Baptist Health
HEART INSTITUTE

OSA and cardiovascular disease- what is the evidence?

Mohan Edupuganti, MD, FACC.
Baptist Health Cardiology.

Disclosures: None

OSA basics

- Affects 20-30% of males and 10-15% of females in North America
- Repetitive collapse of a narrow pharynx that triggershypopnea/apnea during sleep

Risk factors

- Increased Age
- Male Gender
- Obesity- Neck Circumference, Waist Hip Ratio
- Racial Predisposition
- Craniofacial Predisposition
- Other- FH, smoking, congestion, menopause, pregnancy, substance abuse, ESRD, CVA, COPD, etc.

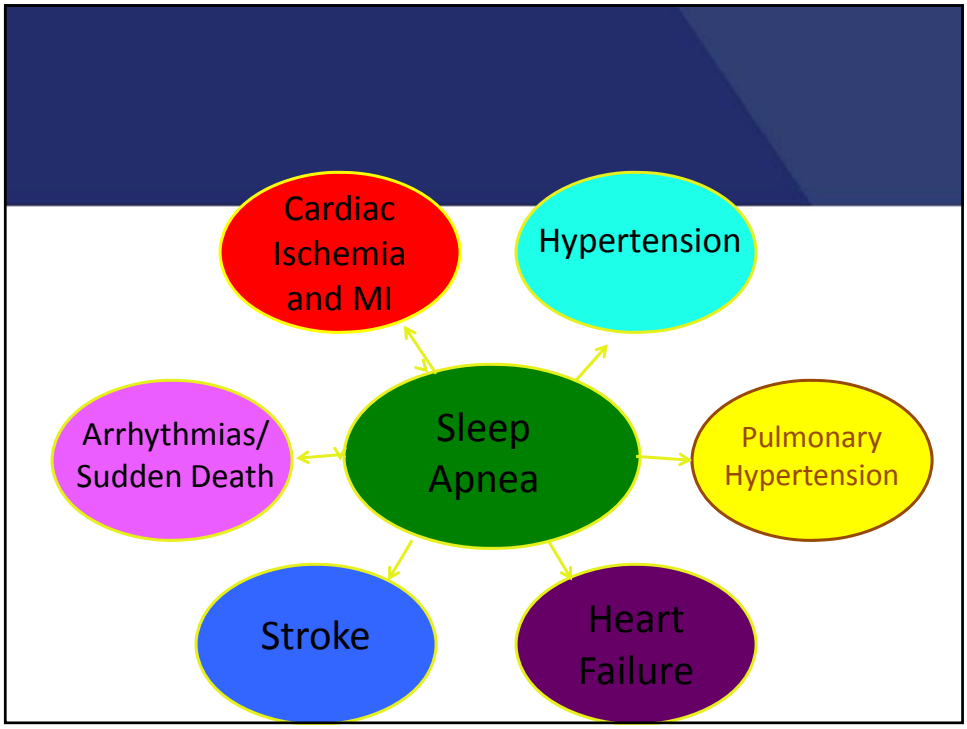
Symptoms.

- Snoring
- Choking/Gasping during Sleep
- Recurrent Awakenings
- Unrefreshing Sleep
- Daytime Sleepiness/Hypersomnolence
- Daytime Fatigue and Irritability
- Impaired Concentration or Memory

Diagnosis.

- Apnea-Hypopnea Index (AHI)

- Mild
  - AHI 5-15 with any SDB symptom
  - ≥ 15 without symptoms
- Moderate
  - AHI 15-30
- Severe
  - AHI > 30



CAD and sleep disordered breathing.

- SDB is associated with coronary artery calcification.
- In a study of 200 consecutive patients without a history of coronary artery disease who underwent electron-beam computed tomography within 3 years of polysomnography, the median coronary artery calcification score (Agatston units) was 9 in OSA patients and 0 in non-OSA patients (P0.001).
- Median calcification score increased as OSA severity worsened (P for trend by AHI quartile 0.001).
- Multivariate analysis confirmed an independent association between OSA and subclinical coronary artery disease, as measurable by coronary artery calcification.

Nocturnal angina and SDB

- Sleep apnea has been implicated in patients with nocturnal angina pectoris. Nocturnal angina and ST depression are diminished during treatment of sleep apnea by CPAP.

