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Sleep and Stroke: New Updates on Epidemiology, Pathophysiology, Assessment, and Treatment

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Abstract

Purpose of review—This review aims to discuss the most recent data on sleep disorders and stroke, highlighting relevant findings for the practicing neurologist or health providers who encounter patients with sleep disorders and stroke.

Recent findings—Sleep apnea and abnormal sleep duration have the strongest association with stroke risk. Possible mechanisms include non-dipping of blood pressure during sleep, hypoxemia or reoxygenation leading to sympathetic activation, hypertension, atrial fibrillation and impaired cerebral hemodynamics. Treatment studies suggest that continuous positive airway pressure (CPAP) for sleep apnea could improve primary prevention of stroke, but data is equivocal for secondary prevention. However, CPAP could improve functional outcomes after stroke.

Summary—Sleep disorders present an opportunity to improve stroke risk and functional outcomes. However, new strategies are needed to determine the patients at high-risk who would most likely benefit from targeted care. Novel methods for phenotyping sleep disorders could provide personalized stroke care to improve clinical outcomes and public health strategies.

Keywords

Stroke; Sleep Disordered Breathing; Obstructive Sleep Apnea; Positive Airway Pressure

Introduction

Sleep is a crucial part of daily function and is increasingly recognized as a determinant of long-term health. Stroke is one of the leading causes of death and disability in the United States and worldwide.(1) Stroke may be broadly divided into ischemic stroke, accounting for approximately 85% of cases, and hemorrhage stroke in the remaining 15% of cases. The management of stroke has rapidly evolved in the last two decades where stroke thrombolysis

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and thrombectomy have become standard of care. There are extensive studies into management of stroke risk factors such as atrial fibrillation and hypertension, often attributed to untreated sleep apnea. Sleep disorders, particularly sleep apnea, are recognized as novel modifiable risk factors for stroke, however the mechanism, vascular pathways and the role of sleep in stroke prevention and treatment remains unclear.

There are six main categories of sleep-wake disorders according to the International Classification of Sleep Disorders: sleep-related breathing disorder, insomnia, central disorders of hypersomnolence, circadian rhythm sleep-wake disorder, sleep-related movement disorders and parasomnias.(2, 3) Here we will focus primarily on sleep-disordered breathing (SDB), particularly obstructive sleep apnea (OSA) and stroke.(4, 5) The first depiction of the close relationship between sleep and stroke originated from a case report in 1985 describing a 34 year-old male with severe OSA and hypertension who developed a right hemiplegic stroke.(6) Subsequently, research in this area has grown exponentially but guidelines for how to manage sleep disorders in stroke care are lacking. OSA is present in 60 to 80% of patients presenting with stroke or transient ischemic attack (TIA). SDB is an independent risk factor for future stroke and mortality, may complicate management of treatable risk factors (atrial fibrillation, hypertension).

The criteria for diagnosing SDB varies, but all require confirmation with nocturnal polysomnography or home-sleep testing (HSAT). Most studies reviewed define SDB using the apnea-hypoxia index (AHI), which is the total number of apneas (complete airway obstruction) or hypopneas (partial airway obstruction) per hour of sleep. Obstructive sleep apnea is unlikely in those who have an AHI < 5, patients with mild OSA have $5 \leq AHI < 15$, moderate OSA $15 \leq AHI < 30$ and severe OSA an $AHI \geq 30$.(7)

This review emphasizes two different clinical perspectives: one focusing on the sleep perspective and the second on the stroke perspective allowing the reader a unique appreciation of how sleep and neurologic disorders impact one another.

Methods

We searched PubMed using the terms “stroke” and “sleep” for articles dating January 1st 2014 to October 1st 2018. We excluded animal studies, pediatric studies (<18), narrative reviews, case reports, papers written in languages other than English, commentaries and conference abstracts. A total of 1410 articles were reviewed. The authors also searched major sleep and stroke journals (e.g. Sleep Medicine Reviews). A Total of 127 articles were included based on relevance and importance to this review.

