Sleep and Stroke

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Objectives

1. Understand what sleep apnea is
2. Understand the relationship between sleep apnea and stroke.
3. Understand the relationship between insomnia and stroke

Why Sleep Apnea and Stroke?

Sleep Apnea

- One billion people world wide

Stepenowsky 2019

Stroke

- 80 million people world wide
- Leading cause of adult disability

Johnson 2019

Sleep Apnea and Stroke

Sleep apnea is present in > 50% of stroke survivors

Sleep Apnea (SA)

- Sleep related breathing disorders composed of the following events:
  - Apneas: Cessation of breathing and/or
  - Hypopneas: Partial reduction in airflow
- Two types of sleep apnea:
  - Central (CSA)
  - Obstructive (OSA)

SA Types

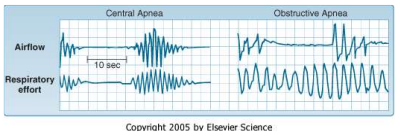

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Figure shows the relation between airflow and respiratory effort in demonstrating an obstructive and a central apnea. During a central apnea, there is cessation of airflow for at least 10 seconds with no associated ventilatory effort. An obstructive apnea is defined as a similar cessation of airflow but with continued respiratory effort.

Image from Chapter 81 Principles and Practice of Sleep Medicine

SA Severity

- Apnea and Hypopnea Index (AHI) = total of the apneas and hypopneas noted per hour of sleep.

AHI	Severity
5 to < 15	Mild
15 to < 30	Moderate
30 or more	Severe

OSA ICSD 3TR Definition

- Repetitive episodes of complete (apnea) or partial (hypopnea) upper airway obstruction occurring during sleep.
- These events may lead to arousal from sleep and/or desaturation.

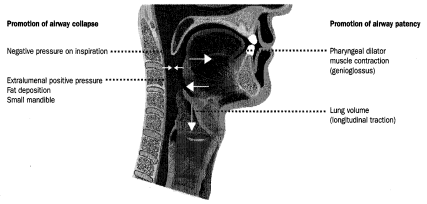
Epidemiology of OSA

- Incidence in United States approximately 8% of population.
  - Men more commonly than women
- Certain subpopulations at increased risk
  - Ie Stroke, Downs syndrome
- Obesity not necessary for diagnosis

Symptoms of OSAS

- Nighttime
  - Snoring
  - Witnessed apneas
  - Dyspnea upon awake
  - Restlessness
  - Nocturia
  - Diaphoresis
  - Reflux
- Daytime
  - Sleepiness
  - Fatigue
  - Depression
  - Poor concentration
  - Inattention
  - Morning headaches
  - Decreased Libido

Pathophysiology of OSA – The Pharyngeal Airway

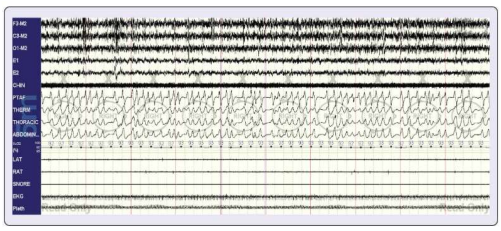


CSA ICSD 3TR Definition

- Repetitive episodes of complete (apnea) or attenuated (hypopnea) drive to breathe during sleep.
- These events may lead to arousal and/or desaturation.
- Two main types:
  - Cheyne-Stokes Respirations (CSR)
  - Ataxic Breathing
  - Either type can be seen after a stroke

Central Sleep Apnea

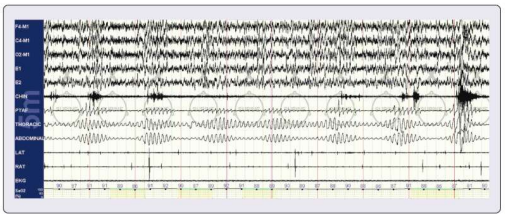
CSA Ataxic Subtype: ie Opiate induced



Five minute window
Chapter 125 Principles and Practice of Sleep Medicine 7th edition

Central Sleep Apnea

CSA Cheyne Stokes Breathing Subtype: ie CHF induced, Stroke induced



Five minute window
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Sleep Apnea and Stroke