Long term outcomes

- SDB in patients with coronary artery disease was associated with a significant increase in the composite end point of death, myocardial infarction, and cerebrovascular events at a 5-year median follow-up interval.
- However, neither oxygen desaturation index nor AHI was independently predictive of single end points of myocardial infarction or death.
- In a case-control study, there was a graded increase in the odds of acute myocardial infarction with increased sleep apnea severity, even after adjustment for possible confounding factors.

Timing of sudden cardiac death.

- In patients experiencing sudden cardiac death, those proven to be free of OSA have the greatest likelihood of death between 6 and 11 AM, the traditional window of cardiovascular vulnerability.
- In striking contrast, more than half of sudden cardiac deaths in patients with proven OSA occur during the sleeping hours, between 10 PM and 6 AM

Effect of the treatment of OSA

- 3 observational studies have shown that treatment of OSA reduces fatal and non fatal cardiovascular events with the use of CPAP.
- There are no randomized controlled studies.

Effect of treatment of coronary artery disease on OSA.

- The benefits are limited to whatever improvement in LV function.

Arrhythmia

- NSVT
- Sinus arrest
- PVC
- Second degree AV block
- Atrial fibrillation

Causality

- Those with severe SDB have a 2 to 4 fold higher risk of arrhythmias.
- likelihoods of atrial fibrillation (OR, 4.02; 95% CI, 1.03 to 15.74).
- Ventricular tachycardia (OR, 3.40; 95% CI, 1.03 to 11.20),
- Complex ventricular ectopy (OR, 1.74; 95% CI, 1.11 to 2.74)

Bradyarrhythmias

- Vagal response often will elicit a discernible bradycardia, in a minority of OSA patients (perhaps 10%).
- Bradyarrhythmias such as atrioventricular block and asystole may develop, EVEN in the absence of cardiac conduction disease.
- These are most likely to occur during REM sleep and with a drop in oxygen saturation of at least 4%.
- First line treatment of these bradyarrhythmias is CPAP in the absence of cardiac conduction system disease.

OSA and pacemakers

- In one study of patients with pacemakers, OSA was present in 68% of patients – were pacemakers really needed in all these patients?

Atrial fibrillation- the evidence is indirect!!

- Data from Framingham and from the Danish Diet, Cancer and Health Study examining independent predictors of atrial fibrillation found obesity to be an important marker.
- Unfortunately the above studied, did not include OSA in their study.
- However, after adjustment for left atrial enlargement in the Framingham data, the effects of obesity were no longer significant.
- Sleep apnea has been associated with left atrial enlargement. That OSA leads to atrial fibrillation is an appealing but presently unproven hypothesis.

Atrial fibrillation and OSA- What is the evidence?

- In a retrospective cohort study of 3500 adults without past or current atrial fibrillation who underwent complete overnight polysomnography, both obesity and nocturnal oxygen desaturation were independent predictors of incident atrial fibrillation, but only in subjects 65 years of age.
- In patients with OSA, episodes of atrial tachyarrhythmia's mainly occur at night.
- Postoperative atrial fibrillation also may be more likely to occur in patients with OSA.
- The role of atrial fibrillation in any increased risk of stroke in patients with OSA remains to be determined

OSA and ventricular arrhythmias

- Premature ventricular contractions, have been reported in up to 66% of patients with sleep apnea, which is significantly higher than the rates reported in persons without sleep apnea (0% to 12%).
- In most OSA patients, ventricular arrhythmias appear most often during sleep, with the greatest frequency occurring during apneic periods.
- Although investigators may disagree on whether OSA patients without coexisting cardiovascular disease are more susceptible to ventricular arrhythmias compared with the non-OSA patient population, there is a perception that ventricular arrhythmias are most likely to occur in persons with the more severe forms of OSA and comorbid cardiovascular diagnoses.

OSA and Ventricular arrhythmias.

- Authors from a study found an increase in the frequency of premature ventricular beats when oxygen saturations fell intermittently below 60%.

Treatment of arrhythmias.