Epidemiology

Sleep Perspective—The prevalence of SDB is estimated to be 2-to-10%, over twice as likely in men, and can affect up to half of older individuals.(5) A recent meta-analysis identified ten high quality cohort studies showing an independent association between SDB and stroke (relative risk 2.5).(7) Less is known about the role of SDB in hemorrhagic strokes, but recent studies described a high prevalence of SDB, 38-to-72%, in intracranial hemorrhages. (8, 9)

Vascular risk factors such as obesity and hypertension confound associations between SDB and stroke risk.(10, 11) Interestingly, a retrospective study of 222 participants tried to disentangle the independent effects of morbid obesity and OSA on cardiovascular risk. Untreated OSA blunted any improvement in cardiovascular profile associated to weight loss after bariatric surgery, except in those that used positive airway pressure. (12)

SDB and stroke risk can be influenced by SDB phenotypes in at-risk populations. For example, other metrics (e.g. hypoxemia) to define SDB severity or worsening AHI during REM sleep could be better predictors of vascular risk, beyond the severity of sleep apnea as reflected by the AHI.(13, 14) Studies using *a priori* definitions of sleep phenotypes described vascular risk among SDB patients with sleepiness.(15) Interestingly, data-driven methods using advanced statistical analyses suggest a heterogeneity of clinical phenotypes associated with increased stroke and vascular risk.(15–20) For example, the *Icelandic Sleep Apnea Cohort* (n = 822) of patients with AHI ≥ 15 described three different SDB phenotypes based on cluster analysis. First, an insomnia SDB group, a minimal symptoms group and a group with excessive daytime sleepiness. Paradoxically, patients with minimal symptoms had the highest odds of hypertension (OR=1.38; $p \leq 0.001$) and cardiovascular disease (OR=1.67; $p < 0.001$) compared to those with sleepiness.(20) *The Sleep Apnea Global Interdisciplinary Consortium* (*SAGIC*) study confirmed and extended these results by including an international sample.(21, 22) Interestingly, SAGIC showed that females had more “disturbed sleep” than other cluster types, in addition to decreased compliance to positive airway pressure.(21, 22) A prospective analysis of the multi-center study, *Determining Risk of Vascular Events by Apnea Monitoring* (DREAM)(13) used Cox proportional hazards models to evaluate which analytical clusters associated with the composite outcome of mortality, stroke, transient ischemic attack and acute coronary disease. Two of the identified seven clusters had worse outcomes. The “PLMS” cluster (periodic limb movements in sleep with mild AHI), hazard ratio (HR) = 2.4, and the “arousal and poor sleep” (severe AHI, without hypoxic burden and many arousals) cluster, HR=2.3. (13) Importantly, the clinical cutoffs of mild, moderate and severe SDB did not predict the composite outcome.(13)

At this time, available studies do not conclusively support an association between SBD specific stroke-subtypes.(23) Importantly, other sleep disturbances are associated with stroke risk. Recent reports have established an association between both short (<6 hours) and long (>9 hours) sleep duration and stroke.(24, 25) A large proportion of people sleep less or more than the recommended seven-to-eight hours of sleep.(26) A prospective study and meta-analysis of 11 high quality studies (n=550,000) showed a stronger association for long sleep duration compared to short sleep duration and stroke.(27) These findings are also supported by other meta-analysis comprising of 100 studies with five-million participants.(28, 29) However, a recent study suggested sleep duration and stroke risk are moderated by race-ethnic, sex, stroke type and age groups.(30) In a Japanese study, long sleep duration was associated with increased risk for all strokes and short duration with decreased hemorrhagic stroke mortality risk in men.(31)

Though less thoroughly studied, restless leg syndrome (RLS) has been associated with increased stroke, while other studies did not find a similar association.(32–34) Periodic leg

movements, which are seen in up to 80% of patients with RLS, were associated with hypertension and white matter disease burden in stroke patients.(35) However, another small prospective study showed no association.(36) Interestingly a large community cohort study (n=12,000) described an association between self-reported REM sleep behavior disorder and stroke.(37) It is still unclear which mechanism or risk factors may lead to these associations.

