Screening and Treatment of Sleep Apnea Post Stroke

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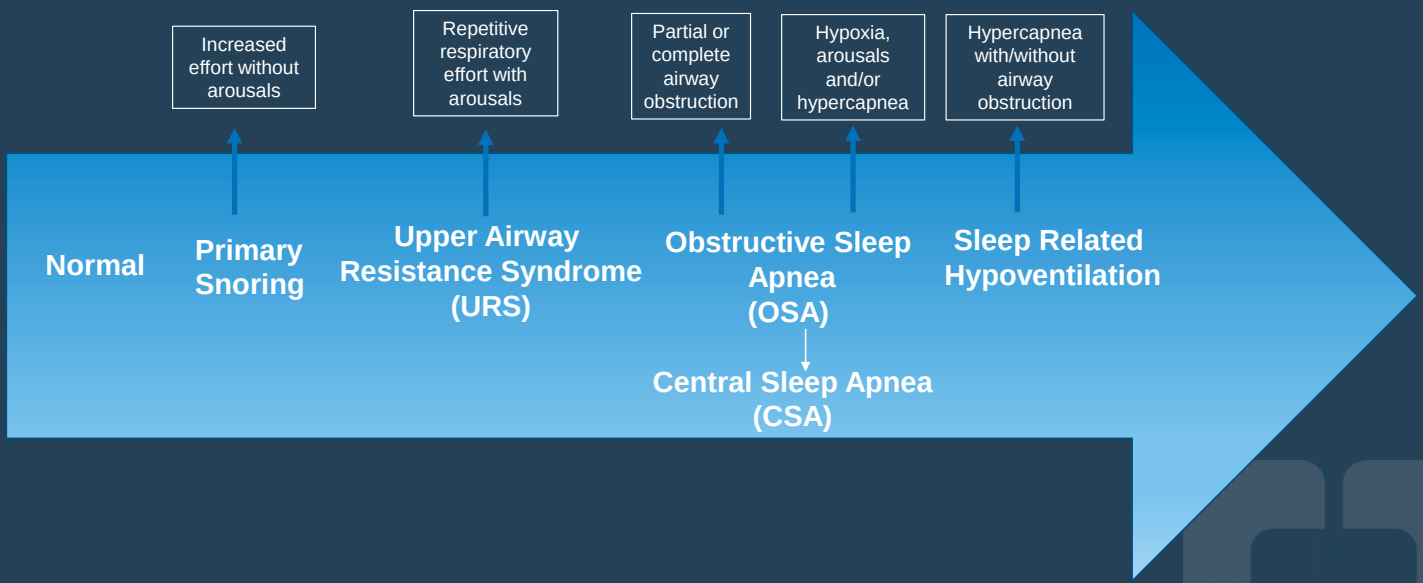
Conflict of interest

- Grant from Resmed
- PI of PAS for Inspire
- Grant support from Inspire

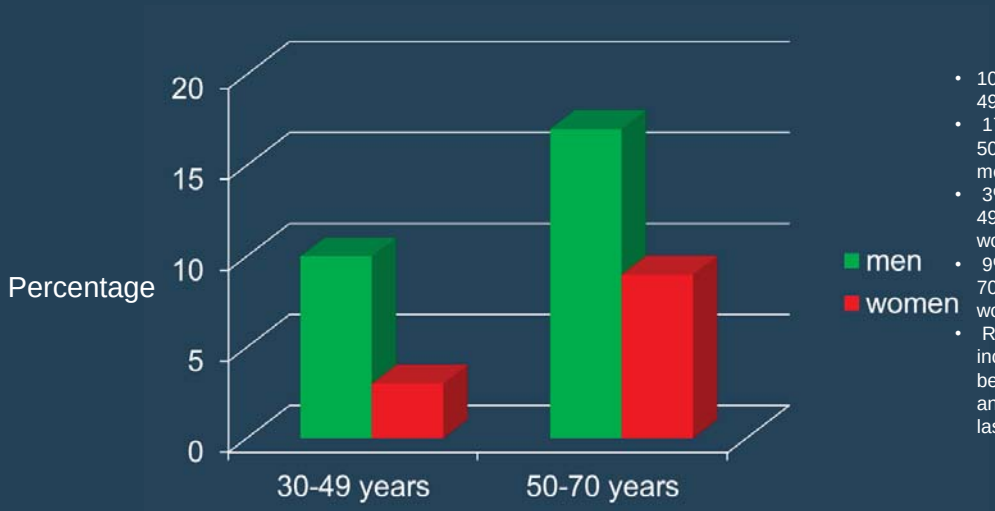
Outline

- Epidemiology of sleep apnea and Stroke
- Biophysiological mechanisms linking Stroke in OSA
- Review data on post stroke screening and treatment of sleep apnea

Sleep Disordered Breathing (SDB)



Increased prevalence of Sleep Disordered Breathing with increasing age

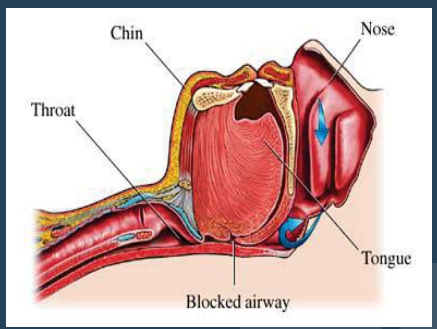


- 10% among 30–49-year-old men
- 17% among 50–70-year-old men
- 3% among 30–49-year-old women
- 9% among 50–70 year-old women
- Relative increases of between 14% and 55% in the last 2 decades

