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REVIEW

Assessing the Pathophysiology, Morbidity, and Mortality of Obstructive Sleep Apnea

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The basic definitions of obstructive sleep apnea (OSA), its epidemiology, its clinical features and complications, and the morbidity and mortality of OSA are discussed. Included in this treatise is a discussion of the various symptomatic and polysomnographic phenotypes of COPD that may enable better treatment and impact mortality in persons with OSA. The goal of this article is to serve as a reference for life and disability insurance company medical directors and underwriters when underwriting an applicant with probable or diagnosed sleep apnea. It is well-referenced (133 ref.) allowing for more in-depth investigation of any aspect of sleep apnea being queried.

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Key words: Apnea, Hypopnea, AHI (Apnea hypopnea index), RERA (respiratory-event related arousal), RDI (respiratory disturbance index), REI (respiratory event index), AI (Arousal Index), UARS (upper airway resistance syndrome), CSA (central sleep apnea), HSAT (home sleep apnea test), PLMS (periodic limb movement of sleep), EES (Epworth sleepiness scale), STOP-bang questionnaire, T90 (time spent with oxygen saturation <90%), COMISA (comorbid insomnia and sleep apnea).

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BASIC DEFINITIONS

Sleep-disordered breathing (SDB) refers to a range of sleep-related breathing disorders that includes primary snoring, obstructive sleep apnea (OSA), central sleep apnea (CSA), Cheyne-Stokes respiration, and sleep-related hypoventilation. OSA is a disorder of sleep that is characterized by repetitive upper airway narrowing or collapse during sleep, which results in sleep fragmentation, oxygen desaturation with hypoxia and excessive daytime sleepiness. When the term OSA is used concurrently with cardiometabolic disease, the medical literature commonly uses obstructive sleep apnea syndrome (OSAS), which functionally is the same thing as OSA. OSA is a clinical diagnosis that requires confirmation with testing called polysomnography (PSG) or simpler but less diagnostic home sleep apnea test (HSAT).

- **Apnea** is defined as a complete cessation of airflow for at least 10 seconds
- **Hyponea** is a partial reduction in airflow (≥30 percent of pre-event baseline) for ≥10 seconds accompanied by a decrease in blood oxygen saturation of at least 3% or the event is associated with an electroencephalogram (cortical EEG) arousal (American Academy of Sleep Medicine-AASM definition) or ≥4% oxygen desaturation (criteria used by Centers for Medicaid

and Medicare Services (CMS) with no requirement for EEG arousal).

- **AHI** is the Apnea-Hyponea Index (as both apneas and hypopneas have identical implications to sleep disordered breathing) is defined as [apneas + hypopneas] ÷ total sleep time in hours. Ideally, a total AHI inclusive of central and obstructive events will be reported along with a separate total for central apnea index.
- Respiratory effort-related arousals (**RERAs**) designate sequence of breaths lasting ≥10 seconds characterized by increasing respiratory effort or by flattening of the inspiratory portion of the flow signal leading to an arousal from sleep when the sequence of breaths does not meet criteria for an apnea or hypopnea. Note that the AASM 'recommended hypopnea rules' allow hypopneas to be recognized as associated with an arousal, thus identifying many events that previously would have been missed without the RERA classification.
- The Respiratory disturbance index (**RDI**) is defined as [apneas + hypopneas + RERAs] ÷ total sleep times in hours. Because of the inclusion of RERAs, the RDI classifies more patients as having OSA than does the AHI, using the same threshold values. There is conjecture that the AHI may correlate better with cardiovascular outcomes, while the RDI may yield more information about daytime sleepiness and symptoms (i.e., from sleep fragmentation). Most polysomnogram reports include both OSA and RDI information
- Respiratory Event Index (**REI**) is defined as [apneas + hypopneas ÷ estimated total recording time] by HSAT. This measurement is commonly recorded in home testing devices which do not include EEG monitoring, and RERAs and hypopneas characterized by arousals cannot therefore be reliably identified. The number of respiratory events per hour of recording time rather than total sleep time is used to generate the REI. The REI correlates well with AHI and RDI, but is typically lower since the denominator (i.e., total recording time) is larger than total sleep time used to calculate AHI and RDI.[1,2]

AHI values are used to classify the severity of OSA. Normal is AHI < 5 events per hour.