Stroke Perspective—Stroke still affects one person every 40 seconds.(38, 39) A meta-analysis of 29 studies of over 2000 patients in the acute stroke setting showed that 72% had at least mild (AHI ≥ 5) and 38% more severe (AHI ≥ 20) OSA. Increasing evidence shows that SDB can lead to worse functional outcome and quality of life in stroke patients.(40–44) Importantly, there could several mediating factors between SDB and worse functional outcomes in stroke. For example, cognitive impairment is described in four-out-of-five stroke patients, most commonly in the domain of attention and executive function.(45) Except for one equivocal study, several small studies have shown that post-stroke patients with sleep disorders have worse cognitive impairment.(45–48) However, it is unclear if sleep treatments reduce stroke risk or improve functional outcomes.

Pathophysiology

Sleep Perspective—Pre-stroke risk factors such as non-dipping blood pressure and hypoxemia/reoxygenation are candidate mechanisms that lead to SDB and stroke via hypertension, atrial fibrillation and impaired cerebral hemodynamics (Figure 1). Recent studies suggest that SBD is associated with a hypercoagulable state with elevated hematocrit, viscosity, clotting factors and altered platelet activity that may be reversible with CPAP.(49) In combination with a hypercoagulable state associated with SBD, the theoretical stroke risk increases with atrial fibrillation, an independent risk factor for stroke in patients with SBD.(50–52) SDB could cause or worsen atrial fibrillation through increase cardiac afterload, left ventricular hypertrophy and left atrial fibrosis/modeling. One retrospective study used Cox proportional hazards regression to show that obesity and magnitude of nocturnal oxygen desaturations (both intrinsically related to SBD) were independent risk factors for atrial fibrillation.(53) Further, an analysis of the *Sleep Heart Health Study* showed that apneas/hypopneas were more likely to be followed by cardiac arrhythmias. Several recent studies showed that short-term CPAP treatment can improve cardiac function and structure, however further studies are needed to confirm its theoretical benefit on stroke risk.(54–59)

Studies have reported an association between SBD and carotid atherosclerosis. Interestingly asymptomatic carotid stenosis is associated with central, but not obstructive apneas.(60–62) There is equivocal evidence that snoring may be an independent risk factor for stroke. Recent studies support this association, for example, by showing that snoring was an independent risk factor for high-risk carotid plaque on MRI.(63) Another animal study in rabbits showed that vibration from snoring resulted in endothelial dysfunction in the carotid arteries, hence increasing atherosclerosis by sheer stress to the vessel walls.(64)

Dipping blood pressure is the normal decrease of blood pressure by 10-to-15% during sleep that may not occur in SDB, non-dipping blood pressure. Approximately, 50% of SDB have

non-dipping of blood pressure, which has been associated with cardiovascular risk.(65) Impaired cerebral hemodynamics is also described in SDB (66–73) and normalized with CPAP (74) in some, but not all studies.(75)

In addition, the negative intra-thoracic pressure during sleep and patent foramen ovale increases the theoretical risk of paradoxical embolism and stroke.(76) Moreover, sleep disorders have been associated with increased white matter disease (leukoaraiosis), a possible harbinger of stroke. More severe leukoaraiosis was associated with higher AHI.(77) Further, both short sleep and longer sleep duration have been associated with white matter disease. (78–81) However, one study suggested that fragmented sleep and not sleep duration was associated with white matter disease.(80)

Stroke Perspective—Stroke could potentially disrupt sleep networks that further impair functional outcomes that interfere with optimal sleep.(71, 82–84) Acute manifestations of stroke such as oropharyngeal dysfunction has been associated with SDB. A prospective study showed that dysphagia and dysarthria after intracerebral hemorrhages were independently associated with SDB.(9) Dysphagia may lead to elevated airway resistance due to a lower threshold for airway collapse. Another small study of hypoglossal nerve activity found an association between hypoglossal nerve dysfunction post-stroke and increasing AHI severity.(85) Moreover, decreased mobility after stroke can increase lower extremity edema resulting in fluid shifts into the oropharyngeal structures exacerbating SBD.(86)