- If the underlying cardiac conduction system is normal and there is no significant thyroid dysfunction, bradyarrhythmias or heart block, both of which occur during apneic periods, may be treated effectively with CPAP or, if necessary, with tracheostomy.
- Observational data suggest that the presence of untreated OSA in patients after successful cardioversion for atrial fibrillation is associated with an 82% risk for recurrence of atrial fibrillation within 1 year, about double the risk seen in effectively treated OSA patients after cardioversion.

Treatment of arrhythmias

- In a randomized controlled trial of 1-month duration involving patients with OSA and systolic dysfunction, abolition of OSA by CPAP resulted in a 58% reduction in the frequency of ventricular premature complexes during sleep and a parallel reduction in nocturnal urinary norepinephrine concentrations.

Does treatment of arrhythmias have an impact on OSA.

- An initial report of atrial overdrive pacing in patients with pacemaker implantation for bradyarrhythmia demonstrated a 50% reduction in obstructive apneas.
- In a study comparing atrial overdrive pacing with CPAP, at both 24 hours and 1 month after initiation of treatment in patients with OSA, atrial overdrive pacing had no significant effect on OSA severity, whereas CPAP was highly effective in treating OSA.
- A prospective, single-blinded, randomized crossover trial of overnight temporary atrial pacing at 75 bpm in patients with moderate to severe OSA also showed that pacing did not significantly affect the AHI or the minimum nocturnal oxygen saturation.

Heart failure and OSA.

- In a study by wang et al. Of the 218 patients with heart failure, OSA with an AHI 15 was detected in 26%. OSA also has been noted in 50% of heart failure patients with preserved systolic function
- Three months of CPAP was reported to attenuate abnormalities in diastolic function, suggesting a potential etiologic role of OSA in diastolic heart failure.
- In the Framingham study, increased BMI, an important predisposing factor for OSA, also was associated with greater risk of developing heart failure.

Mechanisms

- The most direct mechanism by which long-standing OSA might induce left ventricular systolic dysfunction is by raising BP.
- Nocturnal oxygen desaturation is an independent predictor of impaired ventricular relaxation during diastole.
- left ventricular hypertrophy is more closely linked to hypertension during sleep than during wakefulness.
- Heart failure patients with coexisting OSA are exposed to adrenergic activation during sleep and when awake. BP rises above, rather than descends below, waking values. Thus, myocardial oxygen demand increases at times of recurrent hypoxia. Consequent metabolic mismatch could directly reduce myocardial contractility.

Mechanisms

- The repetitive generation of up to 65 mm Hg intrathoracic pressure against the occluded pharynx induces striking hemodynamic and autonomic responses.
- When subjected to such abrupt increases in afterload and therefore myocardial oxygen demand, patients with systolic heart failure experience more profound and prolonged reductions in stroke volume and greater reflex increases in central sympathetic outflow than control subjects with normal left ventricular function.
- These abrupt increases in left ventricular transmural pressure could play an important role in the development of myocardial ischemia, myocyte slippage, contractile dysfunction, and ventricular dilation.

Does OSA increase long term adverse outcomes in heart failure.

- In 78 patients with congestive heart failure being evaluated for possible heart transplantation, the presence of OSA did not affect long-term (52 months) survival .
- On the other hand, more recent data suggest that the presence of untreated OSA (AHI 15) in patients with heart failure is associated with an increased risk of death compared with patients with an AHI 15 independently of confounding factors.

Does treatment of OSA in patients with heart failure help?

- To date, randomized trials in heart failure have evaluated the impact of treating OSA on surrogate cardiovascular end points such as left ventricular ejection fraction rather than on hospitalization rates and mortality.
- The first study to examine the effects of CPAP on left ventricular function during the awake state was uncontrolled.
- Eight patients with idiopathic dilated cardiomyopathy and coexisting OSA were studied. After 1 month of CPAP, mean left ventricular ejection fraction increased from 37% to 49%.

Does treatment of OSA in patients with heart failure help?

- In the first randomized trial involving 24 patients with heart failure (mean left ventricular ejection fraction 45%) and moderate to severe OSA (mean AHI 20), 30 days of CPAP lowered daytime heart rate and systolic BP and increased ejection fraction by 9%..
- In a second larger randomized cohort with heart failure (mean left ventricular ejection fraction 55%) and OSA (mean AHI 5), there was a more modest 5% increase in ejection fraction after 3 months of CPAP treatment in the 71% of randomized patients who completed this trial.