Positional OSA (**POSA**) may be mentioned in a polysomnogram report and refers to the fact that episodes of airway obstruction in OSA are more frequent and more severe in the supine compared to the lateral body position in all patients. Patients with POSA have lower body mass index (BMI), smaller neck circumference, longer posterior airway space measurements, and smaller lateral pharyngeal wall tissue volumes.[3,4]

Another term that may be encountered in polysomnographic reports is rapid eye movement (REM)-related OSA. Several physiological effects uniquely predispose airways to collapse in REM versus non-rapid eye movement (NREM) sleep. In REM, the genioglossus muscle activity is lower, the respiratory drive is lower, and the autonomic drive is higher than in NREM. These factors result in a longer duration of obstructive events and deeper hypoxemia in REM than in NREM. "REM-related OSA" denotes the AHI being at least double the AHI in NREM, and the prevalence of REM-related OSA varies from 13.5 percent to 36.7 percent.[5]

Mild OSA/RDI/REI: AHI 5-15 events per hour. The sleep stages and slow wave sleep are generally preserved in mild OSA. Even when asymptomatic, mild OSA is associated with increased risk of hypertension, especially in younger ages.[6] Using the latest AASM definition of hypopnea, symptomatic patients with mild OSA are without increased cardiovascular risk.[7]

Moderate OSA/RDI/REI: 15-30 events per hour. These patients are usually aware of daytime sleepiness and compensate by taking naps or avoiding driving long distances. These patients do have increased risk of mortality from auto accidents and have increased likelihood of being hypertensive.

Severe OSA: AHI/RDI/REI: > 30 events per hour. These subjects tend to fall asleep during the day even when sitting upright. They are at increased risk for all-cause mortality and a variety of cardiovascular comorbidities, including hypertension, coronary artery disease, and arrhythmias.

Oxygen Desaturation is the blood oxygen level throughout the sleep study. During apneas and hypopneas, blood oxygen levels may drop. The severity of OSA may be determined by the percentage (time), severity, and frequency of oxygen desaturation episodes, usually under the term **T90** (time spent <90% $Sa0_2$).

Sleep Stages: Polysomnographic studies monitor brain wave activity (EEG), eye movements (EOG), and muscle activity (EMG) to determine the different sleep stages throughout the night. These stages include:

- Non-rapid eye movement (NREM) sleep stages 1-3 (progressively deeper sleep)
- Rapid eye movement (REM) sleep (associated with dreaming and relative peripheral muscle paralysis)

Stage 3 is called "restorative sleep" that gives people the feeling that they've gotten a good-night's sleep. With moderate and especially severe OSA, patients rarely achieve Stage 3 sleep are therefore groggy and sleepy the following day.

Arousal Index: this measures the number of brief awakenings or arousals from sleep during the night. Arousals may or may not be consciously perceived by the sleeper. They can be caused by apneas, hypopneas, snoring, or leg movements (periodic leg movements of sleep – **PLMS**).

Upper airway resistance syndrome (**UARS**) occurs when airflow limitation is due to increased upper airway resistance that induces arousals from sleep (i.e., RERAs) and leading to excessive daytime sleepiness. These patients do not meet formal criteria for OSA of apneas or hypopneas. On a PSG tracing, these patients usually display respiratory effort-related arousals (RERAs), defined as > 10 second sequences of breaths with increasing respiratory effort or flattening of the inspiratory portion of the flow signal, leading to an arousal.[8,9] UARS is considered a phenotype of sleep-disordered breathing and therefore is a subset of OSA. It is common in thin females with certain craniofacial abnormalities,[10,11] although one study reported a male-to-female ratio of 3.[12]

Unlike patients with classic OSA, patients with UARS have few discrete apneas or hypopneas or episodes of desaturation but do have prolonged flow limitation and evidence of arousals on PSG, albeit with less overall sleep fragmentation than OSA, often leading to a PSG diagnosis of absent or mild OSA. UARS is successfully treated with CPAP with usually good adherence to therapy.[13]

It should be noted that UARS is no longer recognized as a nosological entity by the current edition of the International Classification of Sleep Disorders, as its pathophysiology is the same as OSA. But as much as the term UARS has fallen out of favor, the value of this designation lies in underscoring the importance of respiratory-related sleep fragmentation in causing symptoms of sleepiness and impaired daytime functioning that may not be reflected by the AHI.[14]

Central sleep apnea (CSA) is a disorder characterized by repetitive cessation or decrease in both airflow and ventilatory effort during sleep encountered mostly in older male adults. CSA is less common than OSA and is often associated with cardiac, stroke, or opioid abuse; rare cases are primary or idiopathic ("Ondine's Curse"). In a population-based study that included 5804 community-dwelling adults aged 40 years and older, the overall prevalence of CSA on polysomnography was 0.9%. Approximately half of CSA cases are associated with Cheyne-Stokes breathing (0.4 percent overall). The implications for mortality in this disorder is greater than with obstructive apneas, likely due to the common comorbidity with heart

failure.[15] Primary CSA requires ≥5 central apneas and/or central hypopneas per hour of sleep and the number of central apneas/hypopneas is ≥50 percent of the total number of apneas and hypopneas, with no evidence of daytime hypoventilation.

