The Cardiovascular Effects of Sleep Disorder Breathing

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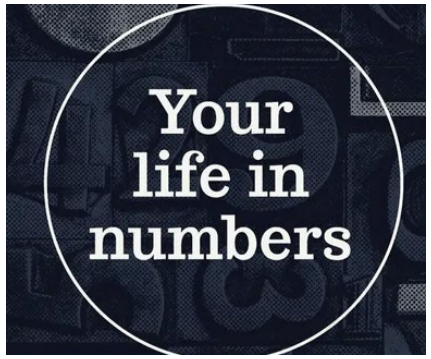
- No disclosures

Objectives

1. Recognize and diagnose patients with Obstructive Sleep Apnea (OSA).

2. Understand the pathophysiologic mechanisms that are associated with the cardiovascular consequences of OSA.

3. Understand the current and emerging treatment options for OSA.



In bed

33 YRS [12045 DAYS]

Throughout our lives, we spend an enormous 26 years sleeping. Surprisingly, we also spend 7 years trying to get to sleep. That's 33 years or 12,045 days spent in bed!

Sleeping
26 YRS

BUT WHAT'S SO SPECIAL ABOUT SLEEP?

Boosts mental health

Improves phsycial wellbeing

- Immunity
- Weight regulation
- Fertility

Trying to sleep
7 YRS

IF YOU'RE TOSSING & TURNING TRY:

Breathing exercises

Reading a book

A Relaxing bath

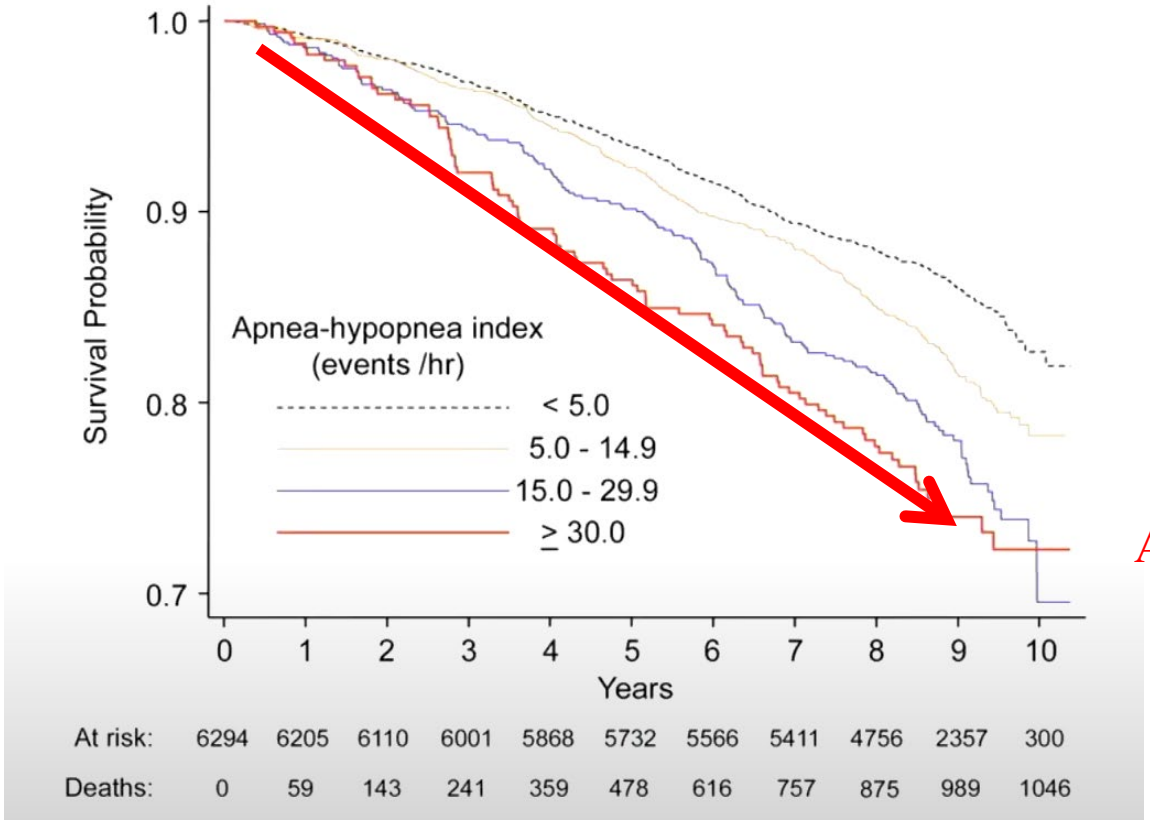
AHA Life's Essential 8 (2022)

American Heart Association.

- Despite its high prevalence in patients with heart disease, the most common type of sleep disordered breathing -- OSA --is often under-recognized and under-treated in cardiovascular practice.

  JAm Coll Cardiol. 2017;69:841–858

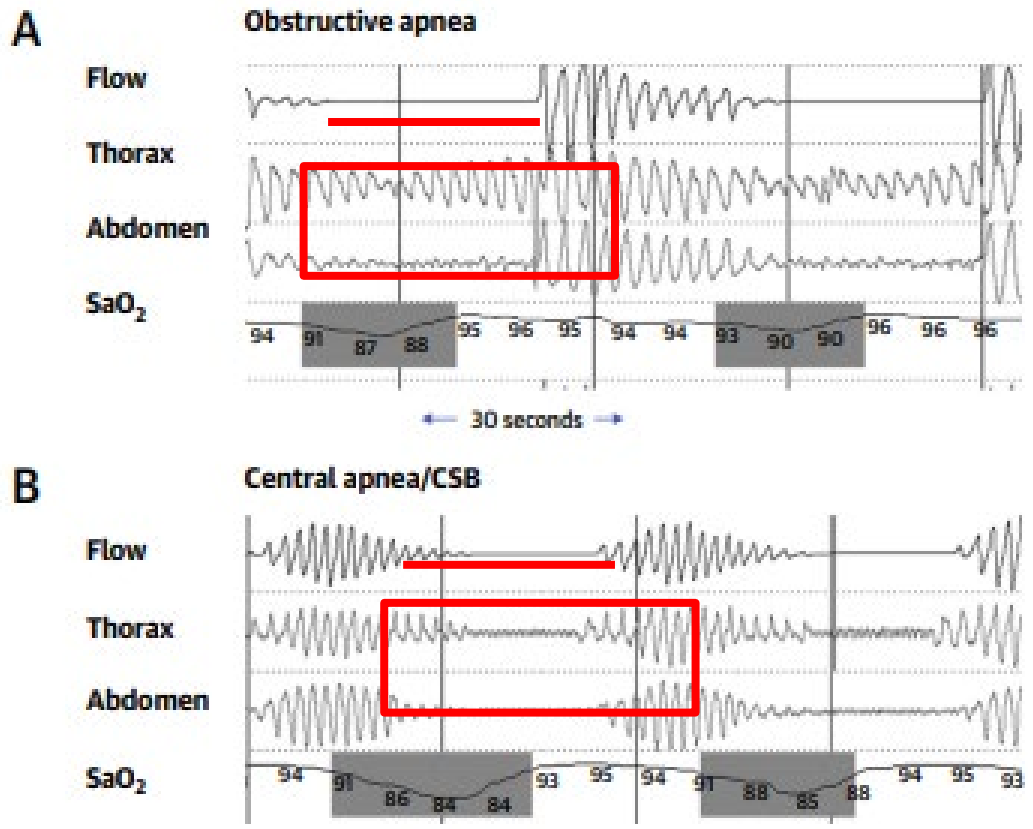
OSA and Mortality



AHI >30

Punjabi et al, PLoS Medicine, 2009

Classification of Sleep Disordered Breathing in Adults



JACC VOL. 78, NO. 6, 2021 Sleep Disordered Breathing and CV Disease AUGUST 10, 2021:608 – 624

Screening for OSA

Screening methods

Activity
Sitting and reading
Watching television
Sitting inactively in a public place
As a car passenger for one uninterrupted hour
Lying down in the afternoon when able
Sitting and talking to someone
Sitting quietly after lunch with no alcohol
In a car, while stopped for a few minutes in traffic

Epworth Sleepiness Scale

>24 his OSAS risk

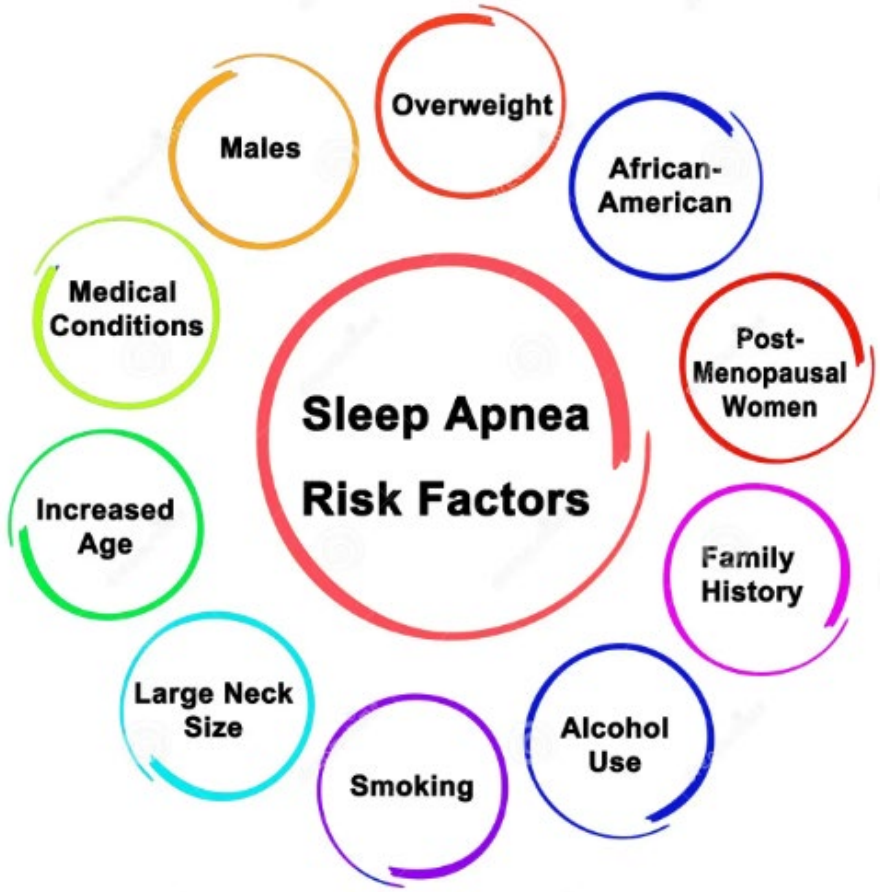
Likelihood of Dozing score

(Sens 42%, Spec 67%)

Snoring
Tiredness
Observed apnea
Pressure
BMI
Age
Neck circumference
Gender

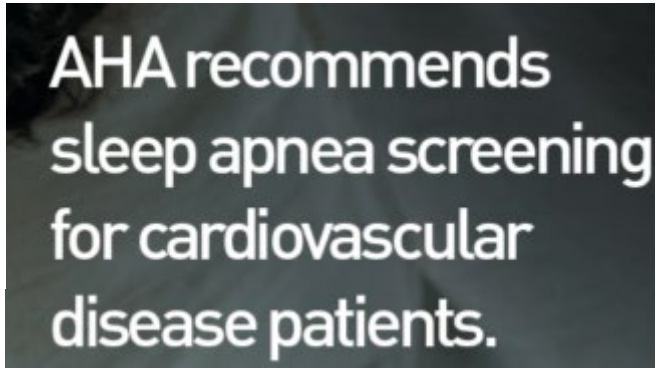
STOP-BANG questionnaire

(Sens 77-89%, Spec 32-34%)



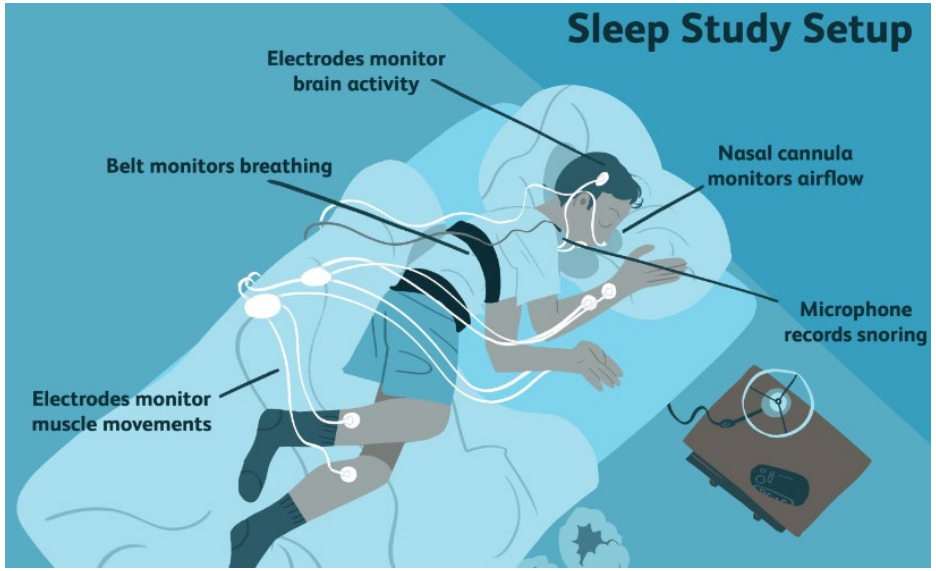
Screening

American Heart Association.