Chronic manifestations of stroke such as physical disability may alter sleep positioning throughout the night resulting in increased supine sleep, a known to contributor to increased AHI. Chronic sleep architecture and cognitive impairment can occur after stroke.(37, 45) Recent studies have showed that memory consolidation is dependent on sleep architecture after stroke.(87) One small study reported that nocturnal hypoxia was not associated with functional outcome in 20 participants.(88) Whereas other studies suggest that nocturnal hypoxia underlies the deleterious effects leading to stroke. Interestingly, in this study, CPAP use was still associated with better functional outcomes post-stroke. Hence, it is unclear which sleep metrics are the best to predict stroke recovery. Of importance, SDB symptoms may not be apparent after a stroke. For example, a large study found that the most affected self-reported domains after a stroke were physical function, social roles and executive function but less so for sleep symptoms (snoring, sleepiness).(89)

The presence of SDB after stroke may disturb stroke recovery through many inflammatory cytokines and hormonal disturbances (Figure 1).(90–92) A novel mechanism that may impair stroke recovery is altered tryptophan metabolism.(91, 93) SDB also contributes to endothelial dysfunction. A recent study associated SDB post-stroke with altered peripheral arterial tone, a proxy for endothelial dysfunction. Interestingly after one, year endothelial dysfunction normalized as SDB normalized.(94)

Assessment

The *Epworth Sleepiness Scale* (0 to 3 self-reported likelihood of dozing during eight common activities) and *STOP-BANG questionnaire* (point score or risk of SBD: **S**noring,

Tiredness during daytime, **O**bserved apnea at night, high **B**lood pressure, **B**ody mass index, **A**ge >50, **N**eck circumference >40cm, female **G**ender) are among the available tools to evaluate symptoms associated with SDB. Objective sleep testing is classified from type I to IV according to the American Academy of Sleep Medicine criteria. Major limitations of type III and IV studies are the lack of EEG to corroborate sleep, hence the AHI is calculated based on patient-reported sleep duration and or recording time, which typically underestimate the AHI. See Table 1 for a summary of assessments for stroke and SBD risk discussed below.

Sleep Perspective—In a large Canadian cohort , in addition to AHI, there were other sleep predictors of stroke events: time spent with oxygen saturation <90%, short sleep duration, number of awakenings or arousals from sleep, periodic leg movements, increased mean heart rate and daytime sleepiness.(95) Studies with small sample sizes suggested that OSA patients with increased red blood cell distribution width may have higher stroke risk.(96) Of importance is the evaluation of stroke risk associated to SBD beyond the AHI as exemplified by the analysis of the DREAM study (see epidemiology section).(13) The treatment guidelines for SDB do not require therapy with positive airway pressure in patients who are asymptomatic (i.e. lacking symptoms of excessive sleepiness) or have mild OSA. However, it is foreseeable that patients at high risk of stroke and mild OSA (AHI < 15) may require treatment with CPAP and vascular preventive therapy if coexistent with the aforementioned sleep phenotypes. Evaluation of SDB phenotypes represents a novel strategy to risk stratify and personalize preventive and therapeutic strategies for stroke.(15)

Stroke Perspective—In the inpatient acute stroke setting, aggressive risk factor control and identification of stroke etiology are immediately initiated. However, comorbidities such as SDB have largely been neglected. Further, SDB questionnaires in the acute stroke setting are underutilized. This may, in part, be due to inpatient obstacles when administering questionnaires; and subjective SBD symptoms such as hypersomnolence are less common in stroke patients. In 2016, the *American Heart Association and the American Stroke Association* recommended polysomnography and treatment of SDB in ischemic stroke or TIA,(97) however there are no specific recommendations on how to screen and when to refer to polysomnography.

A recent large prospective trial using an integrated 4.2-minute questionnaire (“DOC” screen) showed an association with depression, cognitive impairment and SBD in acute stroke inpatients.(98) The *STOP-BANG questionnaire* is validated but has only modest predictive value during an acute stroke for which the *STOP-BAG questionnaire* (similar to the *STOP-BANG* but without neck circumference score) and 4-Variable screening tool (sex, blood pressure level, body mass index and self-reported snoring) was a better predictor.(99) In a recent randomized-control trial in TIA and stroke patients, a new *SLEEP Inventory* was developed to model and predict AHI ≥ 5. The *SLEEP Inventory* (Sex, Left heart failure, *Epworth Sleepiness Scale*, Enlarged neck, weight, Insulin resistance/diabetes, and National Institutes of Health Stroke Scale) performed modestly better than the *Berlin Questionnaire, Epworth Sleepiness Scale, STOP-BANG questionnaire* and the *Sleep Apnea Clinical Score*, with the most robust negative predictive value for OSA.(100) Screening patients with the

STOP-BAG questionnaire, even from family members, (101) followed by the *SLEEP Inventory* may be the best inpatient strategy to select for polysomnography.