Obesity hypoventilation syndrome (OHS, also known as the Pickwickian Syndrome) is the most extreme of sleep-disordered diseases, defined by awake hypercapnia ($PaCO_2$ ≥45 mmHg) in obese individuals (BMI ≥30 kg/m^2) that is not otherwise explained by restrictive lung disorders or neuromuscular disease. The prevalence of OHS in the general population is no more than 0.4 percent, but when these individuals are referred to sleep clinics, prevalence rate increases up to 10 percent. In approximately 70 percent of those with OHS, severe OSA (AHI ≥30/hour) is present while in 10 percent the abnormality is non-apneic sleep-dependent hypoventilation only, particularly in REM sleep. Non-invasive ventilation has proven to be superior to CPAP in this disorder.[16,17]

EPIDEMIOLOGY OF OSA

OSA is the most common sleep-related breathing disorder, with an estimated prevalence in North America of approximately 15 to 30 percent in males and 10 to 15 percent in females when OSA is defined as an apnea-hypopnea index (AHI) greater than five events per hour of sleep. When more stringent definitions are used (i.e., AHI ≥5 events per hour plus symptoms or AHI ≥15 events per hour), the estimated prevalence is approximately 13 percent in males and 6 percent in females.[18] Global estimates using criteria for moderate to severe OSA are up to 1 billion people between the ages of 30 and 69 years of age.[19]

Consistent across all epidemiological studies, the prevalence of OSA is associated with sex, obesity, and age. Prevalence is higher in men by 2:1, but rates increase in women after menopause and become nearly equal.[20]

The prevalence of OSA also varies by race. OSA is more prevalent in African Americans who are younger than 35 years old compared with White Americans of the same age group, independent of body weight.[21,22] Individuals with a first-degree family member with OSA have approximately a two-fold increased risk of having the disorder suggesting a genetic component and the family aggregation is not explained by obesity.[23]

Clinical Features and Screening for OSA

As BMI increases, the risk of OSA rises, with an increase in prevalence of AHI ≥15 from 3.6% percent in normal weight to 56 percent in those with BMI ≥40 among men aged 50-70 years.[16] OSA increases with age through, and perhaps beyond, age 50, and there also appears to be a genetic predisposition as well.[24] Most patients with significant OSA complain of daytime sleepiness, or their bed partner reports loud snoring, gasping, choking, snorting, or interruptions in breathing while sleeping. Daytime sleepiness may be underestimated because of its insidious onset and chronicity, with patients using terms such as fatigue, tiredness, low energy, or poor focus.[25] The most predictive symptom for identifying individuals with OSA may be nocturnal choking or gasping episodes.[26]

To distinguish fatigue from sleepiness of OSA, clinicians use a series of directed questions that are compiled into the **Epworth Sleepiness Scale (ESS)** to quantitatively document the patient's perception of sleepiness, fatigue, or both. The ESS ratings consist of 0 (would never dose), 1 (slight chance of dozing), 2 (moderate chance of dozing), 3 (high chance of dozing). **See Table 1**.

An ESS score of >10 indicates excessive daytime sleepiness. Scores >16 indicate high levels of daytime sleepiness and are associated with at least moderate severity of OSA. ESS scores significantly distinguish patients with

Table 1. Epworth Sleepiness Scale

Situation	0	1	2	3
Sitting and reading				
Sitting inactive in a public place or meeting				
As a passenger in a car for an hour without a break				
Lying down to rest in the afternoon when circumstances permit				
Sitting and talking with someone				
Sitting quietly after a lunch without alcohol				
In a car, while stopped for a few minutes in traffic				

primary snoring from those with OAS, and ESS scores increase with the severity of OSA. Multiple regression analysis shows that ESS scores are more closely related to the frequency of apneas than to the degree of hypoxemia in OSA.[27] Subjective fatigue and sleepiness can be independent manifestations of sleep disorders.[28]

Another commonly used questionnaire for detecting OSA is the **STOP-Bang Questionnaire**. See Table 2.