Peppart et al, Amer Jour of Epid, 2013, April 14

Obstructive Sleep Apnea

- Repetitive airway obstruction or collapse occurring during SLEEP
- Prevalence is 10-25 %
- OSA → physiologic perturbations → intermittent hypoxia, ventilatory overshoot hyperoxia, intrathoracic pressure alterations, autonomic instability & sleep fragmentation

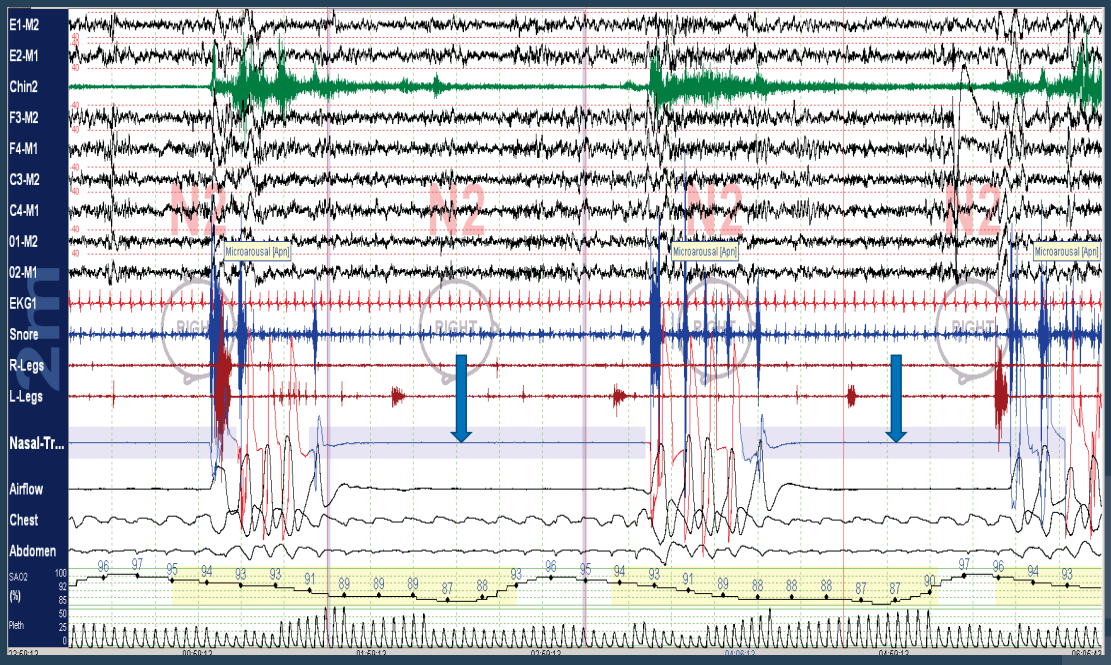


Sleep Apnea Thresholds/Severity Grades

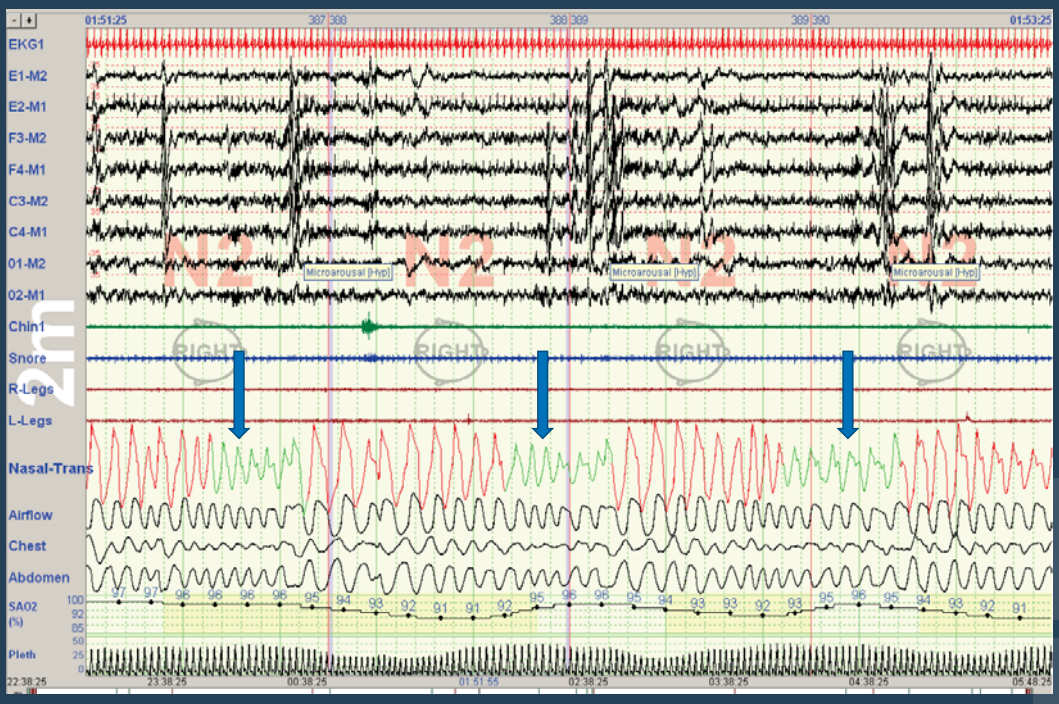
- **Apnea Hypopnea Index (AHI), Respiratory Event Index**
  - Number of apneas plus hypopneas per hr of sleep