- AHA recommends screening for OSA in patients with
  - Resistant/poorly controlled hypertension
  - Pulmonary hypertension
  - Recurrent atrial fibrillation after either cardioversion or ablation.

Diagnosis and Classification of Severity of OSA



Polysomnography -- gold standard for the diagnosis of sleep disorders / multichannel data acquisition.

Obstructive sleep apnea severity

Index	Calculation
Apnea–hypopnea index (AHI)	$\frac{\text{Apneas + Hypopneas}}{\text{Total sleep time, hours}}$
Respiratory disturbance index	$\frac{\text{AHI + Respiratory event-related arousals}}{\text{Total sleep time, hours}}$
Respiratory event index	$\frac{\text{Apneas + Hypopneas}}{\text{Total monitoring time, hours}}$

Respiratory event index is typically used for home sleep apnea testing as it is based on monitoring time as distinct from actual sleep time.

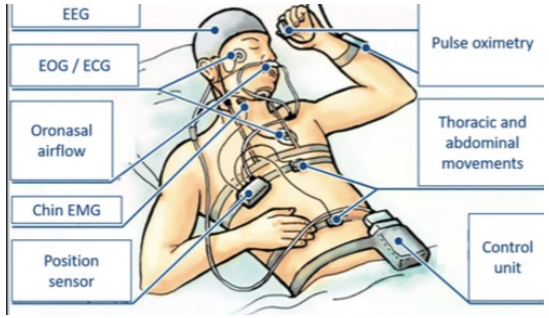
AHI most common used metric to quantify severity

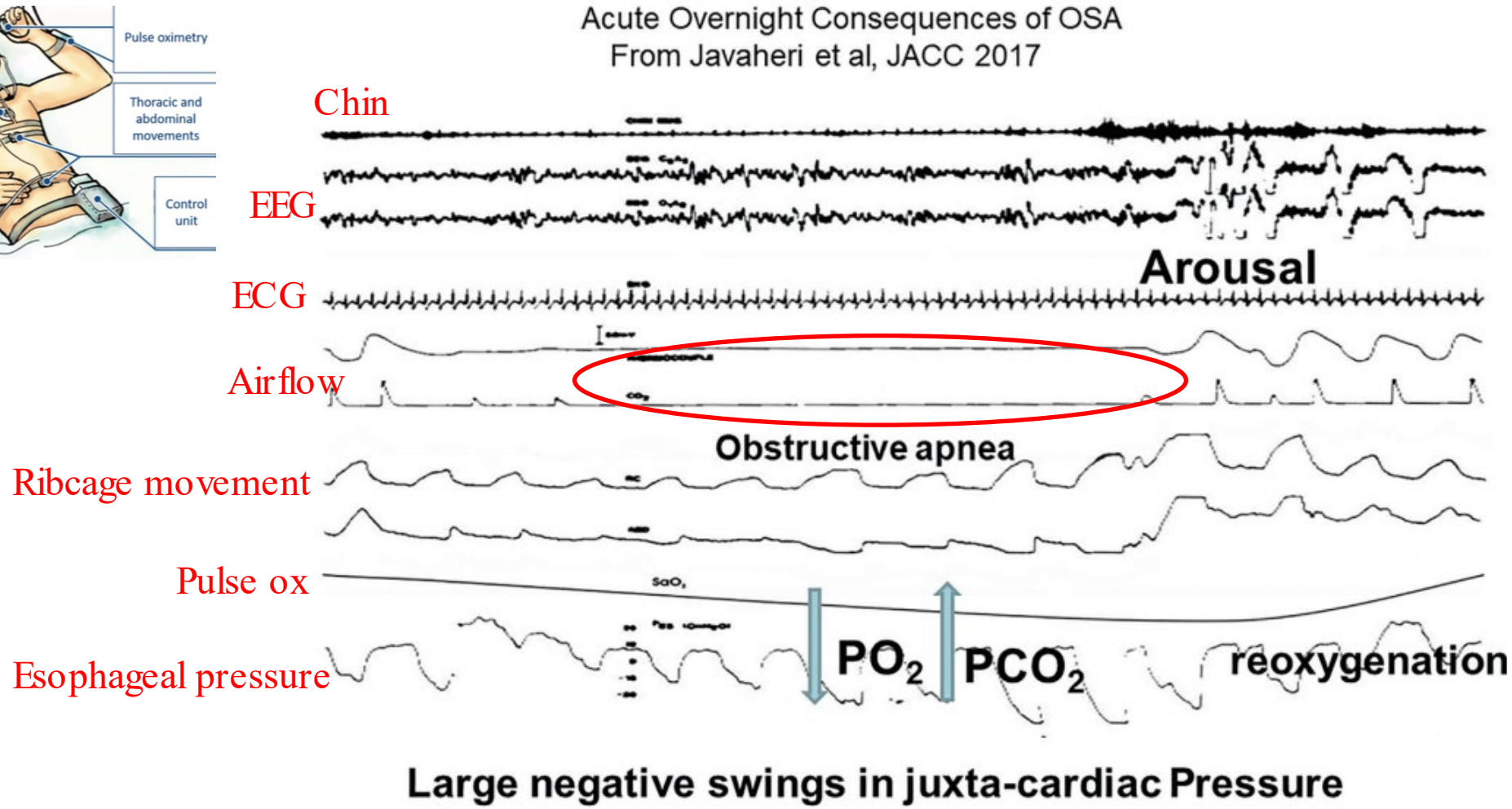
None/Normal	AHI is < 5 per hour
Mild	AHI ≥ 5 per hour, but < 15 per hour
Moderate	AHI ≥ 15 per hour, but < 30 per hour
Severe	AHI ≥ 30

…further classification of OSA severity

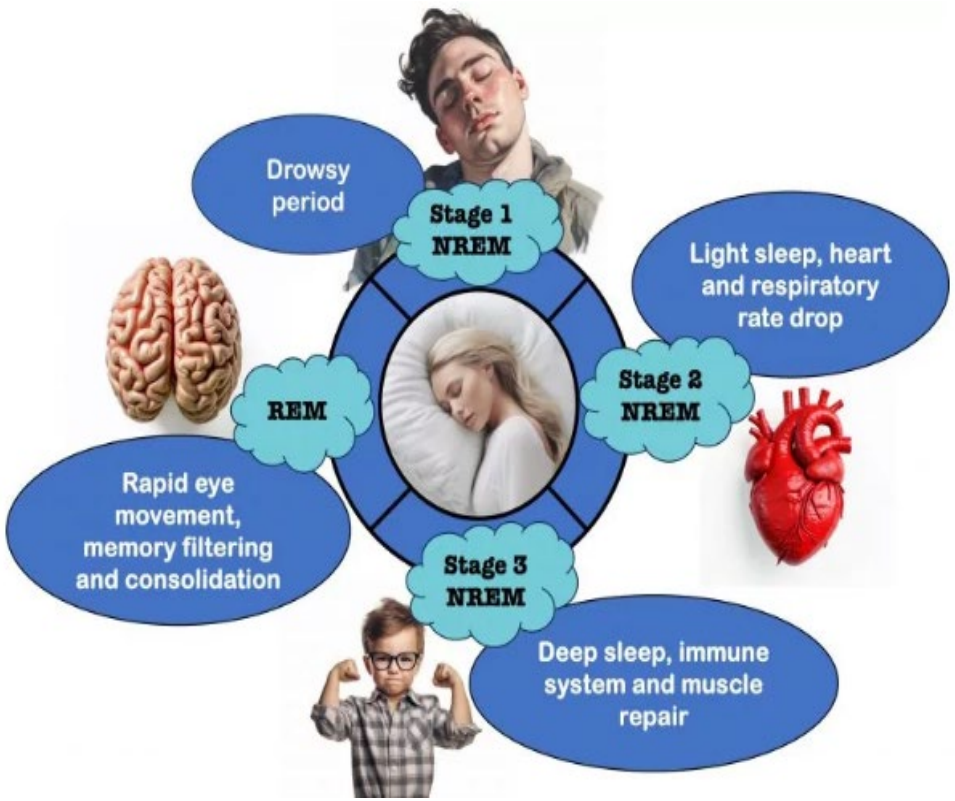
- Based on Polysomnographic features
  - Apnea Hypopnea Index
  - REM AHI
  - Sleep Time below 90% saturation (T<90)
  - Hypoxic burden

30 second period/polysomnogram





Normal sleep cardiovascular hemodynamics



Non-REM:Autonomic and hemodynamic stability

NREM sleep:

↓ Sympathetic Activity

↑ Parasympathetic Activity

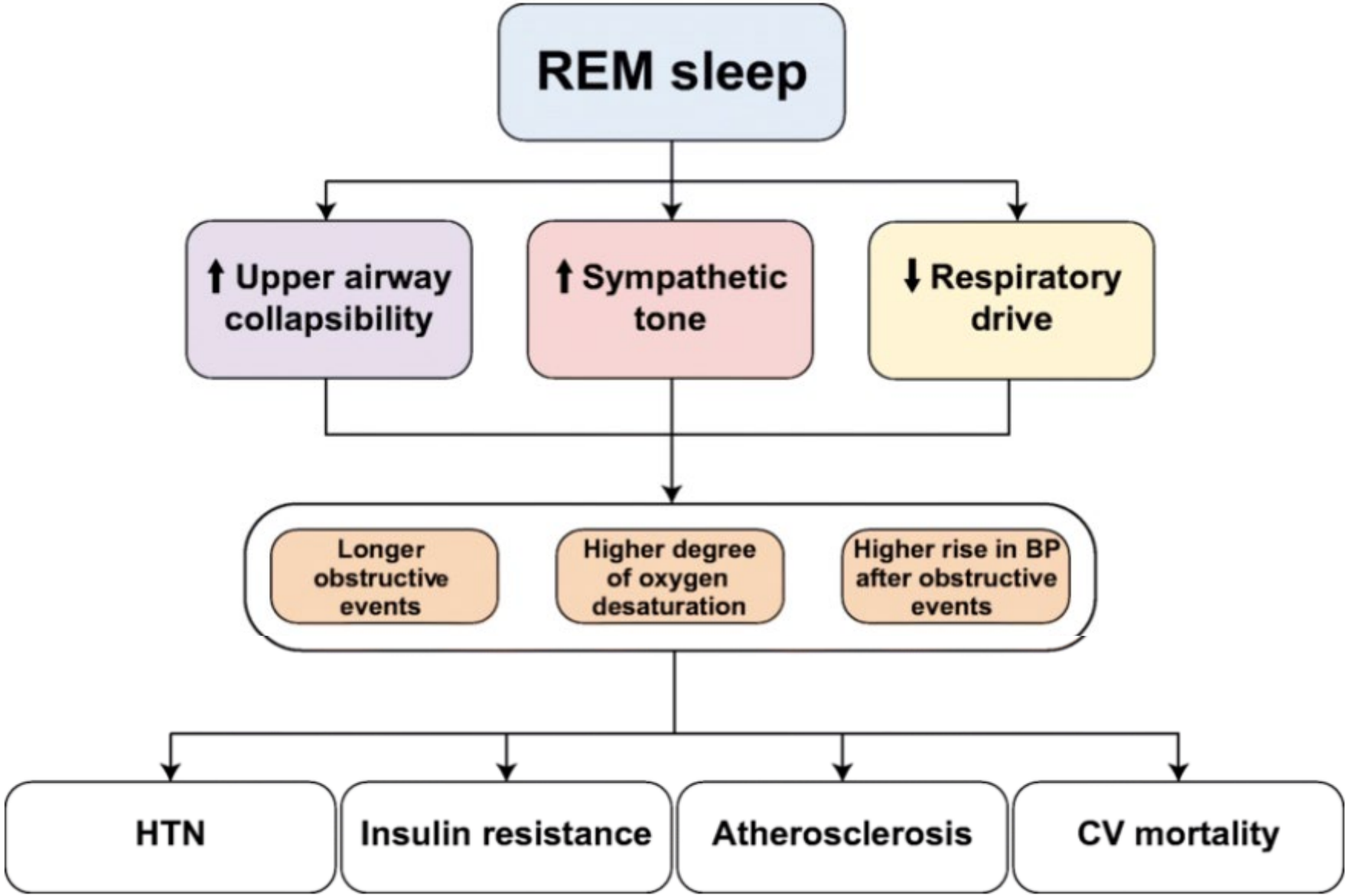
↓ BP, HR, COP
Ventilation
Metabolic rate → Cardiovascular Quiescence

Phasic REM sleep:

↑ Sympathetic Activity

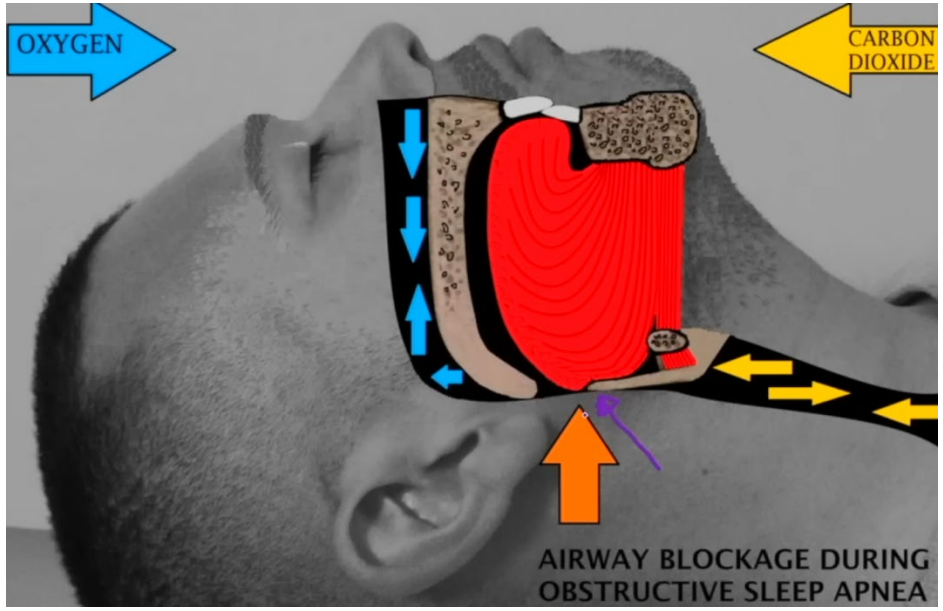
↑ BP and HR

Loss of muscle tone
OSA events more prevalent

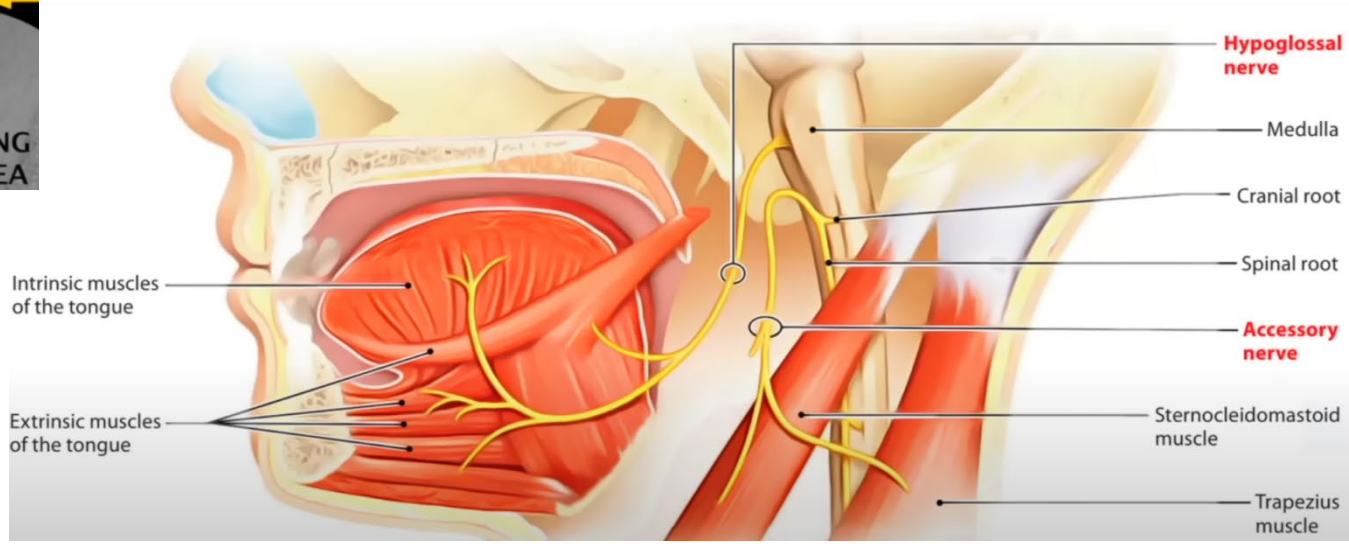


June 2019 Sleep and Breathing 23(2):1-11

Pathophysiology of Obstructive Apnea

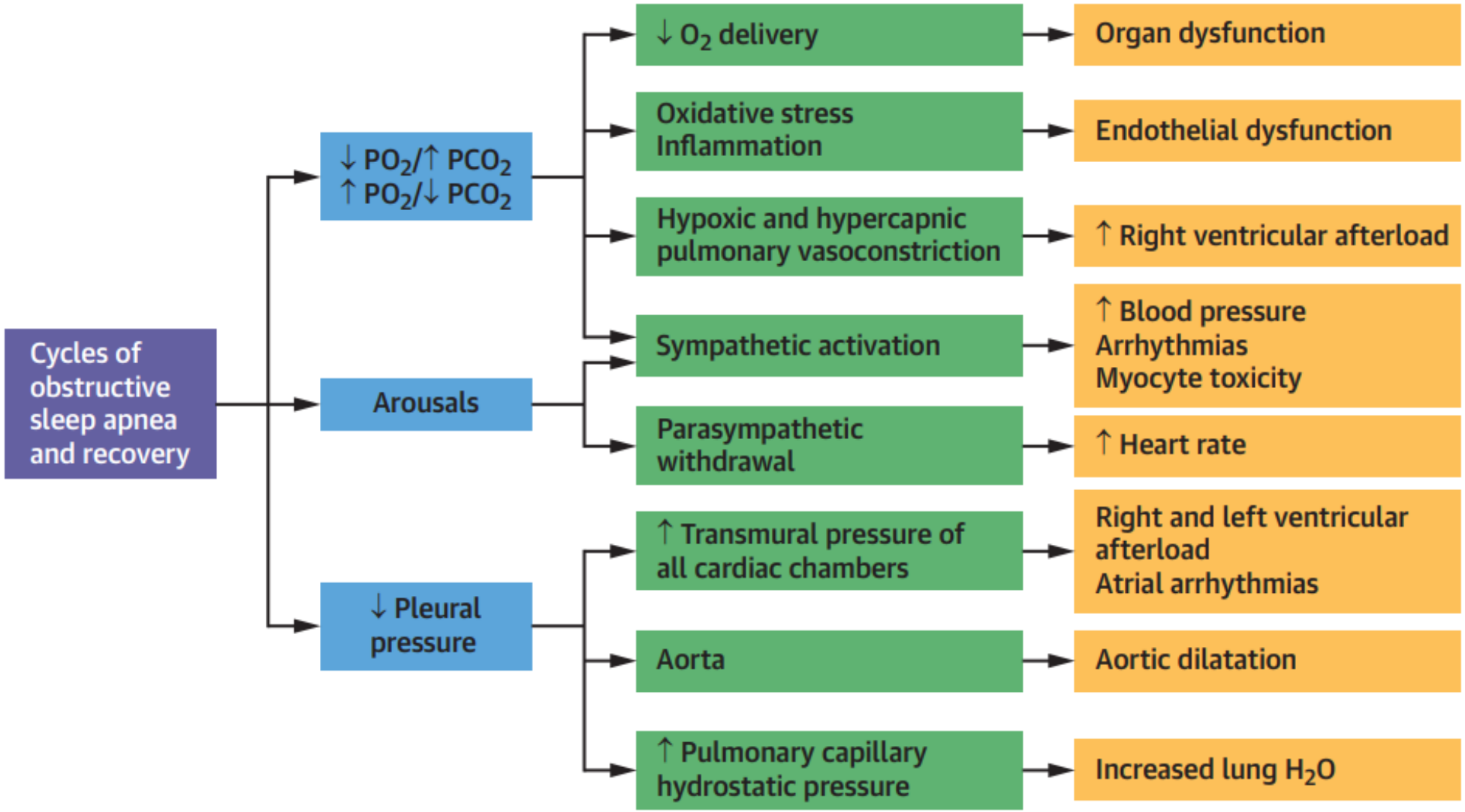


- Anterior-posterior collapse
- Concentric collapse



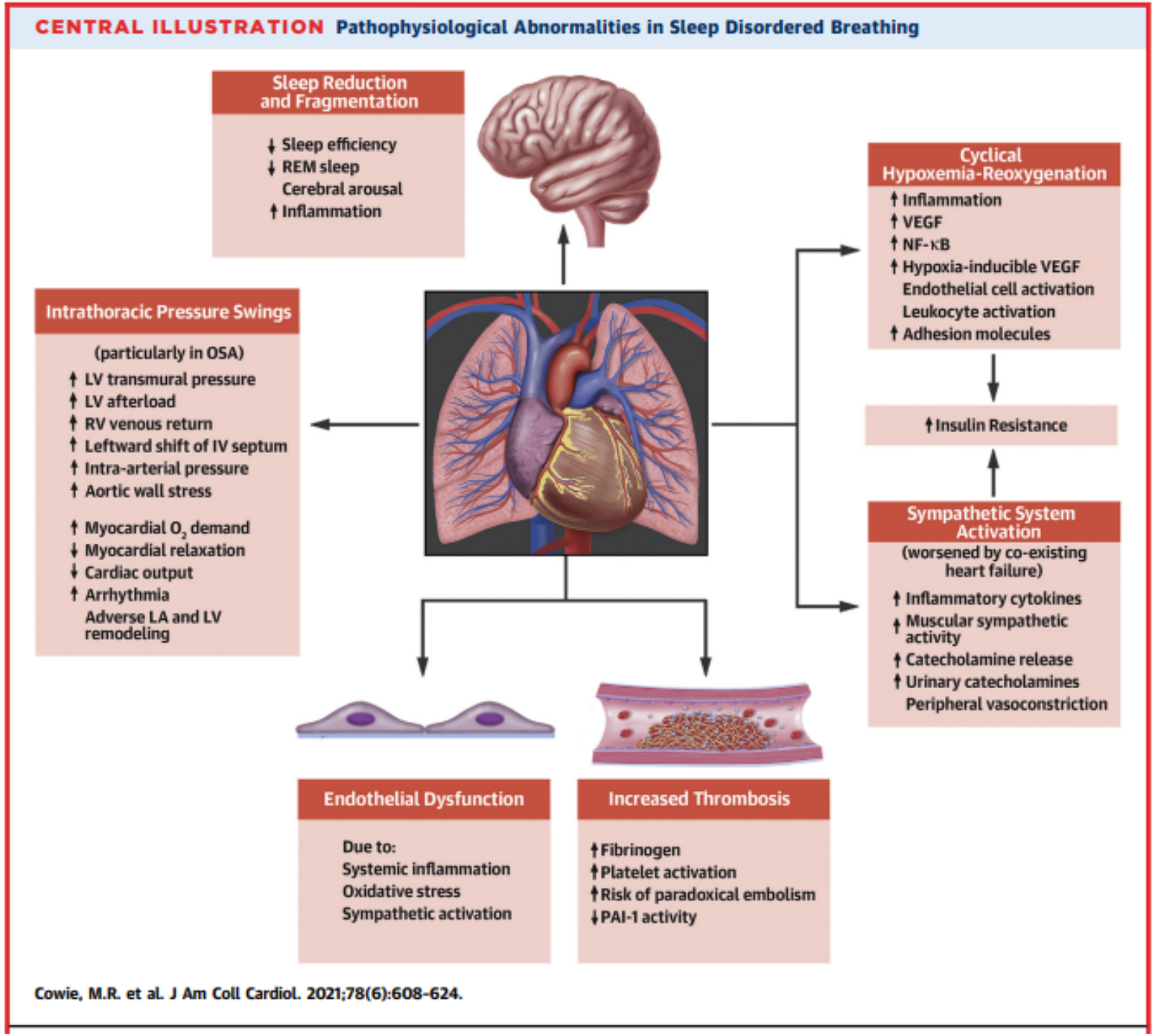
- Relaxation of the dilator muscles--genioglossus

Biological Pathways Mediating Cardiovascular Consequences of Sleep Apnea



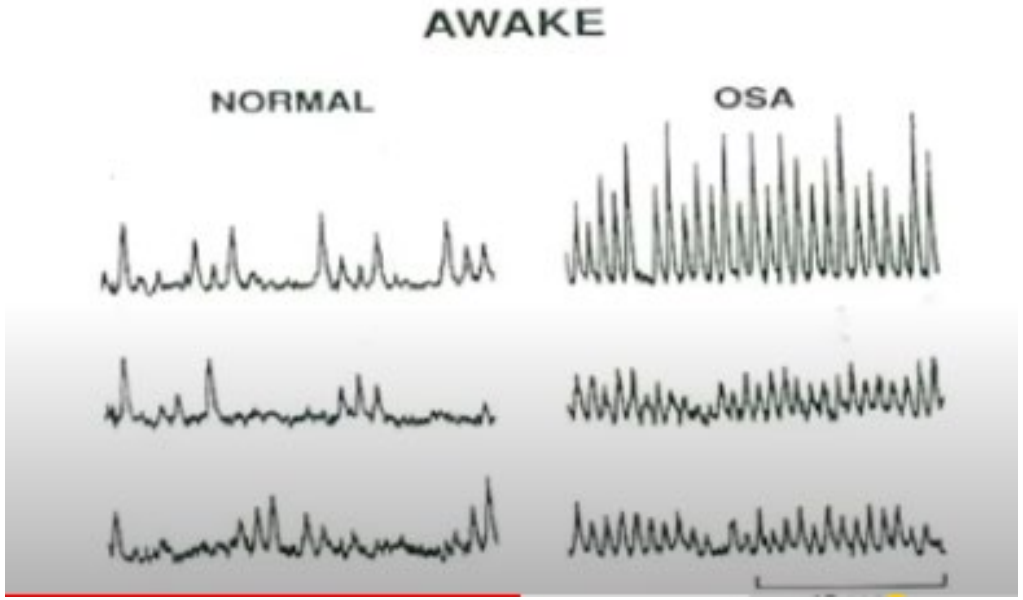
Javaheri S, et al. JACC. 2024;84(13):1208-1223.