Scoring Criteria: Low risk of OSA: Yes to 0 to 2 questions, Intermediate risk of OSA: Yes to 3 to 4 questions, High risk of OSA: Yes to 5 to 8 questions.[29–31]

Other screening tools not covered include the Berlin questionnaire,[32] which contains a total of 10 items, and a newer tool called NoSAS[33] which includes five items assessing mostly objective data such as BMI and neck circumferences with scores ranging from 0 to 17 and a score ≥8 denoting high risk for OSA. The STOP-BANG has the highest sensitivity for moderate-to-severe OSA (87 percent); the evidence is unclear as to which questionnaire is the most specific.

Counterintuitively, approximately one-third of patients with OSA complain of sleep initiation insomnia or sleep maintenance insomnia with repetitive awakenings, and this population of OSA patients complain of insomnia rather than daytime sleepiness. This phenomenon is more common in females.[34,35]

Complaints of snoring, while common in patients with OSA, has been found to have no predictive value in one study (likelihood ratio 1.1).[25] On the other hand, the absence of snoring (particularly in the absence of risk factors such as obesity) reduces the likelihood of a diagnosis of OSA almost to zero.

A study of 1543 subjects with habitual snoring found a significant positive correlation between the severity of the OSA and snoring intensity.[36] Morning headaches are reported by 10 to 30 percent of patients with untreated OSA. However, a comparison of those with OSA with or without headache showed no significant differences, and specifically oxygen desaturation alone did not explain the pathophysiology of sleep apnea headache.[37]

The US Preventive Services Task Force (USPSTF), after reviewing 4 systematic reviews evaluating the effect of positive airway pressure

Table 2. STOP-Bang Questionnaire

Yes	No	**Snoring?** Do you snore loudly (loud enough to be heard through closed doors, or your bed partner elbows you for snoring at night?
Yes	No	**Tired?** Do you often feel tired, fatigued, or sleepy during the daytime (such as falling asleep during driving)?
Yes	No	**Observed?** Has anyone observed you stop breathing or choking/gasping during your sleep?
Yes	No	**Pressure?** Do you have or are you being treated for high blood pressure?
Yes	No	**B**ody mass index more than 35 kg/m^2?
Yes	No	**A**ge older than 50 years old?
Yes	No	**N**eck size large (measured around Adam's apple)? Is your shirt collar 16 inches or larger?
Yes	No	**Gender = Male?**

on AHI and blood pressure, 63 RCTs comparing positive airway pressure with sham treatment, 31 RCTs reporting on mortality, 48 trials reporting on changes in excessive daytime sleepiness using ESS, and 28 RCT on improvements in quality of live, does not recommend screening of OSA.[38]

Physical Examination

Obesity (BMI $\geq$30 kg/m^2) is the most common clinical finding in patients with OSA. Many patients have a crowded oropharyngeal airway, and the modified Mallampati classification is commonly used to quantify airway narrowing, with classes 3 and 4 considered positive for significant airway narrowing and to correlate with OSA severity.[39]

OSA is more strongly correlated with an increased neck size or waist circumference than general obesity,[40] and OSA is particularly prominent among males who have a collar size greater than 17 inches and females who have a neck size greater than 16 inches.[41] Cutoff values for waist circumference and for waist-to-height ratio for females with OSA were 95.5 cm and 0.595, respectively, whereas the values for males were 100.5 cm, and 0.575, respectively.[42]

Several pathophysiological traits have been shown to contribute to the pathogenesis of OSA. All patients with OSA share some anatomic predisposition to upper airway collapse. These endotypes include: (1) s smaller, collapsible upper airway based on obesity and airway anatomy (found in 46%), (2) reduced upper airway dilator muscle responsiveness (36%), (3) lower arousal threshold (found in 88%, 73% and 23% of patients with mild, moderate and severe OSA, respectively, suggesting that this endotype is more important in patients with mild rather than a severe disorder), and (4) increased sensitivity of the ventilatory control system (36%)-loop gain-which is discussed later in this article.[43,44]

Complications of OSA

Motor vehicle accidents are two to three times more common among patients with OSA than without OSA.[45,46] OSA can induce or worsen inattention, memory, and cognitive deficits which, together, can result in impaired executive function and increase the likelihood of errors and accidents.[47–50]

Approximately 50 percent of patients with OSA have coexisting hypertension which is often most elevated in the morning.[51–53] In a study of 1741 men and women, sleep-disordered breathing was independently associated with hypertension when potential cofounders were controlled for in the logistic regression analysis. This relationship was strongest in young subjects, especially those of normal weight, a finding that is consistent with previous findings that SDB is more severe in young individuals.[54]

Patients with resistant hypertension have a very high prevalence (71 to 85 percent) of OSA, with the severity of sleep apnea correlating with the severity of hypertension, and both the incidence and severity of sleep apnea being greater in men than women.[55,56]