  - AHI < 5: Normal (in adults)
  - AHI 5-15: Mild abnormality
  - AHI 15-30: Moderate abnormality
  - AHI ≥ 30: Severe

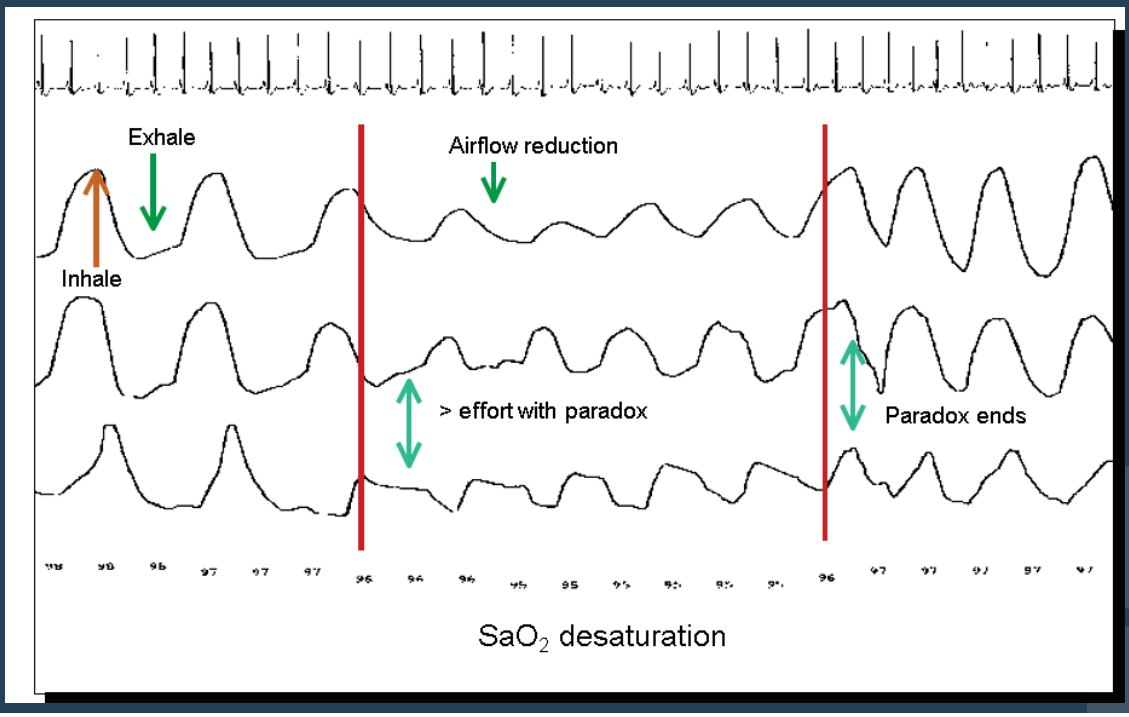
Obstructive Apneas



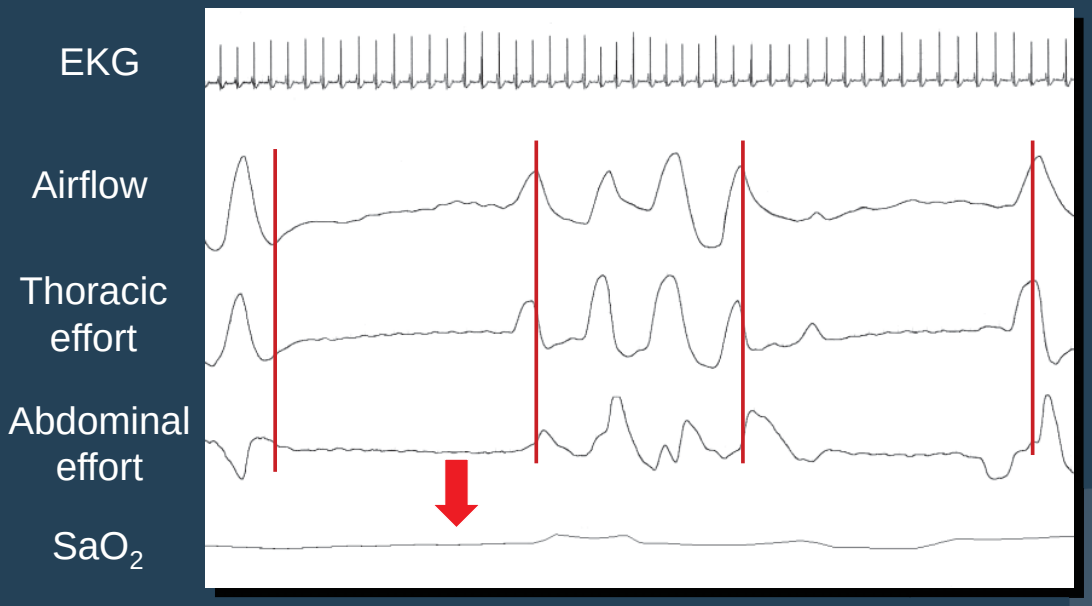
Hypopneas



Obstructive Hypopneas



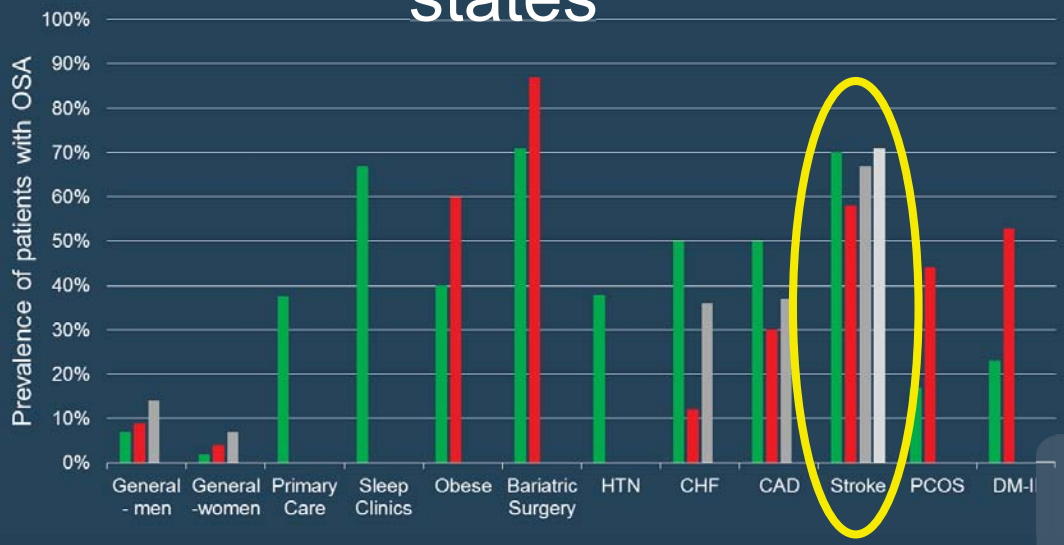
Central Apneas



Two central apneas with minimal oxygen desaturation

*Observed with narcotics

Prevalence of OSA in stroke compared to other disease states



OSA defined as either AHI≥10 or 15
Each bar in the figure represents an individual study

OSA and Stroke: Shared risk factor ?

- Hypertension
- Diabetes
- Dyslipidemia
- Atrial Fibrillation

Goldstein et al. *Circulation.* 2001:103:163

OSA as a risk factor for Stroke and Death

Adjusted for age, sex, race, Smoking, alcohol, BMI, DM, HL, Afib, HTN

HR: 1.97; 95 % CI, 1.12 to 3.48; P=0.01)

Yaggi, NEJM 2005

Obstructive Sleep Apnea and Incident Stroke in Men

Covariate	Unadjusted	Age-Adjusted	Fully-Adjusted*
Quartile of AHI			
IV: 19.13 – 164.5	3.91 (1.55 – 9.86)	3.05 (1.21 – 7.72)	2.86 (1.10 – 7.39)
III: 9.50 – 19.12	2.35 (0.89 – 6.20)	1.97 (0.74 – 5.21)	1.86 (0.70 – 4.95)
II: 4.05 – 9.49	1.96 (0.71 – 5.40)	1.86 (0.68 – 5.13)	1.86 (0.67 – 5.12)
I: 0.00 – 4.04)	1.00	1.00	1.00

*Adjusted for age, BMI, smoking status, SBP, blood pressure medications, diabetes, and race