Frequency of SA Post Stroke

- SA is common post stroke
- Meta analyses by Seiler (2019) on the frequency of SA post stroke
  - SA defined as AHI > 5
  - SA of any severity seen in 71% of patients
  - Severe SA seen in 30% of patients

What Type of SA Post Stroke

- OSA is the most common form of SA post stroke
- Frequency of CSA post stroke is 8-12% (Seiler 2019, Dong 2018)
  - Lack of scoring of central hypopneas may lead to an underestimation of central sleep apnea frequency

Course of Post Stroke SA

- Prospective longitudinal study of sleep apnea post stroke (Ott 2020)
- Of patients with SA in the acute phase, 91% still had SA at the three month mark.

Course of Post Stroke SA Ott 2020

Acute phase		3-months follow-up			
		No-SDB	OSA	CSA	Total
	No-SDB#	10 (66.7%)	4 (26.7%)	1 (6.7%)	15 (14.4%)
	OSA¶	7 (9.9%)	56 (78.9%)	8 (11.3%)	71 (68.3%)
	CSA¶	1 (5.6%)	9 (50%)	8 (44.4%)	18 (17.3%)
	Total	18 (17.3%)	69 (66.3%)	17 (16.3%)	104

- 33% of survivors who had no SA at baseline had SA at 3 months
- 50% of survivors who had CSA at baseline had OSA at 3 months

Clinical Implications

- Consider re-evaluation after 3 months if diagnosed with SA in acute phase.
  - Why? To assess for presence, severity and type of SA

Diagnosis

- Screen stroke patients for SA:
  - Ask about snoring, apneas
  - Screening Questionnaires
    - Ie Stop Bang
    - Screening questionnaires have a high sensitivity and low specificity in stroke patients (Takala 2018)

When to Test for SA

- European guidelines: Recommend evaluation for and treatment of SA in the acute phase of stroke (Bassetti 2020)
- AHA guidelines: Do not recommend evaluation in the acute phase

Why the difference?

- SA may improve after the acute stroke period so delaying testing would allow for identification of patients with more stable/persistent SA.
  - This assumes there is no benefit to treatment of SA in the acute phase.
- There is an assumption in the US that acute stroke patients will not tolerate SA therapy

How to Diagnose

- AASM recommends in lab PSG post stroke but access problematic
  - PSG in lab better at distinguishing CSA and OSA
- Baillieul et al (2022) suggest use of a HST in the acute stroke period unless significant co-morbidies present (ie COPD or CHF)

Chicken or the Egg?

- Is OSA the cause or the consequence of stroke?

OSA = Stroke Risk Factor

- Stroke severity, lesion topography and cause do not generally correlate with severity or type of sleep apnea.
- Frequency of sleep apnea same in stroke and TIA patients

OSA Consequences

Effect	Magnitude (odds ratio)	Reference
Neurocognitive		
MVAs	7	Tehren-Santos
Occ. accidents	2.2	Lindberg
Cardiovascular		
Prevalent hypertension	1.2 – 1.4	Nieto
Incident hypertension	1.3 - 2.9	Peppard
Coronary disease	1.3 – 2.3	Shahar, Hung
Stroke	1.6	Shahar
Congestive heart failure	2.4	Shahar

Acute and Long-term Pathophysiological Mechanisms of Obstructive Sleep Apnea Leading to Stroke

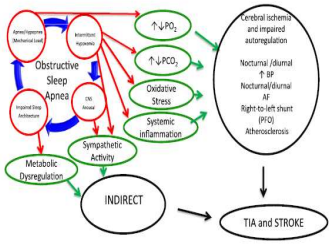


Fig. 2. The depicts the proposed mechanisms linking OSA to stroke. PFO = Patent foramen ovale; AF = atrial fibrillation; ↑ = increase; ↓ = decrease; TIA = Transient ischemic attack.