Patients with OSA have an increased prevalence of insulin resistance as well as type 2 diabetes and diabetic complications.[57,58] Although this association may be manifested through shared risk factors such as obesity, an independent association between OSA severity, insulin resistance, and type 2 diabetes has been reported in a number of studies.[59–64] In one study, about 12 percent of patients with OSA developed diabetes over a 67-month period; patients with severe OSA (apnea-hypopnea index [AHI] $\geq$30 events per hour) had an approximately 30 percent higher risk of incident diabetes compared with patients without OSA.[58]

In patients with the metabolic syndrome, OSA has been independently associated with increased glucose and triglyceride levels as well as markers of inflammation, arterial stiffness, and atherosclerosis, suggesting that OSA may exacerbate the cardiometabolic risk

attributed to obesity and the metabolic syndrome.[65] In addition, patients with severe OSA have a two-to threefold increased prevalence of nonalcoholic fatty liver disease (NAFLD) that is independent of shared risk factors such as obesity and is particularly associated to nocturnal hypoxemia.[66–68]

Pathophysiology of OSA

OSA is associated with a significant increase in sympathetic activity in sleep which appears to be induced through a variety of different mechanisms, including chemoreflex stimulation by hypoxia and hypercapnia, baroreflexes, pulmonary afferents, impairment in venous return to the heart, alterations in cardiac output, and possibly the arousal response. Endothelial dysfunction may also play a role.[69]

"Loop gain" is an engineering term used to define the stability ("low" loop gain) or instability ("high" loop gain) of a negative feedback control system. Control of breathing is a negative feedback system in which chemoreceptors (e.g., in the carotid body; "controller") and the lung ("plant") try to maintain a $PaCO_2$ at roughly 40 mmHg. In this setting, a high loop gain leads to large fluctuations in carbon dioxide (CO_2). For instance, if an individual were to respond to an increase in $PaCO_2$ from 40 to 45 mmHg with hyperventilation lowering the $PaCO_2$ down to 10 mmHg, then major fluctuations in CO_2 would occur. In OSA, the contribution of loop gain to OSA pathogenesis is not clear, but many believe it plays an important role.[70,71] A hypopnea may be destabilizing if a patient experiences a marked response to such as respiratory disturbance. Some have coined the expression "apnea begets apnea" based on the self-perpetuating nature of the control system abnormalities.[1]

Mortality and Morbidity of OSA

Observational studies have demonstrated a consistent association between OSA and hypertension, coronary heart disease, cardiac arrhythmia, and heart failure. Sex-specific differences exist in the relationship between OSA and CV disease. In one study, OSA, assessed in midlife, was independently associated with higher levels of concomitantly measured high-sensitivity troponin T among women but not men, in whom other comorbidities associated with OSA may play a more important role. During a 13-year follow-up, OSA was associated with incident heart failure or death only among women and, among those without an incident event, it was independently associated with left ventricular hypertrophy only in women.[72]

Most studies have demonstrated these associations independent of the confounding influence of obesity.[51] However, the impact of the mortality due to these diseases varies among studies. The short duration of most trials and the small number of total events makes it difficult to assess the effect of positive airway pressure on cardiovascular and cerebrovascular events, leading to the USPSTF's recommendation against screening for OSA.[38] Nonetheless, other studies related to the possible mortality seen in persons with OSAS will be reviewed.

In a study of 6,441 men and women participating in the Sleep Heart Health Study, compared to those without sleep-disordered breathing (AHI:<5 events/h), the fully adjusted hazard ratios for all-cause mortality in those with Mild (AHI: 5.0-14.9 events/hour) was 0.93 (95% CI: 0.80-1.08), moderate (AHI: 15.0-29.9 events/hour) was 1.17 (95% CI: 0.97-1.42), and severe (AHI>30 events/hour) was 1.46 (95% CI: 1.41-1.86). Stratified analyses by sex and age showed that the increased risk of death associated with severe sleep-disordered breathing was statistically significant in men aged 40-70 y (hazard ratio: 3.09; 95% CI: 1.31-3.33).[73]

A meta-analysis by Fu *et al.*[74] examined the relationship between OSA and all-cause and CV mortality in 27 cohort studies. Severe OSA (AHI >30), but not mild or moderate OSA, had increased risk for both all-cause

mortality (HR 1.86, 95% CI 1.81-1.91) and CV mortality (HR 2.36, 95% XI 1.22-4.57). There were no differences in cardiovascular mortality in CPAP-treated OSA patients vs. normal control subjects (HR 0.82, CI 0.52-1.29).