Redline et al. Am J Respir Crit Care Med Vol 182. pp 269–277, 2010

Nocturnal Hypoxia: Predictor of Stroke

Older men (n=3028) with severe nocturnal hypoxemia (≥ 10% of the night with SpO2 levels below 90%) had a 1.8-fold increased risk of incident stroke compared to those without nocturnal hypoxemia (HR= 1.83; (1.12–2.98; P trend = 0.02).

Percent of sleep time with SaO2<90%		
< 1% (reference)	1.00 (reference)	1.00 (reference)[1]
1 to <3.5%	1.29 (0.87-1.92)	1.32 (0.88-1.99)
3.5% to < 10%	1.24 (0.74-2.07)	1.14 (0.66-1.96)
>10%	1.87(1.12-2.98)	1.66 (0.99-2.79)
P trend	0.02	0.09

[1]Adjusted for DM, CODP,HF, HT, Cholesterol, statins use, HDL

Stone KL, et al Sleep. 2016

Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Nocturnal Desaturation is Associated With Atrial Fibrillation in Patients With Ischemic Stroke and Obstructive Sleep Apnea

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JCSM
Journal of Clinical Sleep Medicine

COMMENTARY

Clarifying the Role of Hypoxia in Obstructive Sleep Apnea as a Potential Promulgator of Atrial Fibrillation in Ischemic Stroke

Commentary on Chen et al. Nocturnal desaturation is associated with atrial fibrillation in patients with ischemic stroke and obstructive sleep apnea. *J Clin Sleep Med.* 2017;13(5):729–735.