Javaheri 2022

Stroke Survivors with SA

1. Stroke recurrence higher and
2. Outcomes worse

Recurrent Stroke

- Population based prospective cohort of 842 patients with ischemic stroke
- Association between sleep apnea (REI > or = 10) and recurrent ischemic stroke after 591 days
  - But not all cause mortality
  - See next slide

Brown 2019

Recurrent Stroke

Table 2. Association Between REI With Recurrent Ischemic Stroke (n=775,* Events=84)

Parameter	HR	Lower CI	Upper CI	*P* Value	HR	Lower CI	Upper CI	*P* Value
REI	1.02	1.01	1.03	<0.01	1.02	1.01	1.03	<0.01
Mexican American					1.31	0.80	2.14	0.29
Age					0.99	0.97	1.01	0.50
Female					1.34	0.86	2.11	0.20
Body mass index					1.00	0.97	1.04	0.99
Diabetes mellitus					1.24	0.78	1.98	0.36
Hypertension					0.98	0.53	1.84	0.96
NIHSS					0.96	0.91	1.01	0.08

HR indicates hazard ratio; NIHSS, National Institutes of Health Stroke Scale; and REI, respiratory event index.
*Adjusted analysis included n=775; unadjusted analysis included n=778 as 3 individuals had missing NIHSS scores.

Brown 2019

Functional Outcomes

- Prospective study of165 patient with stroke shows an association between AHI and neurological outcome as assessed by the Rankin scale at 3 months (Ott 2019)

Functional Outcomes

Predictors of unfavourable neurological outcome (modified Rankin score >3) in logistic regression model (dichotomised modified Rankin 0–2 *versus* 3–6)

	OR	95% CI	p-value
Age years	0.900	0.770–1.040	0.11
Sex male	0.377	0.038–3.718	0.53
BMI $kg \cdot m^{-2}$	0.904	0.719–1.138	0.24
Admission NIHSS	1.188	0.940–1.500	0.23
Hypertension	0.238	0.011–5.383	0.22
Atrial fibrillation	0.000	0.000–∞	1.00
Stroke on awakening or during sleep (*versus* no or unknown)	15.699	0.726–339	0.10
Infratentorial stroke (*versus* other or unknown)	0.216	0.006–7.566	0.40
Cheyne–Stokes respiration	0	0–∞	0.99
Baseline AHI	1.107	1.010–1.214	0.052

BMI: body mass index; NIHSS: National Institute of Health stroke scale; AHI: apnoea–hypopnoea index.

OSA Treatment

PAP

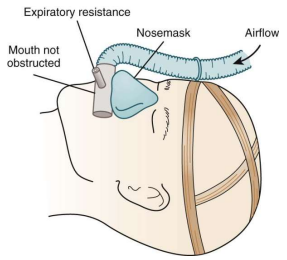
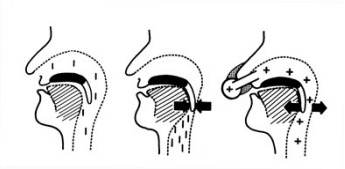


Image from Principles and Practice of Sleep Medicine 5thed

PAP



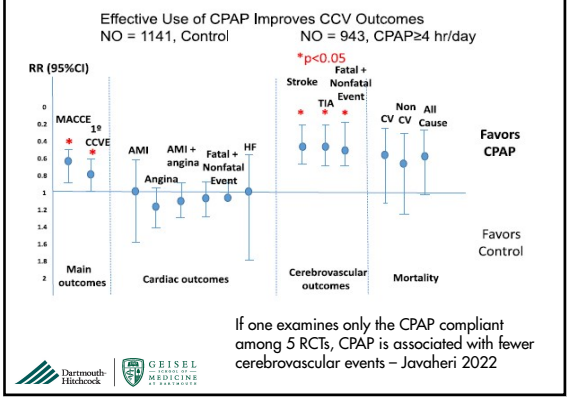
Uses air to splint the airway open at all levels

SAVE Trial McEvoy NEJM 2016

- 2717 patients with CAD and Cerebrovascular Disease and OSA randomized
  - CPAP or
  - Usual care
- Mean follow up 3.7 years
- CPAP treatment did not prevent recurrent CV events
- BUT CPAP adherence low

SAVE Trial McEvoy NEJM 2016

- If you look at only those who used CPAP at least 4 hours per night
  - Stroke risk reduced in the CPAP group
  - Non-CPAP group relative risk of stroke 2.3 x



If one examines only the CPAP compliant among 5 RCTs, CPAP is associated with fewer cerebrovascular events – Javaheri 2022

Does PAP Improve Outcomes in Stroke?