In a population of 10,700 adults referred for polysomnography, OSA predicted incident sudden cardiac death, and the magnitude of risk was predicted by multiple parameters characterizing OSA severity. Nocturnal hypoxemia, an important pathophysiological feature of OSA, strongly predicted SCD independently of other well-established risk factors, with a hazard ratio (HR) of 2.93 with mean nocturnal oxygen saturation $< 93\%$ and HR of 2.60 with lowest nocturnal oxygen saturation $<78\%$.[75]

In a study of 9076 registrants in the National Health and Nutrition Examination Survey (NHANES) 2005-2008, OSA status was positively associated with higher risks of cardiometabolic diseases, including hypertension (odds ratio [OR] 1.28, 95% CI 1.14-1.45; $p<0.001$), diabetes (OR 1.45, 95% CI 1.22-1.76; $p<0.001$), and cardiovascular diseases (OR 1.29, 95% CI 1.08-1.54; $p=0.006$) after adjusting for numerous covariates. However, no associations of OSA with all-cause or cardiovascular mortality were observed.[76]

Contrasting this study was one by Marin *et al.*[77] that showed that untreated severe obstructive sleep apnea-hypopnea significantly increased the risk of fatal (odds ratio 2.87, 95% CI 1.17-7.51) and non-fatal (3.17, 95%CI 3.17, 1.12-7.51) cardiovascular events compared with health persons.

In a Wisconsin Sleep Cohort Study by Hla *et al.*[78], after adjusting for age, sex, body mass index, and smoking, estimated hazard ratios (95% CI) of CAD or CHR was 1.5 for AHI $>$ 0-5, 1.9 for AHI 5 $\leq$ 15, 1.8 for AHI 15 $\leq$ 30, and 2.6 for AHI $>$ 30 compared to AHI = 0.

In another study (4,422 men and women $\geq$ 40 years of age and free of coronary heart disease and heart failure at the time of baseline polysomnography) subjects were followed up for a median of 8.7 years. After adjustment for multiple risk factors, obstructive sleep apnea was a significant predictor of incident coronary heart disease (myocardial infarction, revascularization procedure, or coronary heart disease death only in men $\leq$ 70 years of age (adjusted hazard ratio 1.10 (95% CI 1.00-1.21) per 10-unit increase in apnea-hypopnea index (AHI), but not in older men or in women of any age. Among men 40 to 70 years old, those with AHI $\geq$ 30 were 68% more likely to develop coronary heart disease than those with AHI <5. In this study, OSA predicted incident heart failure in men but not in women (adjusted hazard ratio 1.13 [95% CI 1.02-1.26] per 10-unit increase in AHI. Men with AHI $\geq$ 30 were 58% more likely to develop heart failure than those with AHI <5).[79]

Nadir SpO_2 was the only independent sleep-disordered breathing predictor of sudden cardiac death in one observational study of 10,700 individuals.[80] However, other observational studies have found severe OSA to be associated with higher odds of CV death, increasing levels of OSA and degree of hypoxemia associated with complex ventricular ectopy and central apneas associated with atrial fibrillation.[73]

A strong association (up to fourfold higher odds) between OSA and atrial fibrillation (AF), independent of obesity and other confounding influences, has been described in multiple studies. Gami *et al.*[81] was the first to report a strong association existing between OSA and AF, such that OSA is strikingly more prevalent in patients with AF than in high-risk patients with multiple other cardiovascular diseases. The adjusted odds ratio for the association between AF and OSA was 2.19 (95% CI 1.40 to 3.42, $p=0.0006$).

OSA may contribute to arrhythmias due to several mechanisms, such as generation of negative intrathoracic pressure during futile efforts to breath, intermittent hypoxia and surges in sympathetic activity. In addition, OSA may lead to heart remodeling and increases arrhythmia susceptibility. Atrial distension and remodeling, that has been

shown to be associated with OSA, is a well-known anatomical substrate for AF. Nocturnal hypoxemia may also increase vagal tone, which increases susceptibility to bradycardic and conduction rhythm disorders that have also been described in patients with OSA. Nocturnal hypoxemia predicts sudden cardiac death (SCD) independently of well-established cardiovascular risk factors.[82]

One study of almost 3000 older men found that prevalence of AF correlated better with central versus obstructive sleep apnea, whereas complex ventricular ectopy correlated better with worsening severity of OSA.[83] Whether treatment of OSA improves AF burden and outcomes is unclear. Li *et al.*[84] identified five studies involving 3743 patients with AF. Patients with OSA had a 31% greater risk of AF recurrence after catheter ablation and this risk increased by 57% in patients with OSA not using CPAP.