Reena Mehra, MD, MS[1]; James Bena, MS[2]; Harneet K. Walia, MD[1]

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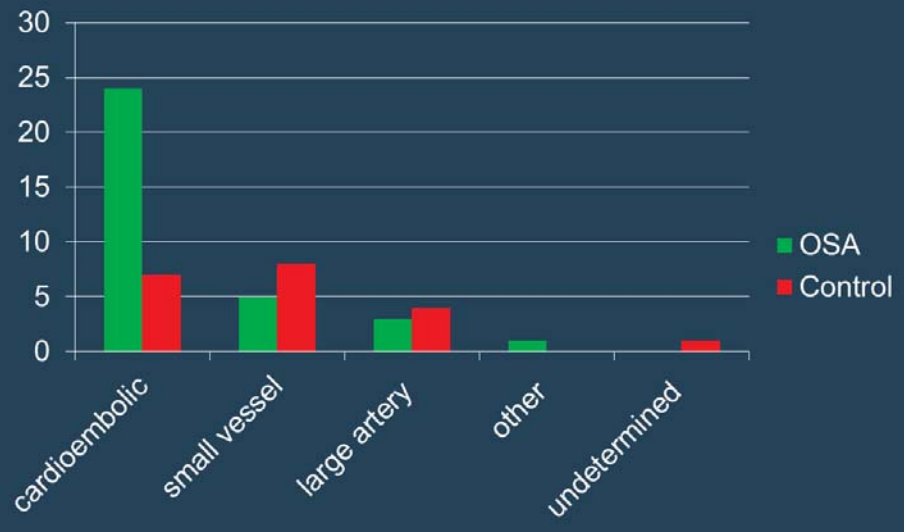
Association of cardioembolic stroke and OSA



Lipford, SLEEP 2015

Wake-up Stroke

- Stroke arising during the major sleeping period counts for 14-29.6% of all ischemic stroke
- Pathophysiology has not been well described but data suggest that WUS vs Non-WUS are more likely to have severe OSA (38.5% vs 8.9%; p=0.003) with more severe hypoxia

Hsieh S, J Neurol. 2012

Prevalence of OSA after stroke

- AHI>5: 71%(95%CI 66.6%-74.8%)
- AHI>30/h: 30 %(95%CI 24.4%-35.5%)

After 1, 1-3, 3 months

- CSA (AHI>5) was 12% (95% CI 5.5%–23.4%)

Seiler, Neurology. 2019

Sleep-disordered breathing is associated with recurrent ischemic stroke

Brown et al Stroke, 2020

Sleep disturbance predicts future health status after stroke

Running title: Sleep symptoms predict health status after stroke

Irene L. Katzan, MD, MS[1,2]; Nicolas R. Thompson, MS[1]; Harneet K. Walia, MD[3]; Douglas E. Moul, MD, MPH[3]; Nancy Foldvary-Schaefer, DO, MS[3]

Dependent Variable	Estimate of PROMIS Sleep Disturbance (95% Confidence Interval)	Holm-Adjusted P-value
PHQ-9 on PROMIS Metric (N=428)	**0.21 (0.13, 0.29)**	**< 0.001**
PROMIS Physical Function (N=468)*	**-0.14 (-0.20, -0.07)**	**< 0.001**
PROMIS Fatigue (N=459)	**0.16 (0.08, 0.23)**	**< 0.001**
PROMIS Anxiety (N=455)	0.10 (0.01, 0.18)	0.064
PROMIS Pain Interference (N=438)	0.06 (-0.02, 0.14)	0.275
PROMIS Satisfaction with Social Roles (N=431) *	-0.14 (-0.23, -0.05)	0.010
NeuroQol Executive Function (N=332) *	**-0.05 (-0.15, 0.06)**	**0.352**

In each model, the dependent variable is the follow-up PROMIS/NeuroQol domain score, and the independent variable is the baseline PROMIS sleep disturbance score. Covariate includes corresponding baseline PROMIS/NeuroQoL score and the variables: baseline PHQ-9 on PROMIS Metric, age, sex, race, marital status, median income by ZIP code, baseline modified Rankin Scale score, time since stroke, and interval between PROM measurements. *higher scores indicate better functioning