CENTRAL ILLUSTRATION Pathophysiological Abnormalities in Sleep Disordered Breathing

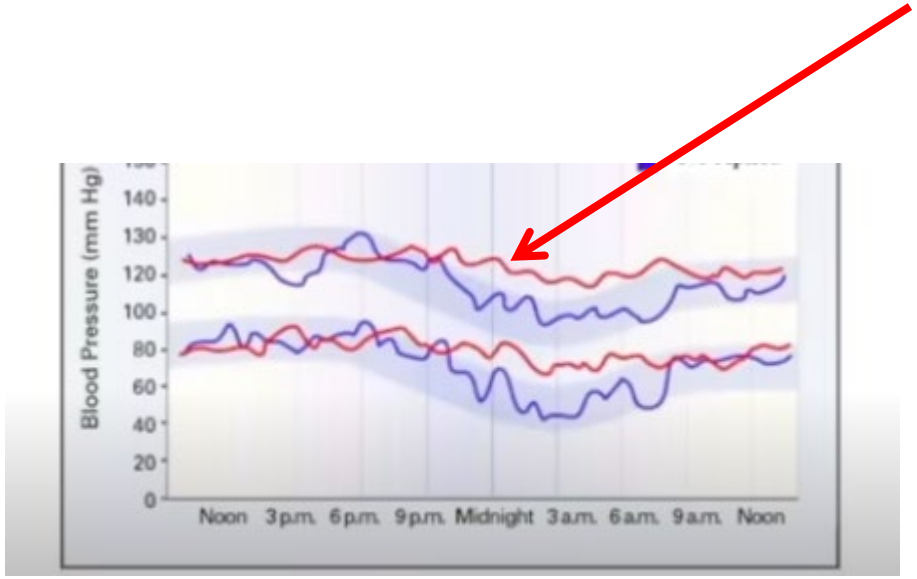


Cowie, M.R. et al. J Am Coll Cardiol. 2021;78(6):608-624.

Increased sympathetic nerve activity in OSA --not only a night time problem



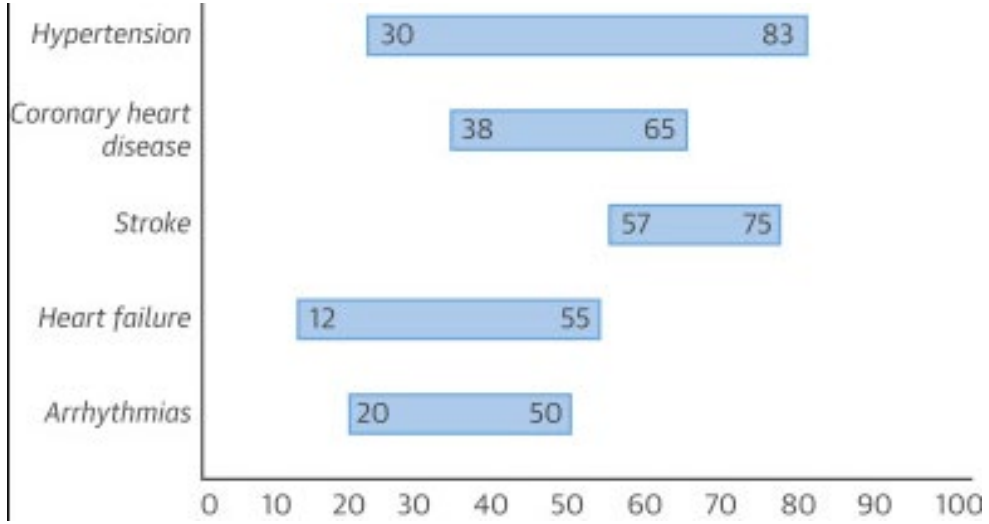
Carry-over phenomenon

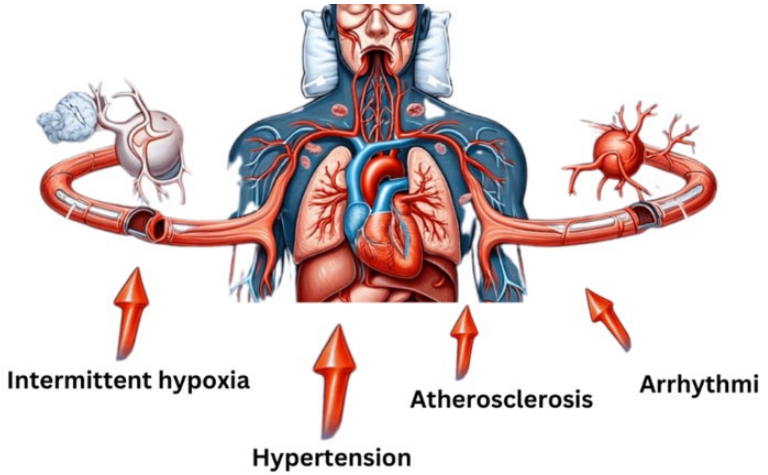


Blood pressure: "Non-dipping" with Apnea
No Apnea: Normal nocturnal dipping pattern

Somers: J Clin Invest 1995

Prevalence of OSA in Cardiovascular Disease





Prevalence (%) of OSA in CVD
Lower limit using AHI >15/h –indicating moderate to severe OSA
Upper part of the range relates to a lower threshold of >5/hr

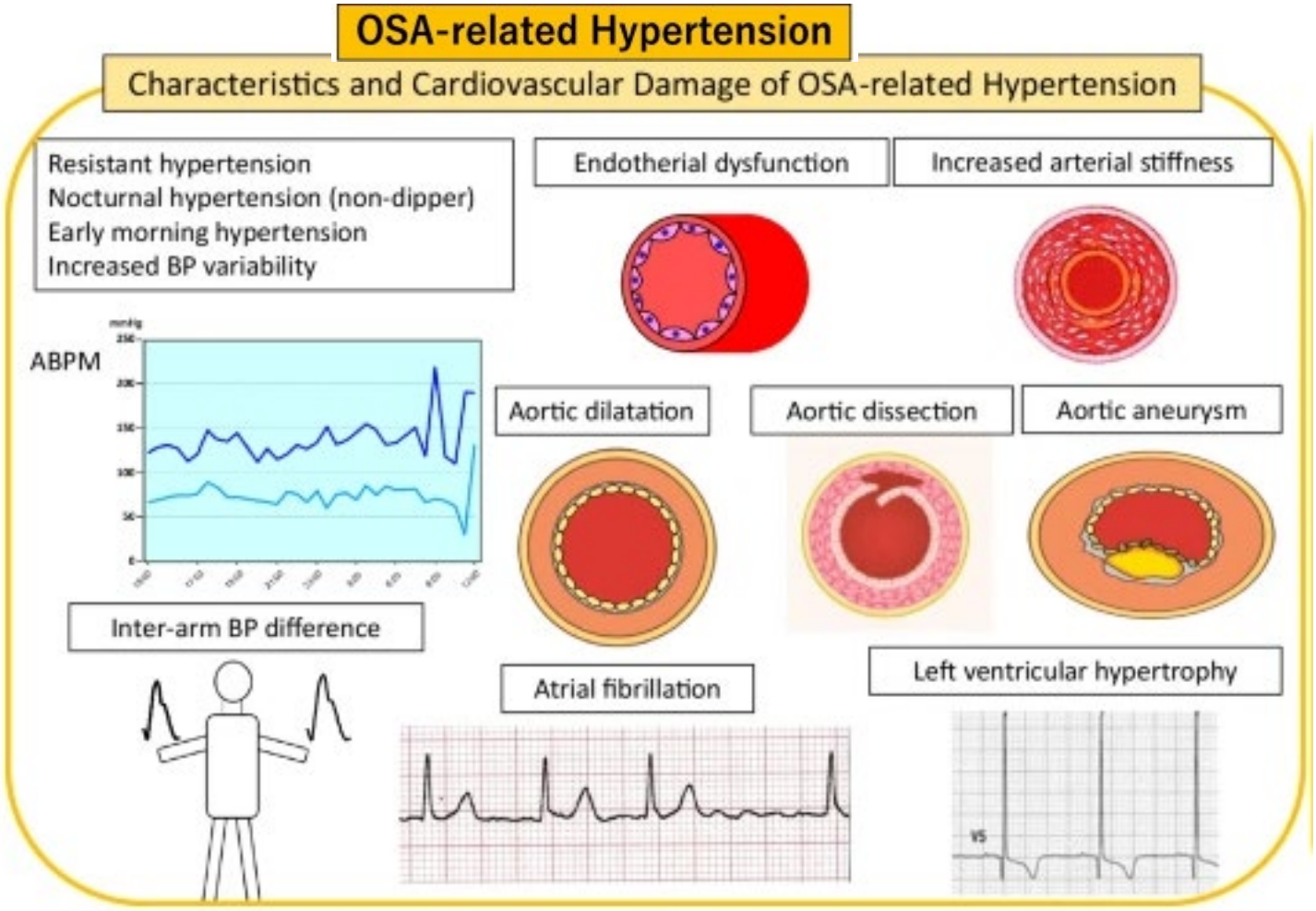
Javaheri et al., JACC Vol 69, Issue 7, 21 Feb 2017, 841:858

OSA and HTN

- OSA is highly prevalent in hypertensive patients, of whom 30% to 50% will have comorbid OSA.
  - J Am Heart Assoc. 2019;8:e010440
- High-quality longitudinal cohort studies show that OSA is an independent risk factor for incident hypertension (about a 2-fold higher risk compared with non-OSA subjects).

- Continuous positive airway pressure (CPAP) therapy on blood pressure (BP) lowering in hypertensive patients with OSA have been disappointing and inconsistent, with a meta-analysis showing reductions of BP of between 2 and 3 mm Hg.
  - Chest. 2014;145:762–771.
- More severe OSA, difficult to control HTN and better PAP *compliance* → had more substantial BP reduction with CPAP

OSA and HTN—vascular remodeling



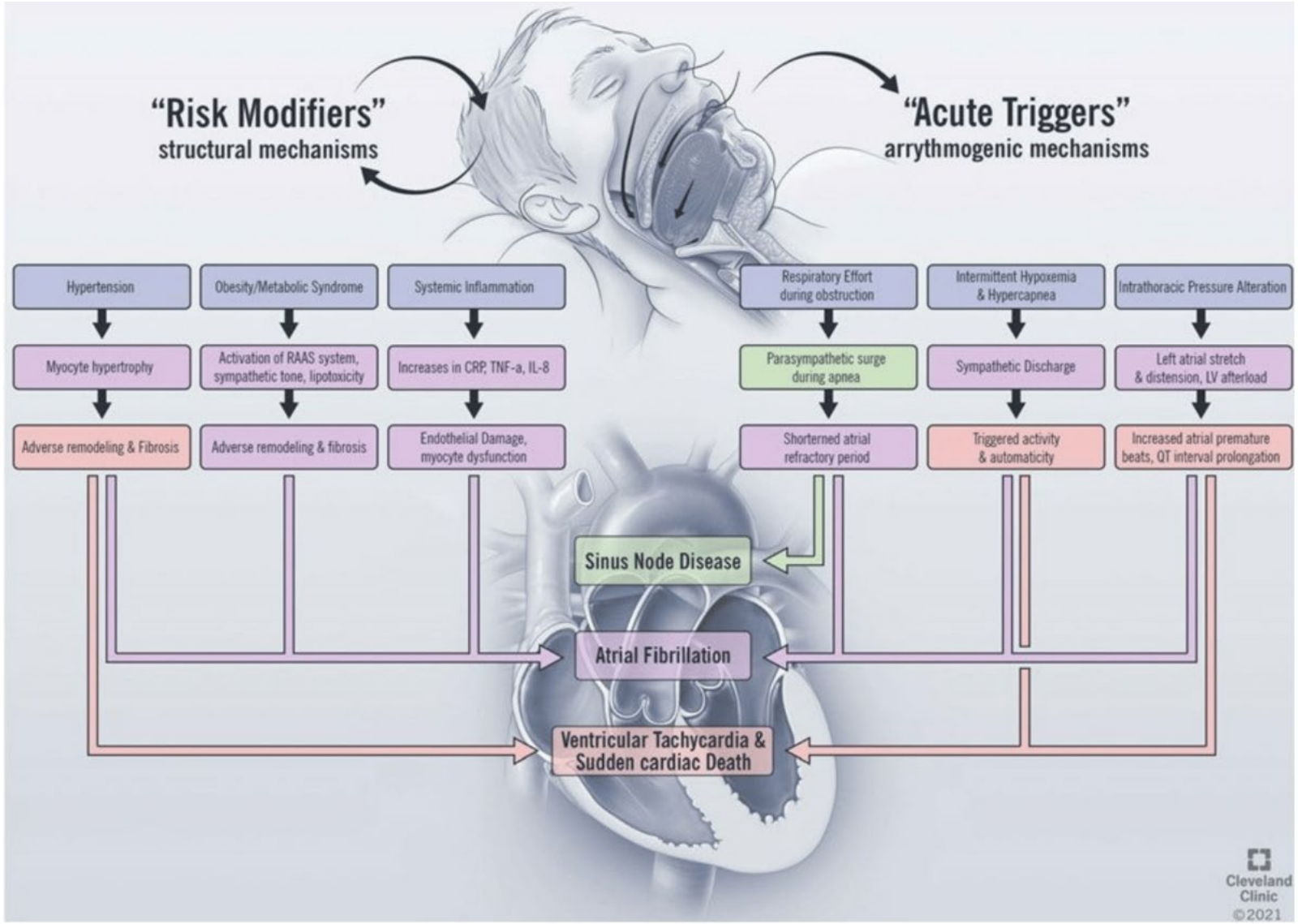
Hypertension Research, Volume 47, pg 3085–3098 (2024)