PAP and Outcomes

- Pooled data from 5 studies with 400 ischemic stroke patients with OSA
  - Better short term neurological improvement with CPAP
- Adquately powered RCT needed

Tsivgoulis G etal Stroke 2017

Non-PAP OSA Treatments

- Oral appliance
- Surgery
  - Inspire
- Not studied in stroke populations

Est. Effect of Weight Change

Peppard 2000

Percent Change in Weight	Percent change in AHI
-20 %	-48%
-10%	-26%
-5%	-14%
+5%	+15%
+10%	+32%
+20%	+70%

Take home message:
20% change in weight results in a
50% change in sleep apnea severity

Insomnia and Stroke

Insomnia

- The persistent difficulty with sleep initiation or maintenance that is associated with concern, dissatisfaction or perceived daytime impairment, such as fatigue… (ICSD3TR)

Insomnia in Stroke Survivors

Insomnia is present in 50% of stroke survivors

(Palomaki et al. Cerbrovascular Dis 2003)

Insomnia (Sterr 2018)

- Sleep study 12 months post stroke in right hemispheric stroke patients compared to age and sex matched controls
  - Stroke patients had worse sleep (longer sleep latency (p=0.035), lower sleep efficiency (p=0.018), increased WASO (p=0.014))
  - No difference in sleep apnea
  - Lesion size did not correlate with these variable

Sleep parameters	Patients	Control	difference
*Sleep latency (SL; Time to fall asleep after lights off)	23.9 ± 4.01	15.9 ± 1.96	8.0
Sleep period time (SPT; sleep onset to awakening (incl. wake))	497 ± 13.64	475.4 ± 12.6	21.6
Total sleep time (*TST; Time spend asleep (i.e. SPT- wake))	394.3 ± 14.49	403.3 ± 10.13	−9.0
Sleep efficiency (SE; % asleep as a function of time in bed)	72.0 ± 2.67	79.1 ± 1.97	−7.1
Wake since sleep onset (WASO; Time spent awake after sleep initiation)	107.2 ± 10.18	72.1 ± 8.90	30.6
% N1; % stage 1 in SPT	15.4 ± 1.88	13.3 ± 1.98	2.1
% N2; % stage 2 in SPT	45.5 ± 2.54	49.4 ± 2.51	−3.9
% N3 (slow wave sleep; % stage 3 in SPT)	1.4 ± 0.46	4.0 ± 1.84	−2.6
% REM (rapid eye movements; REM sleep in SPT)	17.2 ± 1.01	18.3 ± 1.15	−1.1

Table 1. mean and standard error of sleep stage characteristics; *time in minutes.

Insomnia Treatment

- Cognitive behavioral therapy for insomnia (CBTI) effective post stroke in 5 patients (Herron 2018)

Table 3b. Clinically meaningful change is indicated when a participant report falls within at least 1*SD* of normal* and insomnia† populations

Case	Sleep diary parameter	Pre-treatment	Post-treatment	Post minus pre	Follow-up
P1	SOL (min)	300†	75†	−225	210†
	SD (min)	180†	210†	+30	200†
	SE (%)	37.5†	55.7†	+17.2	43.9*
P2	SOL (min)	32.1†	14.3*	−17.8	17.5*
	SD (min)	402.9†*	419.3†*	+16.4	410†*
	SE (%)	74.6†	85.8*	+11.2	84.8*
P3	SOL (min)	115†	51.4†	−63.6	80†
	SD (min)	287†	334†	+47	330†
	SE (%)	57.1†	74.3†*	+17.2	70.7†
P4	SOL (min)	60†	35†*	−25	52†
	SD (min)	385†*	415†*	+30	450†*
	SE (%)	80.6†*	83.4†*	+10.4	91†*
P5	SOL (min)	10*	13.6*	+3.6	11.9*
	SD (min)	445†*	462*	+17	462*
	SE (%)	89.1*	96.2*	+7.1	94.9*