In press, Journal of Clinical Sleep Medicine

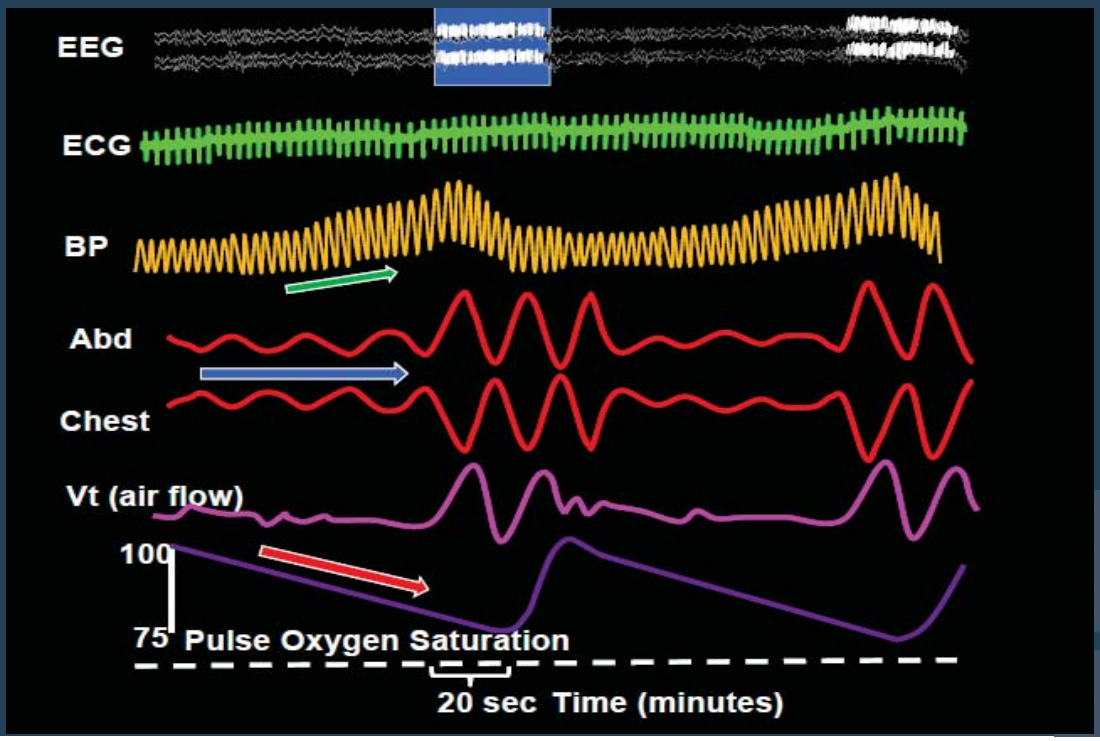
Central Sleep Apnea in Stroke

- Cheyne Stokes Respiration (CSR) and Central Sleep Apnea (CSA) can also been seen in stroke patients
- Prevalence 10%-40% in the initial days following stroke
- Commonly resolves within 1-3 months of acute stroke
- The effects of CSA on stroke outcome and the role of early therapy for CSA after stroke are unclear.

Hermann D, Stoke, 2007

Pathophysiology linking sleep apnea and stroke

Pathophysiological Effects



Sympathetic Nervous System Activity in Sleep Apnea

Decrease CPAP pressure from 8 to 6

Somers et al. *J Clin Invest*. 1995;96:1897.

BP = blood pressure; CPAP = continuous positive airway pressure; REM = rapid eye movement; RESP = respiration; SNA = sympathetic nerve activity

Bidirectional relationship

Alexiev F, J Thorac Dis 2018

Physiologic changes in sleep in patients with OSA

Yaggi, H Lancet, 2004

Other Direct Mechanism relating to Stroke

Cerebral blood flow velocity is decreased by the negative intrathoracic pressure
Alternatively, cerebrovascular dilatory responses to hypoxia in patients with OSA may be decreased
Recurrent reductions of cerebral blood flow velocity then precipitate ischemic changes in patients with poor hemodynamic reserve (e.g, intracranial arterial stenosis)

Beaudin, J Am Heart Assoc,
Behrens, Sleep Breath, 2002

Outcomes

- Stroke patients with OSA have worse:
  - Cognitive functioning
  - Worse functional capacity
  - Reduce motility
  - Greater impairment ADL
  - Longer stays in inpatient rehabilitation than those without OSA

Aaronson J, Sleep. 2015

Impact of Treatment of Sleep Apnea on Stroke

CPAP Reduces Incident Nonfatal CV Events in Stroke Patients with OSA

- 223 patients admitted for stroke w/ 7 yr follow-up
- Pts w/AHI ≥20 CPAP intolerant had increased adj incidence of nonfatal CVE esp. new ischemic stroke (HR 2.87, 95% CI 1.11-7.71, p 0.03) compared w/other groups

Martı´nez-Garcı´a MA. Eur Respir J 2012; 39: 906–912.

Effect of CPAP on hospitalized patients post stroke with OSA

- RCT, single center
- CPAP x 4 weeks (n= 20 AHI ≥ 15 but < 60/h) vs control group (n=16 nCPAP) for 28 days

<u>Results:</u>

- CPAP improved attention (p=0.04) and executive functioning (0.001)

Aaronson et al, JCSM 2016

Improvement in Neurological parameters

Parra, Eur Respir J. 2011.

RCT of PAP the effect on stroke

- 34 in CPAP and 24 in non CPAP group
- At 12-month follow-up, there was 1 vascular event (3.33%) in the CPAP group and 6 events (15%) in the non-CPAP group (*P* = .23)
- Modified Rankin scale score improvement by ≥ 1 at 12-month follow-up was found in significantly more patients in the CPAP group than in the non-CPAP group (53% versus 27%).

Gupta et al, JCSM, 2018

CPAP as treatment of sleep apnea after stroke
A meta-analysis of randomized trials

- 10 RCTs, n=564
- 2 studies CPAP with sham CPAP, 8 CPAP to usual care
- Neurofunctional improvement with CPAP (NIH Stroke scale and Canadian Neurological scale) SMD 0.5406
- Large trials are needed

Brill 2018 Apr 3;90(14):e1222-e1230.

CPAP for Prevention of Cardiovascular Events in Obstructive Sleep Apnea

R. Doug McEvoy, M.D., Nick A. Antic, M.D., Ph.D., Emma Heeley, Ph.D., Yuanming Luo, M.D., Qiong Ou, M.D., Xilong Zhang, M.D., Olga Mediano, M.D., Rui Chen, M.D., Luciano F. Drager, M.D., Ph.D., Zhihong Liu, M.D., Ph.D., Guofang Chen, M.D., Baoliang Du, M.D., Nigel McArdle, M.D., Sutapa Mukherjee, M.D., Ph.D., Manjari Tripathi, M.D., Laurent Billot, M.Sc., Qiang Li, M.Biostat., Geraldo Lorenzi-Filho, M.D., Ferran Barbe, M.D., Susan Redline, M.D., M.P.H., Jiguang Wang, M.D., Ph.D., Hisatomi Arima, M.D., Ph.D., Bruce Neal, M.D., Ph.D., David P. White, M.D., Ron R. Grunstein, M.D., Ph.D., Nanshan Zhong, M.D., and Craig S. Anderson, M.D., Ph.D., for the SAVE Investigators and Coordinators*

ABSTRACT

BACKGROUND

Obstructive sleep apnea is associated with an increased risk of cardiovascular events; whether treatment with continuous positive airway pressure (CPAP) prevents major cardiovascular events is uncertain.