Does treatment of OSA in patients with heart failure help?

- A third randomized study, and the only one that used a crossover design, showed no effects of auto titrating CPAP compared with subtherapeutic CPAP on peak$\dot{V}$O2, 6-minute walk distance, plasma catecholamines, or left ventricular ejection fraction.
- Recent observational data suggest a trend (P0.07) to a lower mortality rate in heart failure patients with CPAP-treated OSA compared with untreated OSA. However, whether CPAP treatment of patients with OSA and heart failure leads to mortality benefit has yet to be tested in a randomized clinical trial.

Does treatment of heart failure reduce OSA

- By improving left ventricular function and reducing edema, there may be an improvement in the degree of pharyngeal edema.
- There are no studies examining this effect.

OSA and Hypertension.

- In the Wisconsin Sleep Cohort Study, Hla et al and Young et al found a linear relationship between 24-hour BP and AHI that was independent of confounding factors such as BMI.
- Those patients with an attenuated nocturnal BP decline (nondippers) may be more likely to have coexisting OSA.
- A blunted nocturnal BP decline has been associated with greater leukoaraiosis (white matter disease).
- OSA has been proposed as an independent risk factor for the development of essential hypertension because it can precede and predict the onset of hypertension.

OSA and Hypertension.

- Effects of OSA on hypertension may be especially evident in middle-aged compared with older subjects, and OSA may predominantly raise systolic BP .
- OSA has also been implicated in pregnancy-associated hypertension. The severity of sleep apnea and the associated BP responses measured in the third trimester improve significantly (P0.03) after parturition, further supporting the concept that pregnancy may exacerbate sleep apnea.

OSA and resistant hypertension.

- Logan et al noted that the prevalence of OSA, defined as an AHI of 10, was 83% in those with resistant hypertension defined as a BP more than 140/90 while on 3 blood pressure medications.
- Increased aldosterone has been suggested as a possible contributor to resistant hypertension in sleep apnea.
- The weight of evidence has led the most recent Joint National Committee on the Detection and Management of Hypertension to identify OSA as an important identifiable cause of hypertension

Effect of treatment of OSA on hypertension- mixed results.

- Chronic effects of CPAP treatment are less clear because of the relative lack of robust longitudinal controlled studies.
- Three studies reporting a fall in BP used subtherapeutic (sham) CPAP in the control arm.
- The largest of all the studies (118patients) reported a reduction of 3.4/3.3 mm Hg (slightly larger during the day than during the night).
- In patients taking antihypertensive drugs, the 24-hour mean BP fall was about twice as large (6.7 versus 3.3 mm Hg), and the benefit was greater in patients with more severe OSA.

Effect of treatment of OSA on hypertension-mixed results.

- The second study found that both placebo CPAP and real CPAP reduced daytime BP equally well but that only real CPAP lowered the nighttime pressure.
- The third study found that therapeutic CPAP lowered daytime BP by 10.3/11.2 mm Hg more than subtherapeutic CPAP and nighttime pressure by 12.6/11.4 mm Hg.
- In another study comparing the effects of CPAP in hypertensives with and without OSA, CPAP lowered the nighttime pressure in those with OSA but had no effect on the daytime pressure.

Effect of treatment of OSA on hypertension-mixed results.

- A randomized placebo-controlled study of 1 month of therapeutic CPAP versus subtherapeutic CPAP on ambulatory BP showed no significant changes in systolic, diastolic, daytime, or nighttime BP.
- In 2 meta-analyses overall, the net reduction in BP (2 mm Hg) was significant but modest.
- A third meta-analysis included randomized controlled trials that reported systolic and diastolic BPs before and after CPAP/control and noted modest (1.5 mm Hg) decreases in both systolic BP (P0.23) and diastolic BP (P0.06).
- In 6 trials that evaluated more severe OSA (AHI 30), CPAP reduced systolic BP by 3 mmHg (P0.10) and diastolic BP by 2 mmHg (P0.05).

What does it mean?

- Patients with more severe OSA, difficult-to-control hypertension, and better CPAP compliance may have more substantial BP reduction with CPAP.

Effect of treatment of hypertension on OSA.