However, even with appropriate screening for referral for polysomnography, most institutions take weeks to months to schedule polysomnography. This window maybe crucial as stroke recurrence in TIAs or mild stroke is approximately 5% during the first week, then approximately 10% one month after stroke. There is a paucity of studies defining the timing of sleep treatments that could affect early recurrences of stroke. However, similar to established risk factors, SBD should be promptly recognized and treated.

The *American Academy of Sleep Medicine* does not support treatment of SBD based solely on questionnaires or type IV testing.(102) However, in the setting of stroke, overnight oxygen desaturation has been shown to be a stronger predictor of stroke than AHI. For example, recent studies showed that oxygen desaturations were associated with wake-up strokes, atrial fibrillation(103), neurological deterioration after stroke(104) and stroke in older men.(105)

A recent study used high-resolution pulse oximetry (HRPO) in acute mild-moderate stroke inpatients.(106) The investigators showed that the oxygen desaturation index (number of desaturations <88% by 4%) and total time spent below 88% predicted the presence of atrial fibrillation and a higher probability of discharge to a rehabilitation center versus home. Though, this study was limited by the lack of polysomnography, its feasibility is promising in the inpatient setting. Several type IV studies have also shown promise in post stroke inpatients, such as a recent study of an acoustic device for patients with severe strokes.(107) Though these type IV devices are insufficient to initiate treatment, they can be tailored to determine the need for further sleep studies.

Many studies used type III sleep testing such as Home Sleep Apnea Testing (HSAT) to study SDB and stroke. Two recent prospective studies showed promising results in diagnosing and treating SDB in selected stroke patients.(108, 109) In addition, evolving SDB diagnostic criteria is moving towards using HSAT with lower AHI (5-14.9) and desaturations, which were better predictors of SDB in stroke patients than AHI.(110) Other type III sleep testing in stroke inpatients, such as a Finnish study using three channels (electrooculogram, mattress respiratory monitor and oximetry) yielded similar rates of OS A when compared to polysomnography. (111)

Treatment

Sleep Perspective – Primary stroke prevention—CPAP improves daytime sleepiness and quality of life in stroke naive patients; in addition to lowering of blood pressure, the main modifiable risk factor for stroke.(112) Atrial fibrillation is a common arrhythmia associated with a 5-fold risk of stroke. The guidelines of the *American Academy of Sleep Medicine* suggest that patients with atrial fibrillation should be screened and stratified for evaluation of SDB.

Importantly, future studies should consider including sleep apnea in risk-stratifying strategies to evaluate the risk of stroke in atrial fibrillation. An available tool is the

CHA_2DS_2-VASc (CHF, Hypertension, Age, Diabetes, disease, Stroke/TIA/ Thromboembolism), a risk estimator for stroke in patients with non-valvular atrial fibrillation. Interestingly, SDB was found to increase stroke risk by more than 3-fold in patients with atrial fibrillation, particularly among patients with a low CHA_2DS_2-VASC, seemingly at “low risk” for atrial fibrillation-related stroke.(50) This study was limited by its retrospective design and highly selected population. However, the findings did support the inclusion of SDB to the CHA_2DS_2-VASC score, but larger prospective studies are needed.

Few studies have evaluated CPAP therapy in the primary prevention of an incident stroke. A meta-analyses of eight studies (five cohort studies, one randomized trial and two used health administrative data) showed that CPAP may be associated with decreased stroke risk.(112) CPAP was associated with a 27% risk-reduction of incident stroke based on observational studies, however data from other study designs were equivocal. Another meta-analysis showed that CPAP treatment was associated with improved blood pressure.(113) These findings suggest that CPAP could protect against incident stroke, however randomized trials are needed.(114)

Stroke Perspective – Secondary stroke prevention—Prospective observational studies leading up to the stroke guidelines from 2014 (97) showed an association between CPAP treatment in acute stroke patients and reduced cardiovascular risk. However, randomized trials were limited by small sample size, high drop-out rates and lack of compliance to CPAP therapy.