OSA and Atrial Fibrillation

- OSA is an independent risk factor for AF in patients without other underlying cardiac disorders.
  - J Respir Crit Care Med. 2006;173:910–916

- There are several possible mechanisms for the substrate and trigger of AF in patients with OSA.
  - Acute apneic episodes lead to hypoxia and hypercapnia, alteration in intrathoracic pressure, increased sympathetic tone, and autonomic dysregulation.
  - Chronic recurrence and abrupt negative changes in intrathoracic pressure may lead to structural and functional atrial remodeling and cause atrial fibrosis with downregulation of connexin and electrophysiological alterations.
    - Int J Cardiol. 2017;228:967–970

OSA and arrhythmias



Review
Obstructive Sleep Apnea and Cardiac Arrhythmias: A Contemporary Review

J. Clin. Med. 2021, *10*(17), 3785

Increased arrhythmogenic risk with time

- Negative intrathoracic pressure changes
- Cyclical desaturation/reoxygenation
- Sympatho-vagal activation

Acute (transient) electrophysiological changes

Atrium
- Refractoriness ↓
- Conduction velocity ↓
- Triggers ↑

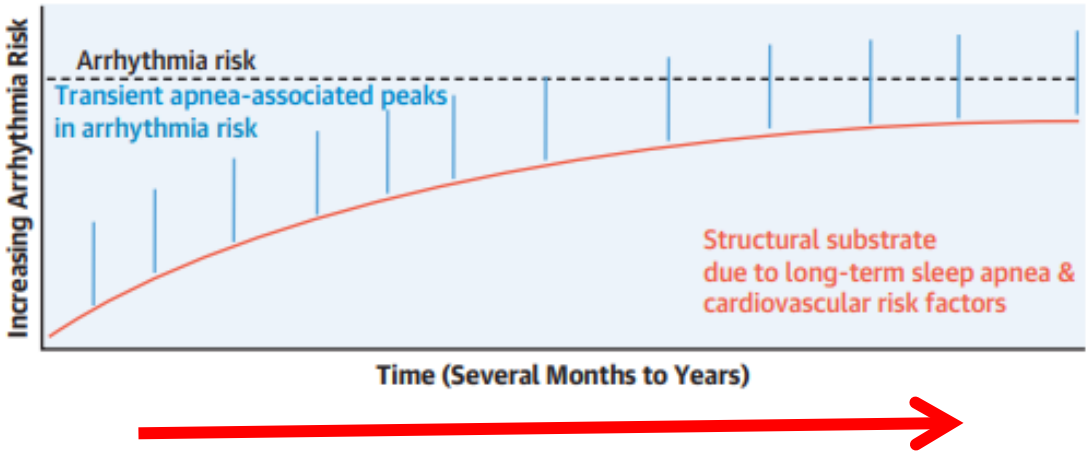
Ventricle
- QT dispersion ↑
- Triggers ↑

Chronic (progressive) cardiac remodeling

Atrium
- Atrial dilatation
- Fibrosis/ connexin remodeling
- Conduction disturbances

Ventricle
- Hypertrophy
- Heart failure

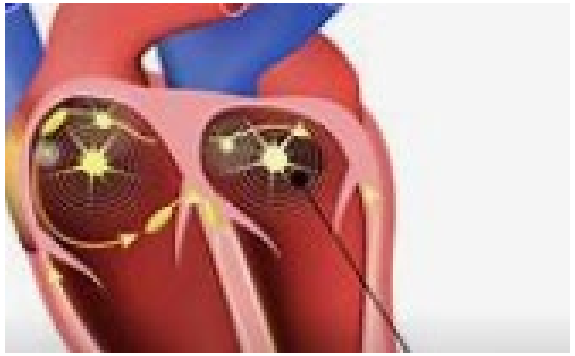
+ Cardiovascular Risk Factors



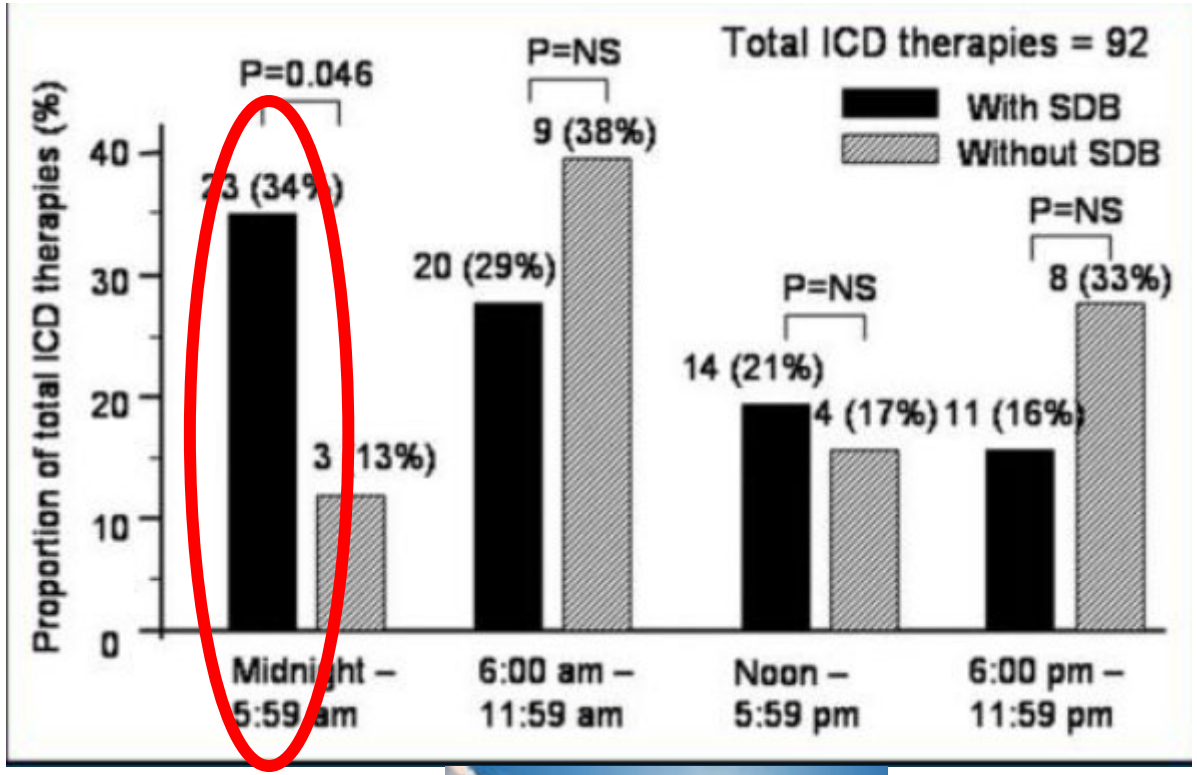
OSA and arrhythmias

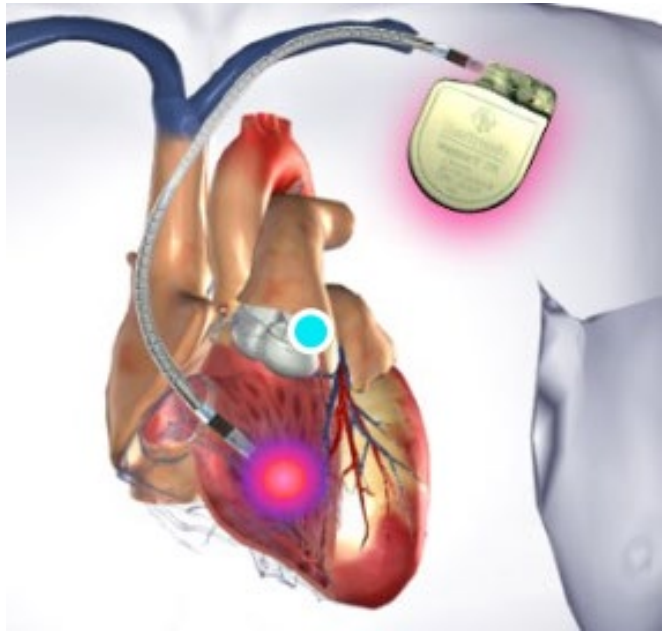
- An increased risk of sudden cardiac death has been reported in patients with severe OSA.
  - Nocturnal asystole

- In a 15-year longitudinal follow-up study of 10 071 adults, OSA predicted incident sudden cardiac death, with the best predictors being
- age >60 years,
- mean nocturnal oxygen saturation <78%,
- and AHI >20.
  - J Am Coll Cardiol. 2013;62:610–616