Another study of almost 1,100 patients with AF found that OSA treated with CPAP led to a reduction in AF recurrence.[85] However, in another study of 108 patients with moderate to severe OSA and paroxysmal AF were observed to have no substantial benefit with the addition of CPAP therapy.[86]

In a small study of patients with OSA and bradyarrhythmias, insertable loop recorders found that approximately half of OAS patients had severe cardiac rhythm disturbances which were significantly reduced by CPAP, whereas Holter recordings seem unable to precisely describe the incidence of severe brady-arrhythmias and the effect of treatment.[87]

In a cohort study of more than 10,000 patients that identified nadir oxygen saturation as a predictor of sudden cardiac death (SCD), 31 percent of those with SCD had definite ventricular arrhythmia as a verified cause, and ventricular ectopy or nonsustained ventricular tachycardia was an independent risk factor for SCD among those with OSA (hazard ratio [HR] 4.1, 95% CI 1.6-10.1).[88]

The prevalence of pulmonary hypertension (defined as a mean pulmonary arterial pressure >25 mmHg at rest) in patients with moderate to severe OSA is approximately 20 percent.[89,90]

When present in patients without coexisting lung disease, the degree of pulmonary hypertension is typically mild. OSA in patients with PAH is associated with worse prognosis in left ventricular heart failure, but nocturnal hypoxemia (and not the severity of OSA) best related to poor prognosis.[91]

Increased mortality has been reported in people with insomnia as well as those with OSA. These conditions commonly co-occur and the combined effect of comorbid insomnia and sleep apnoea (COMISA) on mortality risk was evaluated in 137 patients from the Sleep Heart Health Study (SHHS). Persons with COMISA had a higher prevalence of hypertension (OR 2.00) and cardiovascular disease (OR 1.70) compared with the reference group. Compared with the reference group (persons without insomnia or OSA), COMISA was associated with a 47% (hazard ratio 1.47, 95% CI 1.06-2.07) increased risk of mortality. COMISA was also associated with higher rates of CVD and hypertension compared with persons with insomnia-alone or OSA-alone.[92]

IMPACT OF TREATMENT

While most studies report improvement in sleep-related respiratory events, daytime sleepiness, blood pressure control, and intermediate cardiovascular endpoints with CPAP, none has unequivocally shown benefits in the reduction of cardiovascular events (i.e., cardiovascular mortality, acute myocardial infarction, stroke) as a whole.

The Sleep Apnea Cardiovascular Endpoints (SAVE) study is one of the largest multicenter randomized clinical trials to examine the impact of CPAP on cardiovascular outcomes. This study of 2717 person with moderate to severe OSA and established CVD were randomized to CPAP therapy plus usual care or usual care alone and followed for 3.7 years. Despite a reduction in the apnea-hypopnea

index (AHI) from 20 to 3.7 events per hour per night (indicating overall adequate control of OSA), CPAP was not associated with a significant reduction in cardiovascular deaths, myocardial infarction, stroke, or hospitalization for heart fail, angina, or transient ischemic attack.[93]

Given the extent of conflicting data about effect of CPAP use on CV outcomes, the RCT by Peker *et al.*[94] noted that there is "insufficient and inconclusive evidence to either recommend or withhold CPAP to treat non-sleepy adults with OSA to reduce CV events or mortality. Another RCT by Sánchez-de-la-Torre *et al*[95] concluded that CPAP did not reduce the prevalence of cardiovascular events.

Several meta-analyses of randomized trials of patients with OSA (9 trials with CPAP, 1 trial with ASV [Adaptive Servo Ventilation, which provides a varying amount of inspiratory pressure superimposed on a low level of CPAP] in 7266 persons, mean age 60.9) have reported that, compared with no treatment or sham, CPAP did not result in a reduction in the risk of major cardiovascular events (acute coronary events, stroke, or vascular death) or all-cause death.[96] The lack of benefit was reported despite OSA severity as well as duration of therapy.[97] Craniofacial surgery and uses of oral devices are considered second-line to CPAP in OSA.

Obstructive Sleep Apnea Phenotypes

Subjects with OSA are heterogeneous, with varying risk factors, pathophysiological causes, clinical manifestations, and consequences. Studies using an analytic approach such as cluster analysis have revealed this heterogeneity to identify OSA phenotypes (or subtypes of patients with unique characteristics) that may better estimate treatment and prognosis. The efficacy of OSA treatment and its prognosis may vary depending on these characteristics.[98–100]

However, the current paradigm for diagnosis and management of OSA largely reflects a one-size-fits-all approach whereby polysomnographic data are reduced to a single metric (the apnea-hypopnea index [AHI]) and patients are managed by trial and error initially with CPAP. This approach may be one reason that the field's large, multicenter clinical trials of CPAP therapy have shown modest or no risk reduction in cardiovascular disease, death, or improvement of neurocognitive outcomes.