Since 2016, three randomized controlled trials have investigated the use of CPAP treatment for secondary prevention of stroke and cardiovascular disease. A small randomized controlled trial (n=70) in stroke patients with SDB (AHI > 15) compared CPAP to no-CPAP therapy.(115) After one year, there was a trend for higher cardiovascular events in the no-CPAP arm and significantly better stroke outcomes (activities of daily living and modified Rankin scale) in the CPAP arm. Though this study was limited by a small and select sample size (initially powered for n=160) with a short follow-up at 1 year, it had good CPAP compliance and supports the need for more CPAP studies after stroke. The largest multi-center randomized controlled trial to date enrolled patients after coronary artery or cerebrovascular disease with untreated OSA: *Sleep Apnea cardio Vascular Endpoints* (SAVE) trial (n=2717).(116) There was no significant decreased risk of serious cardiovascular events in the CPAP treatment arm compared to the sham CPAP arm after a mean of 3.7 years. CPAP compliance was poor (average of 3.3 hours nightly) but post-hoc analysis showed a significant cardiovascular risk reduction for participants that used CPAP for >4 hours nightly. Consistent with previous studies they found that CPAP treatment had significant beneficial effects on quality of life, mood, daytime sleepiness and work productivity.(117, 118) Compliance to CPAP is an inherent issue for SDB treatment and these studies have generated more interest in how to improve compliance, particularly in at-risk population.

An analysis from the SAVE trial showed that compliance and side effects at one month were predictors of CPAP compliance at twelve months in acute stroke patients.(119) These findings provide a window of opportunity to improve CPAP compliance. For example, a

randomized controlled open-label trial showed that behavioral interventions such as motivational enhancement (six phone calls over 32 weeks) improved CPAP use (120). Another study showed that a significant “motivator” for adherence to CPAP was the desire to prevent future strokes in stroke survivors.(121) Importantly CPAP improves mood and functional outcomes after stroke; however, mood disorders and decreased function serve as a barrier to CPAP use in stroke survivors. Similar to motivational enhancement, perhaps assessment and intervention for patient participation may prove fruitful.(122)

If CPAP barriers to compliance are overwhelming, alternative therapies to CPAP are available. However, its efficacy in stroke patients remain unclear. One randomized cross-over trial tested whether expiratory positive airway pressure (EPAP) significantly reduced AHI in stroke patients.(123) EPAP consist of nose pieces that decrease inspiratory resistance and increase expiratory resistance thought to splint open the airway for subsequent inspiration. However, EPAP did not significantly reduce AHI in acute stroke patients intolerant to CPAP.

In summary, it is still unclear whether CPAP treatment after stroke will reduce stroke and cardiovascular risk. Recent meta-analyses of both primary and secondary cardiovascular risk prevention suggest CPAP with better compliance is necessary.(124, 125) However, one systematic review was skeptical about the cardiovascular risk reduction of CPAP compliance >4 hours due to borderline significance on meta-analysis and the post-hoc design of these analyses.(126) Nonetheless, CPAP is known to have improved functional outcomes both in SDB and SDB+stroke patients. There are several ongoing randomized controlled trials that will further elucidate the benefit of CPAP and stroke risk: *Sleep for Stroke Management and Recovery Trial* secondary prevention of stroke with CPAP (Sleep SMART), CPAP following acute coronary syndrome (NCT01335087) and the effect of adaptive servo ventilation on survival in heart failure (NCT01128816).

Conclusion

Back to our case of a 34 year-old male with severe OSA and hypertension who developed a right hemiplegic stroke. Prior to his stroke the clinician could discussed evidence associating obesity, increased hematocrit, increased red blood cell distribution width, PLMS, poor sleep and minimal daytime symptoms to increased stroke risk in the setting of SDB diagnosis. Increased vigilance for TIAs, a low threshold for testing for arrhythmias and more aggressive treatment of his OSA may have mitigated his stroke. After his stroke, acute symptoms such as worsening SDB, physical dysfunction, subtle oropharyngeal dysfunction and nocturnal hypoxia should be treated with aggressive physical/occupational therapy and CPAP (considering other treatment alternatives for sleep apnea). This includes long-term cardiac monitoring for arrhythmias. Chronic changes after stroke such as cognitive/mood (DOC screen), social role, weight and sleep architecture changes should be addressed to promote recovery from stroke to further reduce stroke risk.