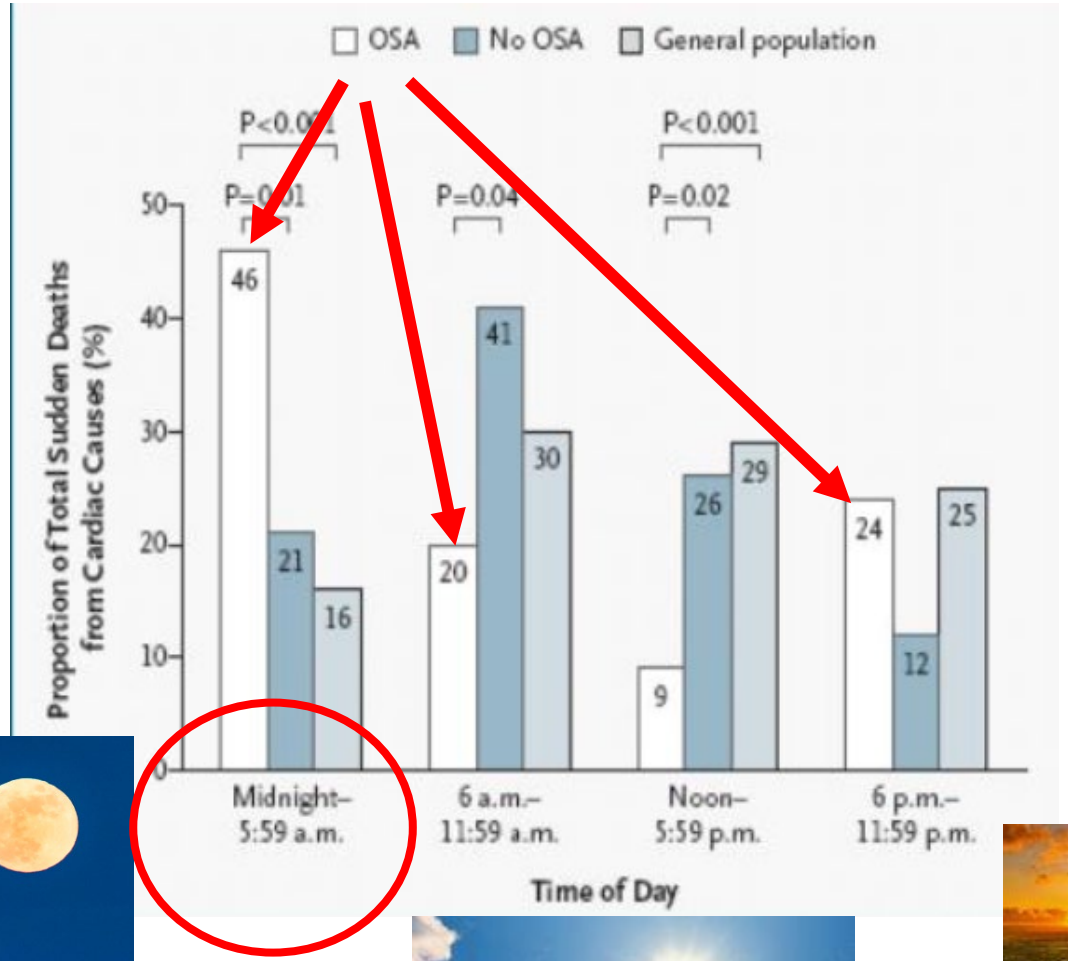
ICD therapy and OSA





Serizawa N et al. Am J Cardiol 2008

Sudden Cardiac Death in OSA



NEJM 2005;352:1206-14

Heart Failure and OSA

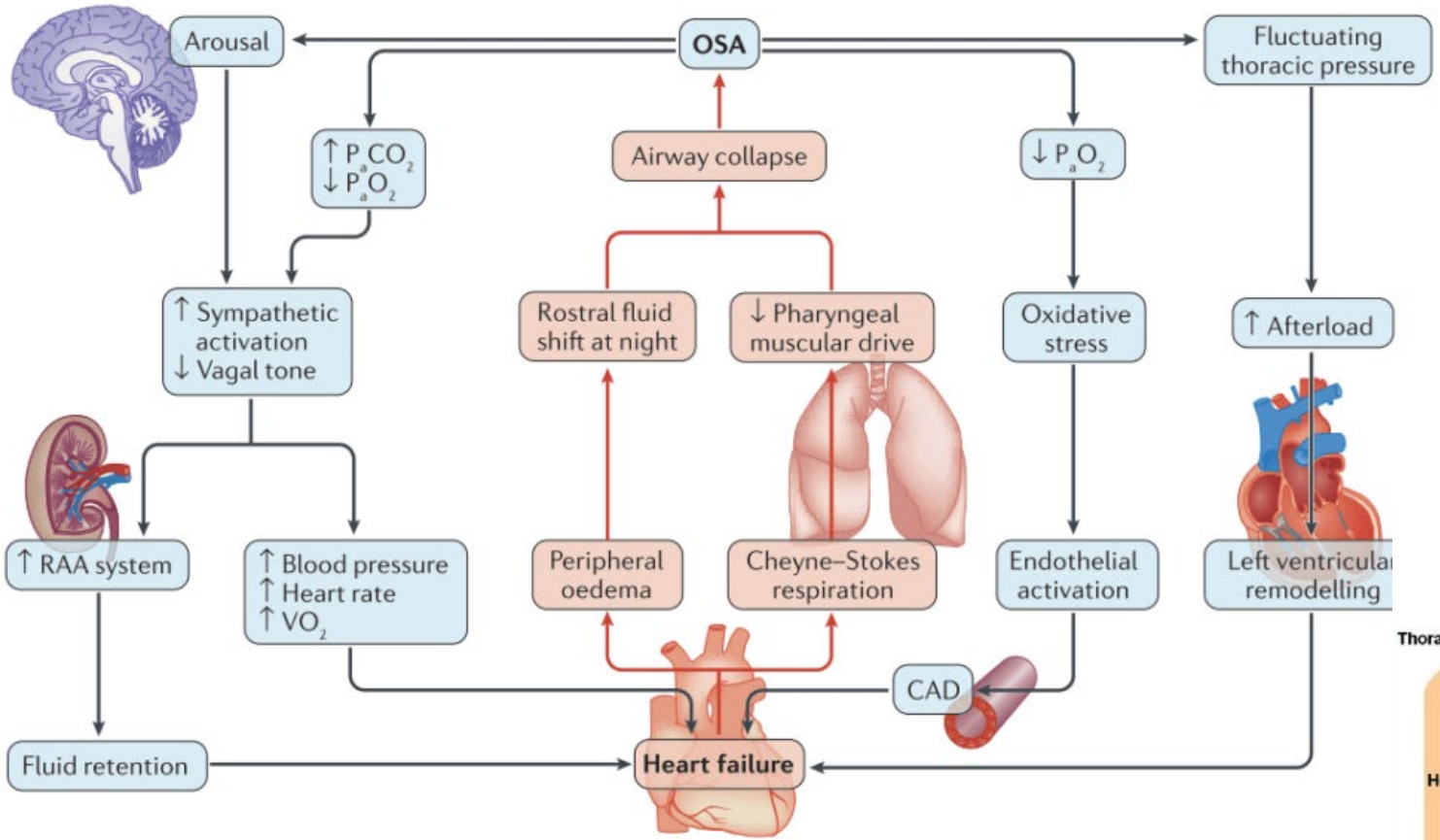
- The mechanistic link between OSA and heart failure is complex and likely bidirectional, with each entity contributing to the other

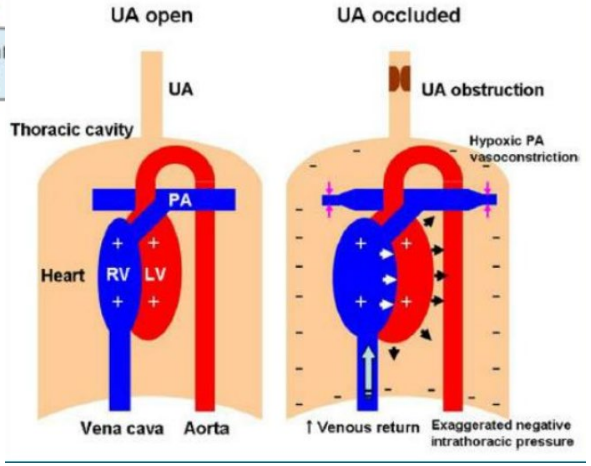
- Men>women (38% vs 31%)
- Major risk factor in men: obesity
- Major risk factor in women: older age

- Most direct mechanism in which OSA can induce LV dysfunction is by raising BP
- 11-37% of patients with systolic dysfunction had OSA detected on polysomnography
  - Very few complained of excessive daytime sleepiness (hyperadrenergic state)

– Spaak J et al., Hypertension 2005

Heart Failure and OSA—all roads lead to Rome (CHF)





Pressure and Volume overload: impact SV

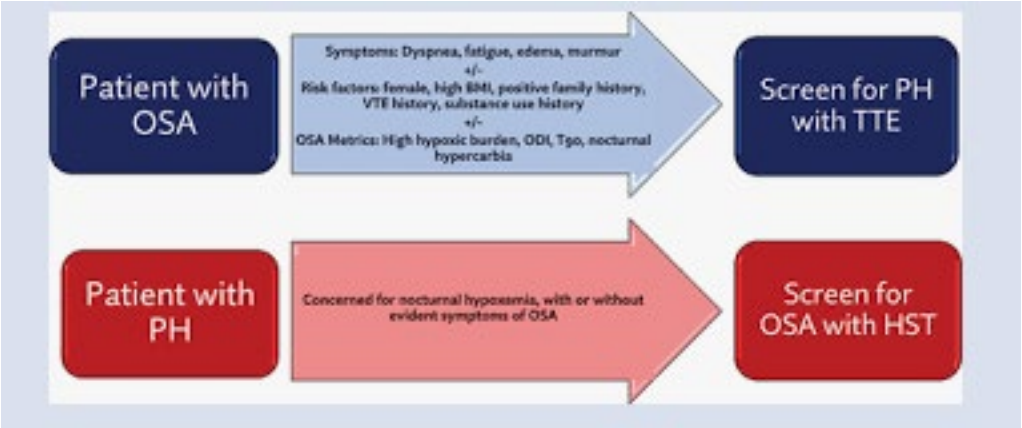
OSA and HF

- The 2017 American Heart Association/American College of Cardiology HF guideline identified CPAP as a possibly reasonable treatment strategy (Class IIb) to improve sleep quality and daytime sleepiness in patients with CVD and OSA.
  - Circulation. 2017;136:e137–e161

- Although several small-scale studies have reported benefits associated with CPAP improved LVEF, reduced sympathetic tone and MVO2, and lower rates of HF hospitalization and mortality, a meta-analysis of patients with OSA reported that CPAP did not have significant effects on either left ventricular ejection fraction or hospitalization rates.
  - J Clin Sleep Med. 2019;15:301–334

OSA and pHTN

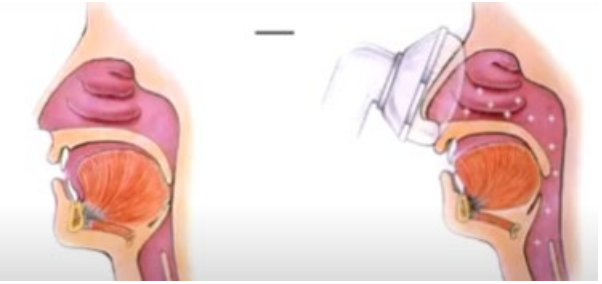
- Observational studies have found consistent yet modest reductions in pulmonary artery pressure (≈5 mm Hg) and pulmonary vascular resistance among PH patients receiving CPAP therapy.
  - Am J Respir Crit Care Med. 2002;165:152–158.
- The AHA/ACC expert consensus recommend polysomnography to rule out OSA for all patients with PH.
  - This recommendation is based on the notion that targeted therapy of OSA may either improve or prevent further deterioration in pulmonary hemodynamics.



Coronary Artery Disease and OSA

- OSA has also been implicated in coronary artery calcification, plaque instability, and plaque vulnerability and has been associated with a 2-fold increase in risk of cardiovascular events or death.
  - Sleep Breath. 2010;14:131–136
- The severity of hypoxemia is a major determinant of ST depression occurring during sleep, and in patients with OSA, the onset of MI is more likely to occur during the nighttime.
  - Chest. 2000;117:1597–1602.
- Whether CPAP therapy decreases the risk of MI remains controversial.
  - Am J Respir Crit Care Med. 2016;194:613–620

Positive Airway Pressure

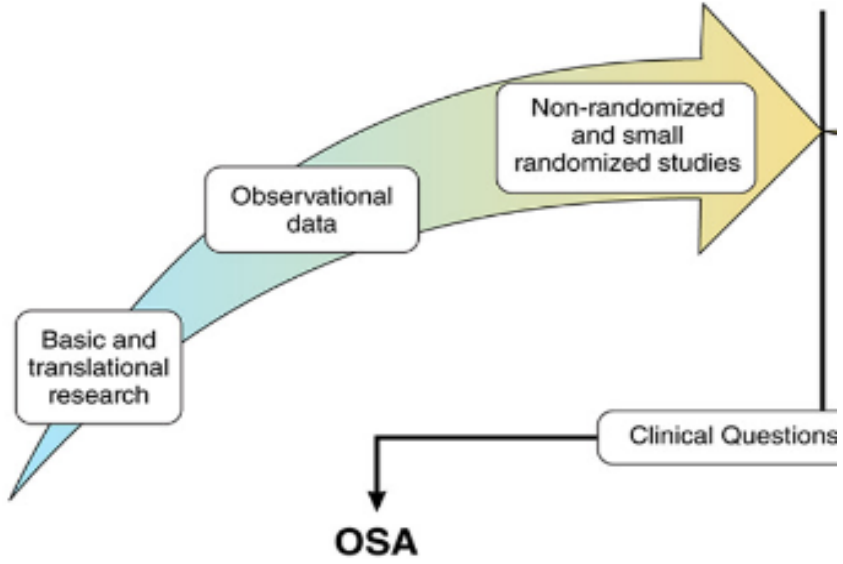


- CPAP :A gold standard treatment for patients with OSA
  - It reduces the risk of CVD by ameliorating apnea severity and nocturnal intermittent hypoxia.

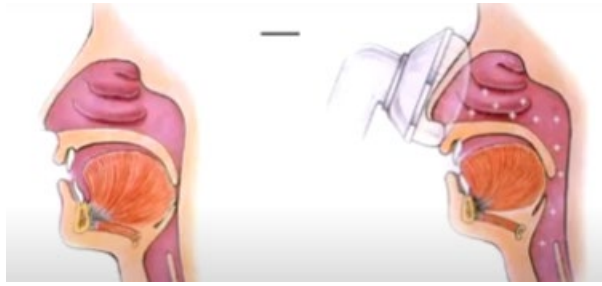
- Large RCTs
  - Not shown long-term benefits of CPAP on hard cardiovascular outcomes
  - Post hoc analyses of these RCTs have demonstrated improved hard outcomes in those who use CPAP adequately (> 4 hrs)

- In theory, low CPAP adherence and patient selection may have contributed to neutral results in intention-to-treat analyses.

Canadian Journal of Cardiology Volume 37, Issue 5, May 2021, Pages 756-765



Role of OSA treatment on primary CV prevention.	• Observational studies that OSA treatment prevent CV events in men, women and the elderly; • Definitive evidence on primary prevention still needed.
Role of OSA treatment on secondary CV prevention.	• Advanced disease and comorbidities may mitigate the impact of CPAP as a secondary cardiovascular intervention; • Current studies not well powered to detect clinically significant improvements in important population subsets; • Additional evidence in secondary prevention from other CV diseases still needed.
Role of CPAP adherence on trial results/clinical impact	• Per protocol analyses in good users suggest some CV benefits. Future interventions need to consider not only duration of CPAP but when in the night CPAP is used • However, current studies define CPAP by average hours used, not pattern of use. CPAP use often decreases in the 2nd part of the night. Respiratory events during REM sleep (commonly in the 2nd part of the night) may have greater CV impact.