Insomnia as a Stroke Risk Factor

Insomnia and Incident Stroke

(Wu 2014)

- Insomnia patients had a 54% increased increase in risk of stroke compared to controls
- Greatest risk in those with persistent insomnia

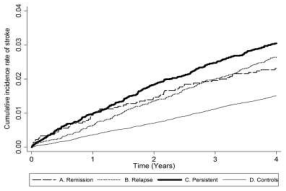


Figure. Kaplan–Meier survival curves for stroke in by insomnia group and insomnia subtypes. Results of the log-rank tests comparing cumulative incidence rate of stroke for 4 years between insomnia groups: overall *P* value <0.0001. A vs B: *P* value=0.3618; A vs C: *P* value=0.0508; A vs D: *P* value=0.0008; B vs C: *P* value=0.0928; B vs D: *P* value <0.0001; and C vs D: *P* value <0.0001.

The Other Category

Shift Work

Table 2. Hazard Ratio of Ischemic Stroke by Years of Working Rotating Night Shifts, Nurses' Health Study, 1988–2004

Type of Ischemic Stroke	Duration of Rotating Night Shift Work[a,b]								Hazard Ratio for Years of Shift Work	P_{trend}
	Never	1–2 Years	3–5 Years	6–9 Years	10–14 Years	15–19 Years	20–29 Years	≥30 Years		
Confirmed + probable										
No. of cases	622	343	287	130	88	68	63	59		
Time-adjusted[c] hazard ratio	1.00	0.96	1.01	1.16	1.11	1.43	1.34	1.47	1.07	<0.001
95% confidence interval		0.84, 1.09	0.88, 1.16	0.96, 1.40	0.89, 1.40	1.11, 1.84	1.03, 1.74	1.12, 1.92	1.04, 1.10	
Fully adjusted[d] hazard ratio	1.00	0.99	1.00	1.10	0.99	1.24	1.17	1.32	1.04	0.01
95% confidence interval		0.87, 1.13	0.87, 1.15	0.91, 1.33	0.79, 1.24	0.96, 1.59	0.90, 1.52	1.00, 1.73	1.01, 1.07	
Confirmed only										
No. of cases	437	237	197	92	57	54	43	35		
Time-adjusted[c] hazard ratio	1.00	0.94	0.98	1.16	1.05	1.65	1.29	1.22	1.06	0.002
95% confidence interval		0.80, 1.10	0.83, 1.16	0.92, 1.45	0.79, 1.38	1.24, 2.20	0.94, 1.77	0.86, 1.73	1.02, 1.10	
Fully adjusted[d] hazard ratio	1.00	0.96	0.96	1.09	0.94	1.42	1.13	1.11	1.03	0.10
95% confidence interval		0.82, 1.13	0.81, 1.14	0.87, 1.36	0.71, 1.24	1.07, 1.89	0.82, 1.55	0.78, 1.57	0.99, 1.07	

[a] At least 3 nights per month of night shift work in addition to days or evenings in that month.
[b] Never (458,880 person-years of follow-up); 1–2 years (274,665 person-years); 3–5 years (168,648 person-years); 6–9 years (76,393 person-years); 10–14 years (51,029 person-years); 15–19 years (30,882 person-years); 20–29 years (29,846 person-years), and ≥30 years (18,702 person-years).
[c] Adjusted for age and questionnaire cycle.
[d] Adjusted for age, questionnaire cycle, hypertension, coronary heart disease, diabetes, elevated cholesterol, aspirin use, body mass index, smoking, alcohol consumption, fruit and vegetable consumption, physical activity, menopausal status, and use of hormone replacement therapy.

Increased stroke risk in shift workers (Nurses Health Study, Brown 2009)

Sleep Duration (He 2017)

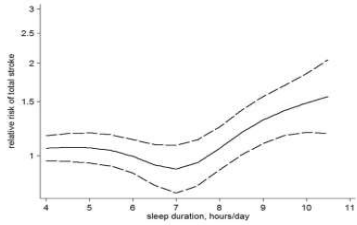


Fig. 3. The nonlinear association between sleep duration and total stroke incidence.

Risk of stroke higher in those sleeping above or below 7 hrs

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