There remains a critical gap in understanding the sleep factors, beyond the AHI (for diagnosis) and CPAP (for treatment) that affect cerebrovascular health. The imperative of personalized care drives the need to develop approaches to define sleep phenotypes and

pathways that lead to improves stroke risk. For example, It is foreseeable that improving sleep could also lead to improvements in nocturnal blood pressure as a way to mitigate cerebrovascular burden and prevent stroke. In addition, studies defining novel genetic loci for sleep and cerebrovascular injury could aid in the diagnosis and stratification of at-risk individuals. Finally, public health policies directed at improving sleep could minimize the excess cerebrovascular burden in at-risk groups and the population at-large.

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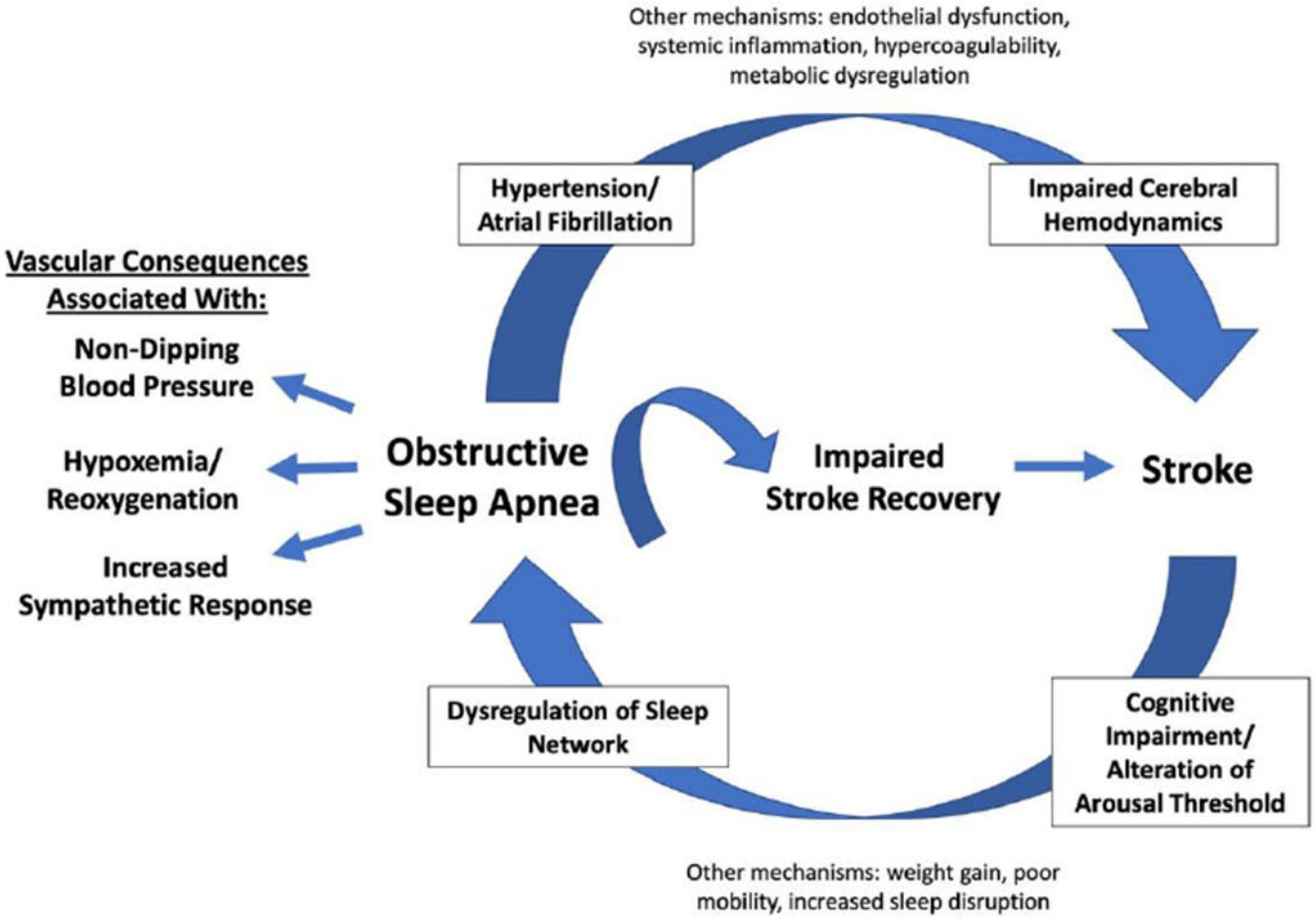