3 Randomized Control Trials

Sleep apnea cardiovascular endpoints (SAVE) trial – a secondary prevention trial, n =2717

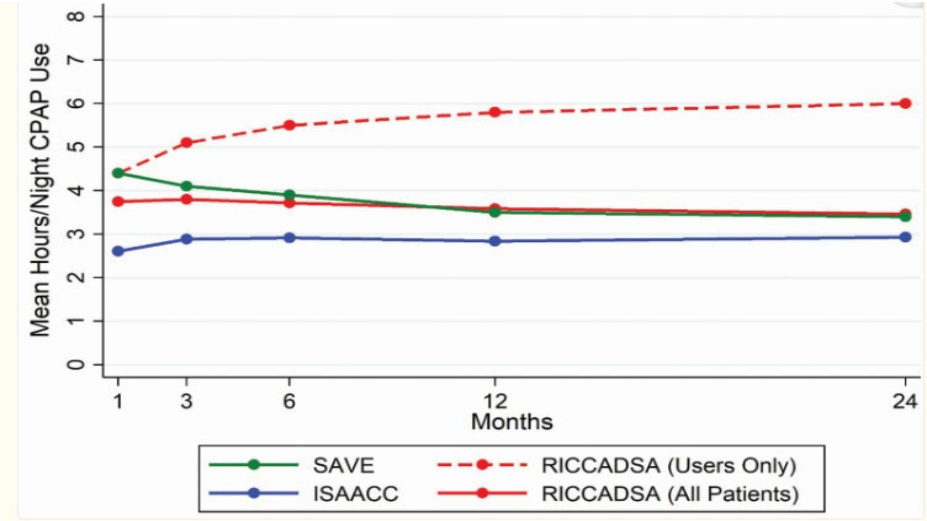
Impact of sleep apnea syndrome in the evolution of ACS-effect of intervention with CPAP (ISAACC) study--ACS with AHI >15; excluded is ESS>10; n =1264

Randomized intervention with CPAP in CA D and OSA (RICCADSA) study—post PCI, AHI >15, excluded if ESS >10

Biases in RCT to explain null results

- Selection bias affected each RCT– subjects recruited were no patients typically presenting for treatment of OSA, excluded pts with excessive daytime sleepiness due to ethical concerns (a group with increased cardiovascular risk and likely to benefit)

- RCT had low adherence to therapy
- Future studies need to include sleepy individuals and maximize adherence.



CPAP Adherence(hrs/night) during 1st 24 months of RCTs

WHITE PAPER

Sleep Apnea and Cardiovascular Disease

Lessons From Recent Trials and Need for Team Science

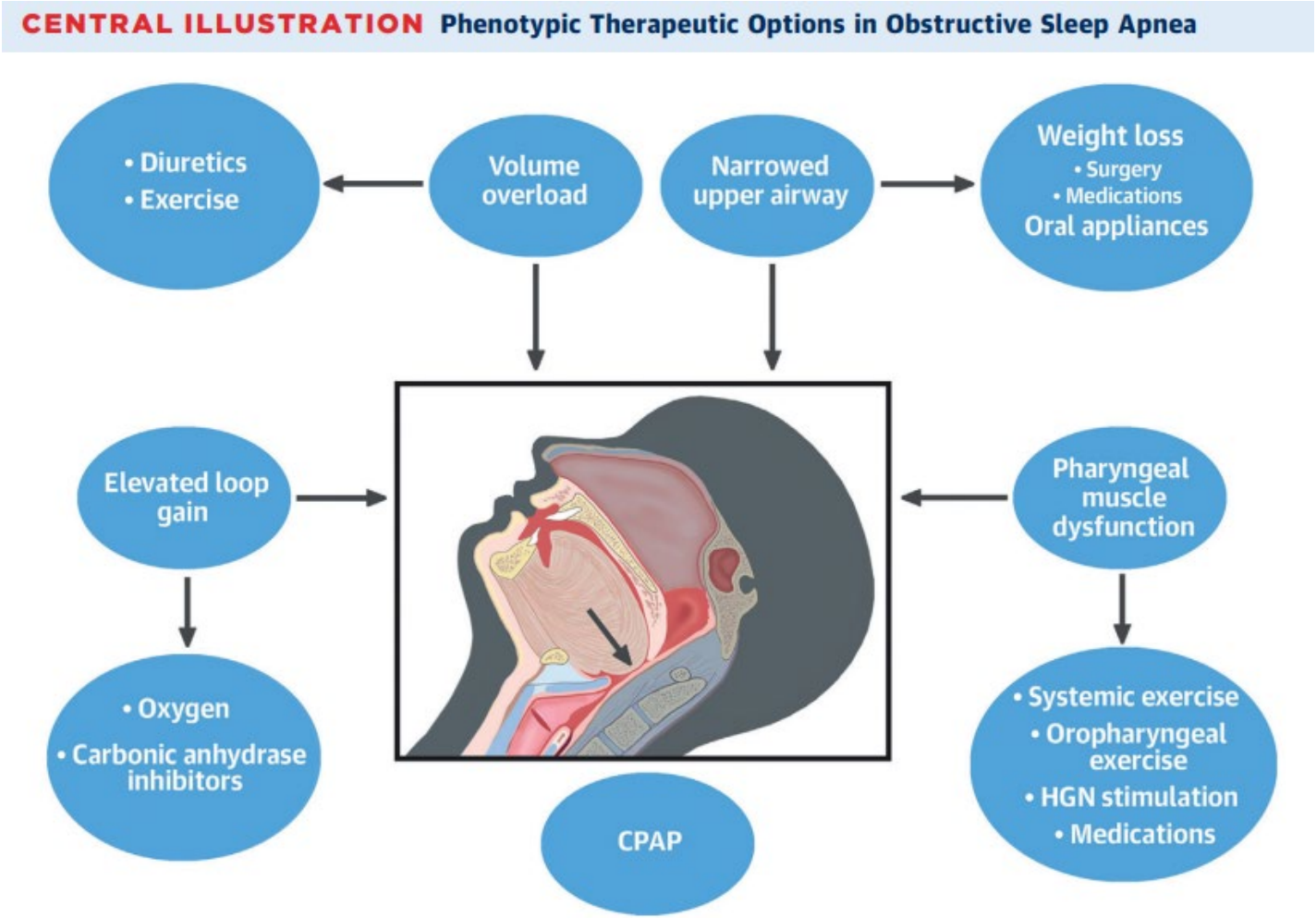
What can we tell our patients?

- Primary prevention
  - CPAP lowers blood pressure and may improve insulin sensitivity.
  - Good adherence to CPAP likely prevents incident hypertension and may reduce the occurrence of adverse cardiovascular events in patients with moderate to severe OSA.
  - Patients should not expect weight loss with OSA treatment.

- Secondary prevention
  - CPAP treatment improves blood pressure
  - Overall quality of life, mood, and work productivity are improved with CPAP therapy.
  - In heart failure, CPAP therapy does not lead to longer survival.
  - Small nonrandomized studies suggest that OSA treatment can prevent atrial fibrillation recurrence.

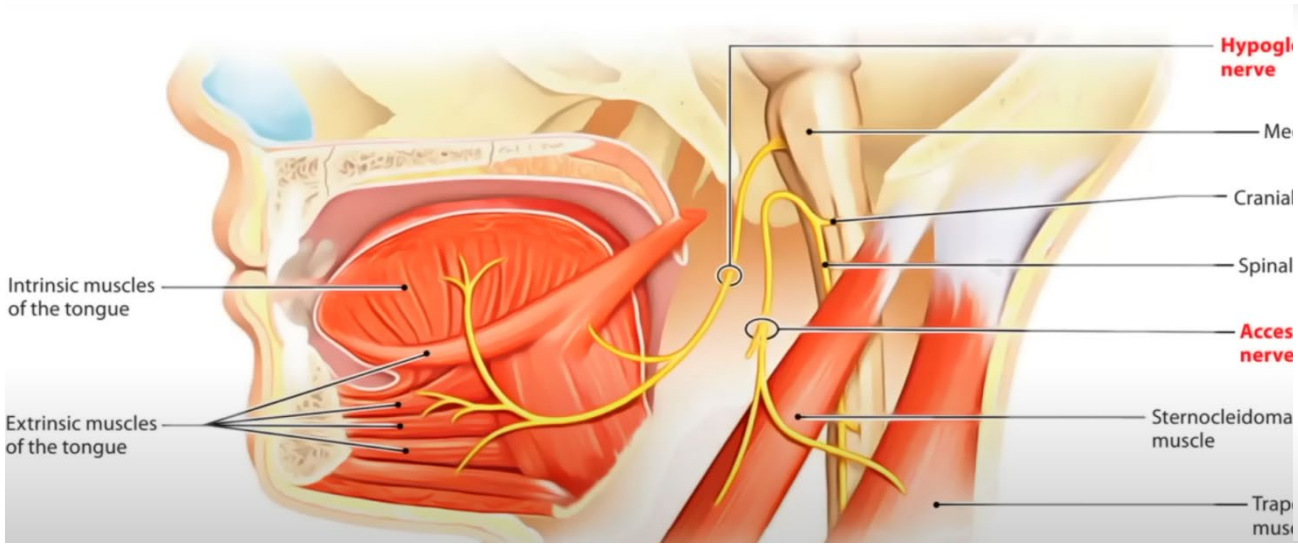
Drager et al., Circulation, Volume 136, Number 19, Nov 7, 2017

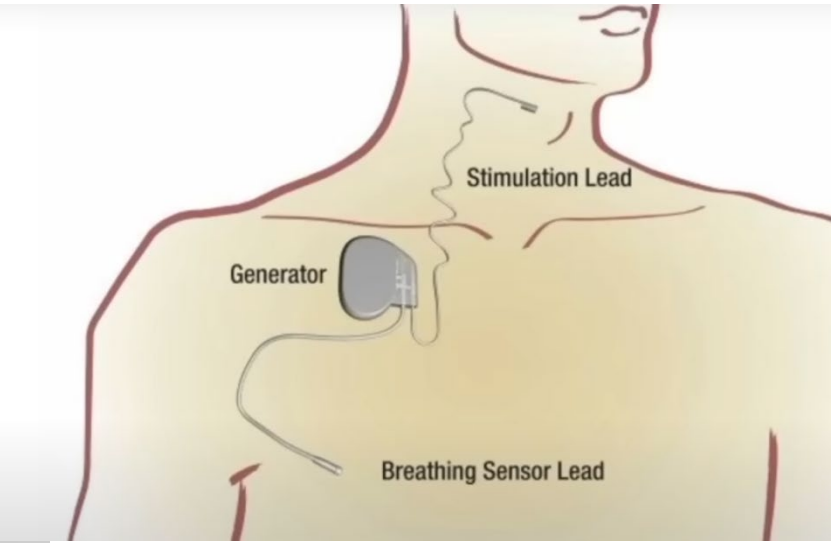
Alternative treatment options



Javaheri S, et al. JACC. 2024;84(13):1224-1240.

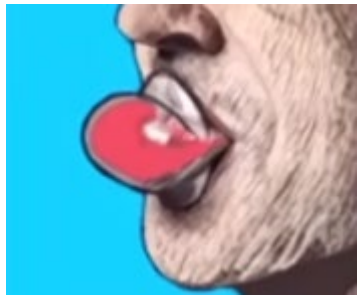
Hypoglossal nerve stimulation



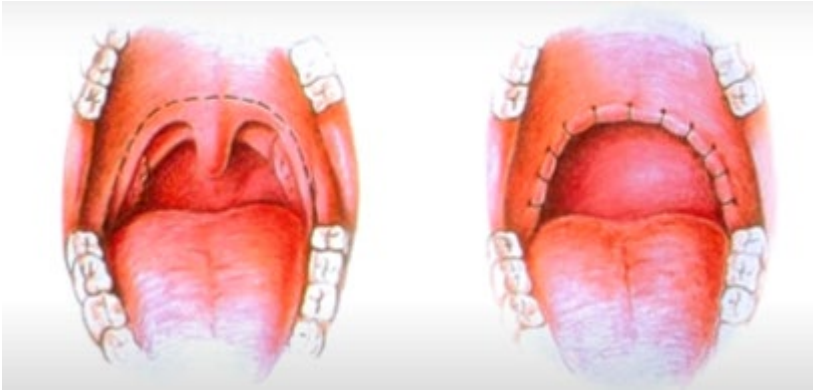


Alternative options

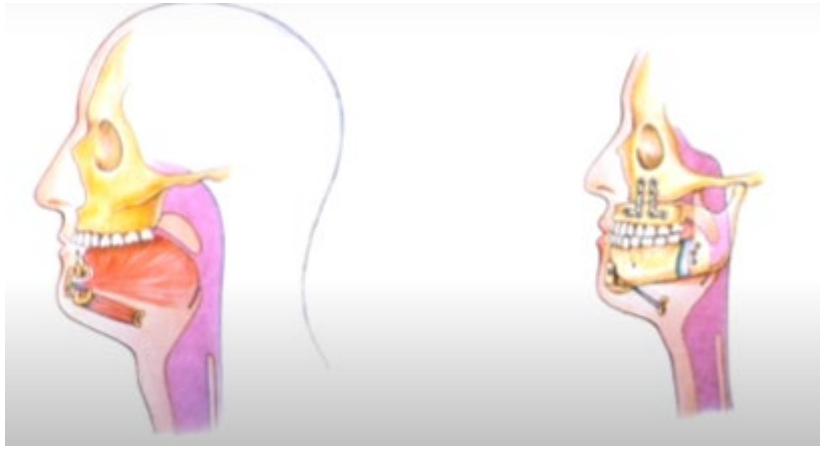
Mandibular advancement splints (MAS)