CONCLUSIONS

Therapy with CPAP plus usual care, as compared with usual care alone, did not prevent cardiovascular events in patients with moderate-to-severe obstructive sleep apnea and established cardiovascular disease. (Funded by the National Health and Medical Research Council of Australia and others; SAVE ClinicalTrials.gov number, NCT00738179; Australian New Zealand Clinical Trials Registry number, ACTRN12608000409370.)

CPAP therapy may reduce the risk of stroke in patients with good adherence and with moderate to severe OSA

Lin et al, Sleep Medicine Reviews, 54 (2020) 101354

Most attrition occurs in first 3 months of PAP

Kendrezerska et al, Sleep and Breathing, 2019

Treatment of OSA in Stroke

- Treating OSA in acute ischemic stroke remains a challenge
  - They have poor tolerance of CPAP interfaces, and difficulty putting masks back on during the night
- Oral appliances, hypoglossal nerve stimulation and weight loss are not well studied and may not be practical options

Screening of Sleep Apnea in Stroke

OSA remains under recognized and undertreated

- Despite increased recognition, OSA continues to remain largely undiagnosed, with 80% of cases unrecognized
- An in-depth cost analysis found that unrecognized OSA produces a large economic burden, costing the US $149.6 billion annually
- Therefore, identifying valid, convenient, effective and inexpensive tools to identify those individuals at high risk for OSA is of utmost importance
- Screening for classic symptoms of SA, and formal testing for SA, are rare within the first 90 days after stroke

Frost, Sullivan https://aasm.org/advocacy/initiatives/economic-impact-obstructive-sleep-apnea/
Gamaldo, JCSM, 2018

Brown, Sleep Medicine, 2019

Screening tools in sleep apnea

- Elements of the clinical history (eg, sleepiness) and physical examination (eg, BMI) are inaccurate markers for sleep apnea among patients with cerebrovascular disease.
- Specifically, stroke patients with sleep apnea do not experience the same degree of sleepiness as non-stroke patients with sleep apnea and have lower BMI values.
- The Epworth Sleepiness Scale is often normal among stroke patients with sleep apnea
- The Berlin Questionnaire also has poor positive and negative predictive values among stroke patients

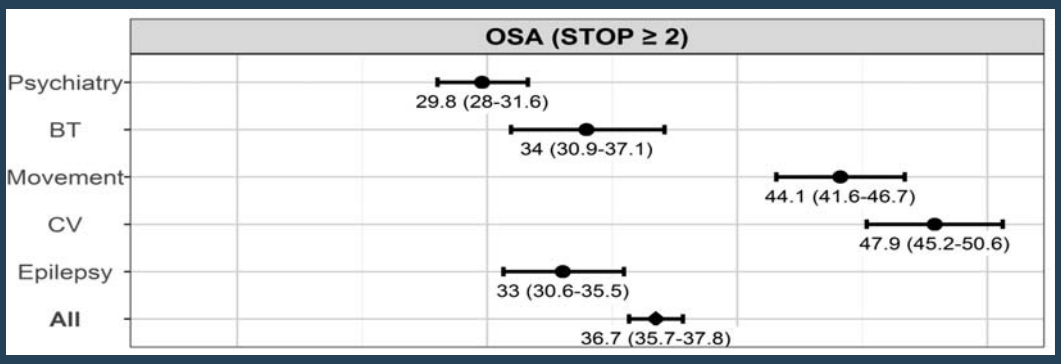
Kernan et al, Stroke, 2014

SLEEP Inventory (Sex, Left heart failure, ESS, Enlarged neck, weight [in Pounds], Insulin resistance/diabetes, and National Institutes of Health Stroke Scale) performed modestly better

Sico et al, Journal of Stroke Cerebrovascular disease, 2017

Sleep apnea screening in CCF

Retrospective analysis of 19,052 first visits from March 2015 to October 2016



- The high rate of positive STOP screens reduced its clinical utility
- Prompted development of revised sleep apnea screen using clinically-derived data from the EHR and polysomnograms of cerebrovascular patients

Walia et al, APSS, 2017

Optimization of OSA Screen
Performance of 6 Models

Models

STOP: Snore (yes/no), tired (yes/no), Stop Breathing (yes/no), High BP (yes/no)

STOP-BANG: STOP score + additional points if: BMI > 35 kg/m^2, age > 0 years, neck circumference > 40 cm, or male gender

STOP-BAG: same as STOP-BANG excluding neck circumference

STOP-BANG$_2$: STOP score + continuous BMI, continuous age, continuous neck circumference, and male sex

STOP-BAG$_2$: STOP score + continuous BMI, continuous age, and male sex

STOP-BAG$_2$+: STOP score + continuous BMI, continuous age, male sex, history of heart disease (yes/no), self-reported average number of hours of sleep per night, smoker status (Never, Former, Current)