Figure 1.
Depicting the relationship between sleep disordered breathing and stroke.

Table 1.

Summary of recommended primary and secondary stroke prevention for sleep disordered breathing.

Sleep Perspective - Primary Prevention	Reason For Use	Statistics	References
Sleep duration in healthy patients	<6 hours of sleep	Risk Ratio=1.16; CI 1.10-1.23; P<0.0005	Itani et al. 2016
	>9 hours of sleep	Risk Ratio=1.25, CI 1.14-1.37; P<0.0005	Jike et al. 2018
Epworth Sleepiness Scale	Commonly used easy clinic screening	Sensitivity (66%) for AHI>5 with a normal cutoff <11 and 76% at cufoff <9.	Rosanthal and Dolan 2008
STOP-BANG	Commonly used easy clinic screening for SBD	Sensitivity for scores ≥ 3 for AHI > 15 and AHI > 30 is 93% and 100%, respectively	Chung et al. 2016
SDB patients: common labs associations	Hematocrit	Mean: Control: 39.8±4%; mild: 41.2±4%; severe: 43.5±3.6%;P<0.05	Choi et al. 206
	RDW	RDW ≥ 15% - AUC: 0.837; sensitivity 0.919; specificity 0.755	Shen et al. 2017
SDB phenotypes with higher associations with stroke:	SBD symptoms with stronger associations with stroke		
	Minimal daytime symptoms	Odds Ratio=1.67; $p < 0.001$	Ye et al. 2014
	Arousal and poor sleep	Hazard Ratio=2.36; CI 1.61-3.46; P<0.0002	Zinchuk et al. 2018
	Periodic Limb Movement in Sleep	Hazard Ratio=2.33; CI 1.32-4.10; P<0.0002	Zinchuk et al. 2018
Stroke Perspective - Secondary Prevention	**Reason For Use**	**Statistics**	**References**
STOP-BAG	Initial screen for SDB	AUC: 0.688 (p = 0.007) and sensitivity was 96.9% for a cutoff of <6	Boulos et al. 2016
4-Variable Screening test	Initial screen for SDB	AUC: 0.677 (p = 0.012); sensitivity was 93.8% for a cutoff of <2	Boulos et al. 2016
SLEEP Inventory	Best negative predictive value	c-statistic 0.731	Sico et al. 2017
DOC screen	Follow up stroke clinic screen	Mood AUC 0.90; Apnea AUC 0.80; Cog AUC 0.81	Swartz et al. 2017
Type IV screening - HRPO	**Associated with Atrial Fibrillation and SDB after stroke**	**Odds Ratio=1.01, CI 1.00-1.03; P<.001**	Yaddanapudi et al. 2018, Patel et al. 2018
Type III screening - HSAT	Unattending testing as a stroke in patient	OSA was detected in 63.4% (52 of 82) of patients	Boulos et al. 2017
		Meta-analysis: sensitivity 0.79-0.97, and specificity 0.60-0.93	Shayeb et al. 2014
Patients with Atrial Fibrillation	ORBIT-AF trial: 18% frequency of OSA. AASM: with comorbid with BMI >35, CHF, hypertension resistant to treatment, Type 2 DM, stroke, pulmonary hypertension, high-risk driving population recommends screening for SDB		Holmqvist et al. 2015; Epstein et al. 2009