Tongue Retaining Devices (TRD)

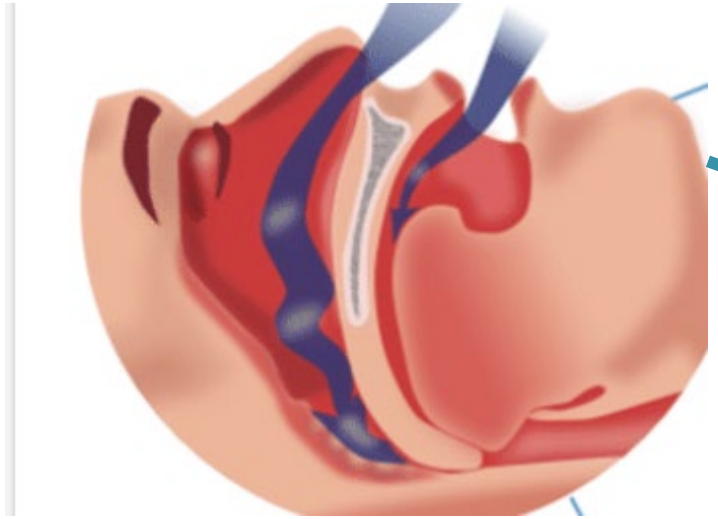


UPPP
Uvulo-palato-pharyngeoplasty



Genioglossal advancement/ Maxillomandibular advancements

Different OSA phenotypes/a heterogenous disorder



Risk Factors

- Obesity (general & regional)
- Craniofacial restriction
- Neural & ventilatory control

Clinical Expression

- Sleepiness
- Insomnia
- Asymptomatic

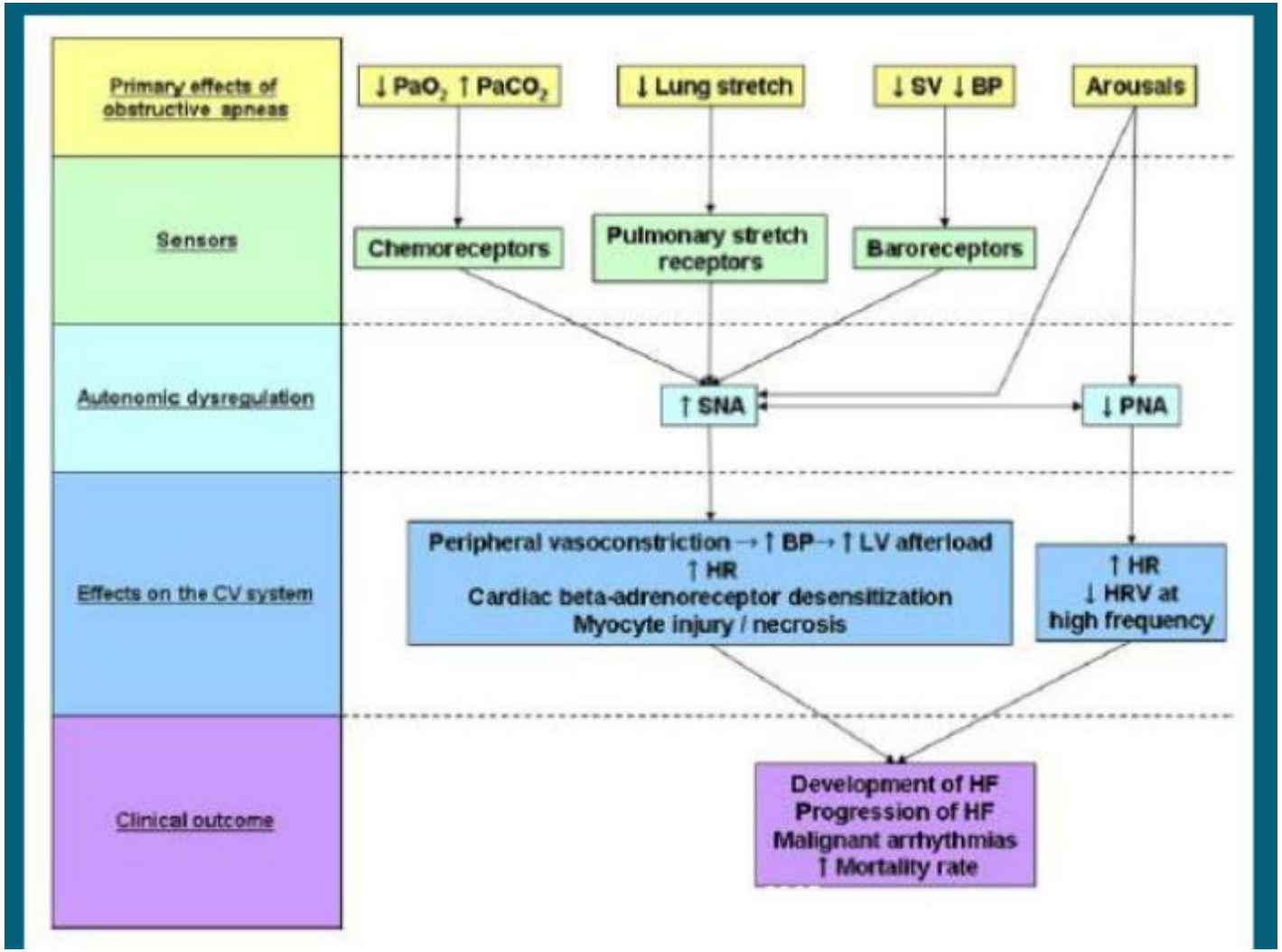
Physiology Features

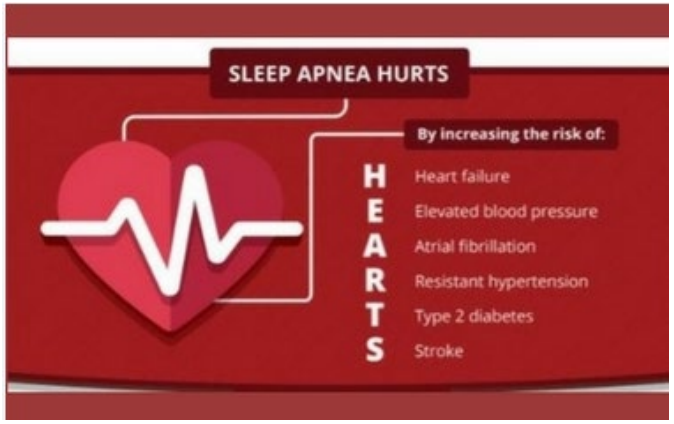
- Sleep stage-dependency
- Body position-dependency
- Hypoxic burden
- Heart rate response

Morbidity

- Hypertension
- Cardiometabolic dysregulation
- Neurodegeneration
- Cancer

Sutherland K, et al. Expert Rev Respir Med. 2018;12(4):293-307





American Academy of Sleep Medicine

OSA has been independently linked to multiple cardiovascular outcomes

Treatment of OSA may represent a novel target to reduce cardiovascular health

Selim et al, Clim Chest Med 2010

Future studies:

- Improved RCT
- REM- AHI tracking, nocturnal hypoxia
- Increase CPAP compliance
- Inclusion of high risk patients

SURMOUNT-OSA

The NEW ENGLAND JOURNAL of MEDICINE

Tirzepatide for Obstructive Sleep Apnea and Obesity

A PLAIN LANGUAGE SUMMARY

Based on the NEJM publication: Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity by A. Malhotra et al. (published June 21, 2024)

In two trials, researchers assessed the efficacy and safety of tirzepatide for the treatment of adults with obstructive sleep apnea and obesity.

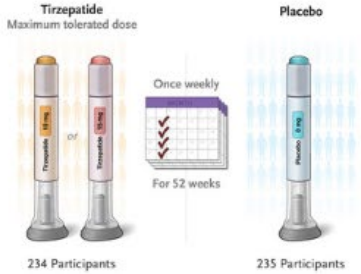
Obstructive sleep apnea is characterized by repetitive pharyngeal collapse during sleep, resulting in apneas and hypopneas. It is also an independent risk factor for cardiovascular disease.

WHY WERE THE TRIALS DONE?

Excess adiposity is a major reversible risk factor for obstructive sleep apnea and its complications. Tirzepatide — a long-acting agonist of the glucose-dependent insulinotropic polypeptide receptor and glucagon-like peptide-1 receptor — has been shown to reduce body weight. Whether tirzepatide can treat obstructive sleep apnea is unknown.

HOW WERE THE TRIALS CONDUCTED?

In two trials, 469 adults with moderate-to-severe obstructive sleep apnea and obesity were assigned to receive the maximum tolerated dose of tirzepatide (10 mg or 15 mg) or placebo subcutaneously once weekly for 52 weeks. Trial 1 enrolled participants who were not receiving positive airway pressure (PAP) therapy. Trial 2 enrolled those who were receiving PAP therapy. The primary end point was the change from baseline in the apnea–hypopnea index (AHI, the number of apneas and hypopneas during an hour of sleep).



PARTICIPANTS

WHO

Trial 1 (no PAP therapy):
234 adults
Mean age, 48 years
Men: 67%; Women: 33%

Trial 2 (PAP therapy):
235 adults
Mean age, 52 years
Men: 72%; Women: 28%

CLINICAL STATUS

Apnea–hypopnea index, at least 15 events per hour (mean, approximately 50)

Body-mass index, at least 30 (mean, 39)

No type 1 or type 2 diabetes

TRIAL DESIGN

- PHASE 3
- RANDOMIZED
- DOUBLE-BLIND
- PLACEBO-CONTROLLED
- DURATION: 52 WEEKS
- LOCATION: 60 SITES ACROSS 9 COUNTRIES

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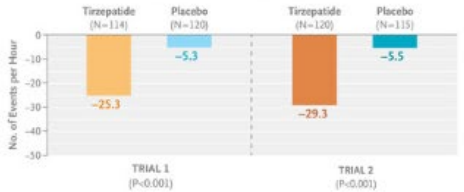
RESULTS

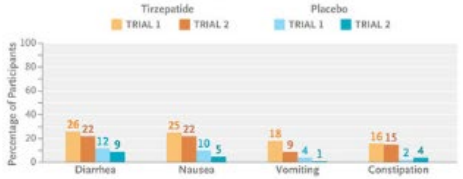
In both trial 1 and trial 2, tirzepatide led to a significantly greater reduction in the AHI at week 52 than placebo.

All key secondary end points also favored tirzepatide over placebo, including the percent change in body weight and changes in systolic blood pressure and high-sensitivity C-reactive protein concentration.

Change in the Apnea–Hypopnea Index



Most Common Adverse Events



The most common adverse events with tirzepatide were gastrointestinal; most were mild to moderate in severity.

LIMITATIONS AND REMAINING QUESTIONS

- Long-term cardiovascular outcomes could not be assessed, given the design and relatively short duration of the trials.
- The trials excluded participants who did not have obesity and therefore did not analyze the effect of tirzepatide in people with overweight or normal body-mass index.
- The trials were not designed to assess whether the results differed according to participants' symptoms at baseline.

CONCLUSIONS

In adults with moderate-to-severe obstructive sleep apnea and obesity, tirzepatide given once weekly led to a significantly greater reduction in the apnea–hypopnea index at 52 weeks than placebo.

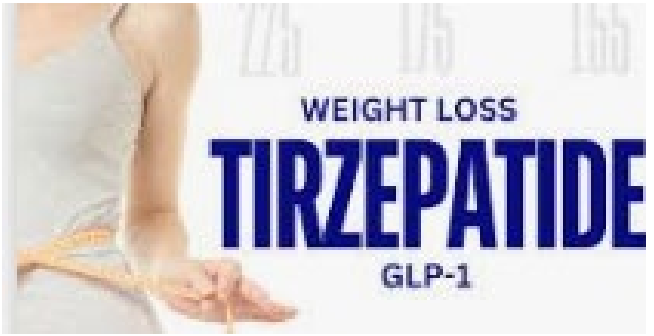
LINKS: FULL ARTICLE | NEJM QUICK TAKE | EDITORIAL

FURTHER INFORMATION

Trial registration: ClinicalTrials.gov number, NCT05412004

Trial funding: Eli Lilly

Full citation: Malhotra A, Grunstein RR, Fietze I, et al. Tirzepatide for the treatment of obstructive sleep apnea and obesity. N Engl J Med 2024;391:1193-205. DOI: 10.1056/NEJMoa2404881



June 2024

Thank you