Optimization of OSA Screen
Performance of Models

Sensitivity and Specificity of Different Cutpoints

	Cutpoint	Sensitivity (95% CI)	Specificity (95% CI)	
STOP	2	0.85 (0.78-0.91)	0.40 (0.29-0.51)	old
STOP-BANG	3	0.94 (0.89-0.98)	0.47 (0.36-0.58)	
STOP-BAG	2	0.99 (0.96-1.00)	0.19 (0.11-0.29)	
	3	0.91 (0.85-0.96)	0.48 (0.37-0.60)	
STOP-BANG$_2$	0.311	0.94 (0.89-0.98)	0.53 (0.42-0.64)	
STOP-BAG$_2$	0.395	0.94 (0.89-0.98)	0.60 (0.49-0.71)	new

Sensitivities and specificities for different cutpoints using the various models predicting AHI ≥ 10.
The cutpoints for the STOP-BANG$_2$, STOP-BAG$_2$, and STOP-BANG$_2$+ are based on predicted probabilities for the respective models

Katzan et al, Sleep Medicine 2016;21:70–76

JCSM | Journal of Clinical Sleep Medicine

SCIENTIFIC INVESTIGATIONS

Sleep-related symptoms in patients with mild stroke

Irene L. Katzan, MD, MS[1,2]; Nicolas R. Thompson, MS[1]; Harneet K. Walia, MD[3]; Douglas E. Moul, MD, MPH[3]; Nancy Foldvary-Schaefer, DO, MS[3]

[1]Neurological Institute Center for Outcomes Research & Evaluation, Cleveland Clinic, Cleveland, Ohio; [2]Cerebrovascular Center, Cleveland Clinic, Cleveland, Ohio; [3]Sleep Disorders Center, Neurological Institute, Cleveland Clinic, Cleveland, Ohio

	All Patients	Ischemic Stroke	Transient Ischemic Attack	Intracerebral Hemorrhage	Subarachnoid Hemorrhage	P-value
PROMIS Sleep Disturbance score ≥ 55	28.6% (624/2183)	27.4% (382/1393)	31.9% (121/379)	27.8% (58/209)	31.2% (63/202)	0.291
ISI Score ≥ 15	17.6% (142/808)	17.2% (88/513)	19.5% (38/195)	10.0% (6/60)	25.0% (10/40)	0.216
SAPS ≥ 0.5	**61.3% (761/1241)**	**63.8% (496/777)**	**67.3% (140/208)**	**52.8% (65/123)**	**45.1% (60/133)**	**< 0.001 †**

	All Patients with Date of last Event	< 90 days	90-365 days	> 365 days	P-value
PROMIS Sleep Disturbance score ≥ 55	27.7% (440/1589)	25.9% (197/761)	29.6% (114/385)	29.1% (129/443)	0.302
ISI Score ≥ 15	16.4% (84/512)	14.1% (43/305)	22.6% (28/124)	15.7% (13/83)	0.097
SAPS ≥ 0.5	62.8% (579/922)	63.3% (278/439)	62.3% (142/228)	62.4% (159/255)	0.951

Poor correlation between SAPs score and other patient-reported sleep scores

Cerebrovascular patients February 17, 2015 to July 5, 2017

		Pairwise Spearman Correlations	
		Insomnia Severity Index (ISI)	SAPS
All Patients (N = 2190)	PROMIS Sleep	0.86 (0.84, 0.88)	0.02 (-0.04, 0.08)
	ISI		0.04 (-0.05, 0.13)
Ischemic Stroke (N = 1396)	PROMIS Sleep	0.85 (0.82, 0.88)	0.01 (-0.05, 0.09)
	ISI		0.04 (-0.07, 0.15)
Transient Ischemic Attack (N = 380)	PROMIS Sleep	0.90 (0.86, 0.92)	-0.04 (-0.17, 0.09)
	ISI		0.03 (-0.16, 0.21)
Intracerebral Hemorrhage (N = 210)	PROMIS Sleep	0.87 (0.72, 0.93)	0.15 (-0.02, 0.31)
	ISI		0.12 (-0.23, 0.44)
Subarachnoid Hemorrhage (N = 204)	PROMIS Sleep	0.80 (0.59, 0.91)	0.09 (-0.10, 0.27)
	ISI		-0.02 (-0.43, 0.36)

Katzan, et al, JCSM 2020

Upcoming Trial: Sleep SMART Sleep for Stroke Management and Recovery Trial

- 3062 randomized subjects
- Multicenter, prospective, open, blinded outcome with confirmed OSA randomized to CPAP plus usual care or care as usual
- Outcomes, composite of recurrent acute ischemic stroke, ACS, all cause morality and modified rankin

Brown et al, Int J Stroke, 2020

Other ongoing study

- **Can respiratory muscle training therapy effectively manage obstructive sleep apnea syndrome after stroke?: A protocol of systematic review and meta-analysis**

Guo, Medicine, 2020

Conclusions

- Sleep Apnea is under recognized in stroke patients, however it represent a therapeutic target that could lead to improve functional recovery
- PAP may help in preventing stroke in those with good PAP adherence
- PAP could improve functional outcomes after stroke.
- Tools that combine clinical information with patient symptoms, such as the SAPS tool or the SLEEP Inventory improve the ability to predict sleep apnea compared to symptoms alone.

Every life deserves **a good night's sleep**

Cleveland Clinic