiple studies showed significant improvement in functional (mRS), neurocognitive, and motor

outcomes; although, these trials are limited in number and power. Several small studies have shown a reduction in subsequent ischemic stroke and cardiovascular events in post-stroke patients with OSA treated with CPAP compared with untreated patients, however, large scale and higher power studies are needed to accurately assess CPAP for secondary prevention of ischemic stroke. Surgical treatments for OSA are second-line therapies and have not been studied in association with ischemic stroke and cardiovascular risk and outcomes.

The association of OSA and stroke risk is well studied and several studies have assessed treatment of OSA and subsequent stroke risk. Other sleep disorders such as CSA, OHS, parasomnias, EDS, and SRMD, such as restless-leg syndrome (RLS) and periodic limb movements during sleep (PLMS), have been associated with an increased stroke risk [15••, 16–20]. However, little data is available demonstrating the impact of treatment of these sleep disorders on ischemic stroke risk. Additionally, epidemiological studies on OSA and hemorrhagic stroke are lacking and require further investigation.

Conclusion

The authors recommend that patients with vascular risk factors and reported OSA symptoms should be screened with STOP-BANG and/or ESS questionnaires. Patients who screen positive for possible OSA should be tested with PSG to establish a diagnosis. Once the diagnosis of OSA is established, patients should be referred to a sleep specialist for further management and the initiation of treatment. Physicians should encourage lifestyle modifications as numerous studies have shown benefit in OSA patients. At this time, CPAP treatment in OSA patients can possibly reduce the risk of ischemic stroke; however, more investigation is required to formally recommend CPAP treatment in OSA as a primary prevention strategy for ischemic stroke. Still, the current data shows support for ischemic stroke risk reduction in OSA patients treated with CPAP, thus the authors would recommend this treatment for primary prevention in OSA patients. CPAP compliance remains an issue and likely limits the effectiveness of prior RCTs evaluating CPAP treatment in OSA and ischemic stroke and cardiovascular risk. Patients should regularly follow up with their sleep specialists to ensure compliance with CPAP and use of CPAP should be for longer than 4 hours per night. Motivational exercises and biofeedback can possibly increase patient compliance.

Hospitalized post-stroke patients can be screened for OSA with continuous oxygen monitoring and/or STOP-BANG and/or ESS questionnaires prior to discharge. Post-stroke patients who screen positive can be referred to a sleep specialist for further evaluation of OSA with PSG and treatment. There is data to suggest improved functional outcome with CPAP treatment in the post-stroke population; however, few studies have shown significant reduction in subsequent ischemic stroke risk. OSA should be treated in the post-stroke population; however, secondary prevention remains to be investigated. The authors do not recommend CPAP treatment for secondary prevention in post-stroke patients without a diagnosis of OSA.

More randomized control trials on CPAP treatment of OSA and ischemic stroke risk, as well as CPAP treatment of OSA in the post-stroke population with improved CPAP compliance, are needed. Additionally, surgical interventions are pursued in patients with poor CPAP compliance, and assessment of surgical

treatment in OSA and future ischemic stroke and cardiovascular risk remains an avenue for investigation. The authors recommend that high-risk patients, both pre- and post-stroke, with OSA and with poor compliance with CPAP should be considered for surgical treatment of OSA.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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