- Clonidine has been reported to suppress rapid eye movement (REM) sleep and hence to suppress the apneas occurring during REM, which resulted in lessened nocturnal hypoxemia.
- A comparison of the effects of 5 commonly used antihypertensive drugs (atenolol, amlodipine, enalapril, losartan, and hydrochlorothiazide) on BP and sleep architecture showed no effect on the severity of the sleep apnea.
- A recent report suggests that cough and rhinopharyngeal inflammation induced by angiotensin-converting enzyme inhibitors may worsen the AHI, which decreases after discontinuation of the drug.

OSA and cerebrovascular disease.

- Epidemiological studies suggest that habitual snoring, a possible marker for OSA, is a risk factor for brain infarction independently of confounding factors such as obesity and age.
- Similarly, excessive daytime sleepiness identified with the Epworth Sleepiness Score was significantly associated with stroke (OR, 3.07; 95% CI, 1.65 to 6.08).
- Some studies (211) noted a high prevalence of leukoaraiosis in those stroke patients who had sleep apnea, suggesting that OSA may lead to leukoaraiosis and consequently to stroke.

OSA and cerebrovascular disease.

- In a cross-sectional study of Japanese men, brain magnetic resonance imaging revealed silent brain infarction in 25% of patients with moderate to severe OSA but in only 8% of patients with mild OSA and in 6% of control subjects, suggesting that OSA may elicit early and asymptomatic cerebrovascular damage.
- In a cross-sectional analysis of 6000 subjects from the Sleep Heart Health Study, the OR of prevalent stroke was modestly greater (1.58) among those subjects with sleep apnea with an AHI 11.

What is the long term effect of OSA in patients with stroke.

- The evidence is mixed.

OSA and rehab potential of stroke.

- Several studies suggest that OSA in the post stroke patient reduces motivation, decreases cognitive capacity, and may increase the risk of recurrent stroke and death.
- Dyken et al noted that patients after stroke have a high prevalence of OSA and that those stroke patients with OSA had a markedly diminished post stroke survival.
- Direct studies of the interaction between sleep apnea and rehabilitation outcome after stroke that used overnight pulse oximetry to evaluate the respiratory disturbance index suggested that hypoxic events during sleep predicted poorer recovery, especially in patients with poor function at admission.

OSA and rehab potential of stroke.

- In polysomnographic studies of stroke patients in a rehabilitation unit, a high prevalence of sleep apnea, predominantly OSA, was accompanied by worse functional impairment and a longer time spent in hospital and rehabilitation.

OSA and pulmonary hypertension

- There are frequent episodes of increased pulmonary artery pressure during sleep in patients with OSA. It is less certain whether daytime pulmonary arterial hypertension also occurs in patients who do not have coexisting pulmonary or heart disease.
- In 1 series of 220 consecutive patients with OSA and an AHI 20, pulmonary arterial hypertension (mean arterial pressure 20 mm Hg) was found in 17% of patients. However, it was relatively mild (only 2 of 37 patients had a pulmonary artery pressure 35 mm Hg).
- Other smaller series of patients with OSA but no clinical history of chronic obstructive pulmonary disorder have reported daytime pulmonary arterial hypertension in 20% to 42% of cases.

OSA and pulmonary hypertension

- The pulmonary arterial hypertension seen in association with OSA is generally mild and can be attributed to an elevated pulmonary vascular resistance because cardiac output and capillary wedge pressure are normal, at least at rest.
- Pulmonary hypertensive OSA patients appear to have increased pulmonary vascular reactivity to hypoxia compared with patients without pulmonary arterial hypertension, and CPAP has been reported to decrease pulmonary vascular reactivity to hypoxia.

OSA and Pulmonary hypertension.

- Sleep studies are probably an appropriate part of the evaluation of the patient with pulmonary arterial hypertension.
- When elevated in patients with OSA, pulmonary artery pressures have been reported to fall after treatment with CPAP.
- In a randomized crossover study of 12 weeks of effective versus sham CPAP in 23 patients with OSA, effective CPAP was associated with decreases in echocardiographic measurements of pulmonary artery systolic pressure.
- Pulmonary artery pressures were especially reduced in those patients with pulmonary hypertension or left ventricular diastolic dysfunction at baseline.

Thank You