An alternative approach is to leverage the heterogeneity of OSA by classifying it into smaller, more homogeneous disorder subtypes, referred to as phenotypes.[44,101] For example, an OSA anatomical phenotype defined by lack of complete concentric palatal collapse has helped identify responders to implanted airway neurostimulation, enabling a new treatment option.[102] Hypothesis-generating approaches, using unsupervised learning methos such as cluster analysis, focus on discovering emerging patterns within the data by grouping subjects into homogenous categories based on unique associations between subject features.

Ideally, members of each cluster are as similar as possible to each other and as different as possible from those in other clusters.[103] These techniques have been used by several groups to identify degree of symptom and sleepiness,[104] polysomnographic,[101] and comorbidity[105] clusters among patients with OSA, with differing quality of life (QOL), treatment use and benefit,[106] and risk for developing cardiovascular disease, where the "excessively sleepy" group was found to have increased risk of incident cardiovascular disease (hazard ratio [HR] of 2.2-2.4, driven by coronary heart disease and heart failure compared with other clusters.[107]

For instance, in one study the rates of composite cardiovascular events were highest in coronary artery + diabetes phenotype (HR 2.08, 95% CI 1.57-2.76) and for stroke were highest in cerebrovascular disease + diabetes phenotype (HR 6.84, 95% CI 3.77-12.42).[108]

Mazzotti *et al.*[107] described four subtypes: disturbed sleep (12.2%), minimally symptomatic (32.6%), excessively sleepy (16.7%),

and moderately sleepy (38.5%). Although no significant associations with prevalent CV disease were found, the excessively sleepy subtype was associated with more than three-fold increased risk of prevalent heart failure compared with the other subtypes.

Zinvhuk *et al.*[103] proposed six subtypes from cluster analyses.

Subtype A includes younger, obese, predominantly male individuals with severe OSA and "classic" symptoms of sleepiness and drowsy driving. The younger age of these patients may reflect an earlier diagnosis given their recognizable symptoms. This subtype tended to benefit most from CPAP treatment in terms of improving symptoms and QOL.[109] These patients were at highest risk of drowsy driving (18%-30%) and, based on this "excessively sleepy" cluster of Mazzzotti *et al.*[111] were at an increased risk (HR, 2.2-2.4) of incident cardiovascular disease (CVD) and stroke. This subtype may represent a higher-yield group for CPAP therapy, although the impact of CPAP on CVD has not been decidedly assessed given the exclusion of the hyper-sleepy patients from previous randomized clinical trials finding no benefit of CPAP for prevention of CVD.

Subtype B consists of older, obese, predominantly male subjects with minimal to moderate symptom burden, frequent comorbidities, and severe OSA with marked hypoxemia. Older age at diagnosis may reflect unrecognized symptoms of OSA or development of the disorder later in life. The high prevalence of hypertension, diabetes, and CVD in this group is consistent with both older age and the impact of profound, ongoing desaturation.[110,111] CPAP has generally not been helpful in this subgroup, particularly in prevention of CVD, except in the excessively sleepy subtype.[112]

Subtype C include middle-aged, mildly obese, predominantly female subjects with symptoms of insomnia (difficulty falling and staying asleep, early awakenings, and nonrestorative sleep). Several studies have shown that 10% to 35% of these patients exhibited analogous symptoms with moderate to severe OSA and hypertension, diabetes, and CVD prevalence that are generally higher than for Subtype A.[12,111] Previous studies have shown that patients with comorbid OSA and insomnia exhibit lower CPAP adherence versus those with OSA alone and that middle-of-the-night insomnia, rather than sleep onset or early awakenings, tends to respond to CPAP.[112–114] Such findings therefore suggest that in patients with OSA and insomnia treatment consist of cognitive behavioral therapy for sleep initiation insomnia and CPAP for middle-of-the-night insomnia (rather than cognitive behavioral therapy or CPAP alone).

Subtype D patients are younger nonobese predominantly male subjects with primarily upper airway symptoms (snoring, sudden awakening, and cessation of breathing). Sleepiness is not a predominant feature, with Epworth Sleepiness Scores consistently <10.[105,109,113,115] Insomnia symptoms occur in a minority in this subgroup.[109,113] The AHIs are in the traditional severe range (38-51 events/hour) and comparable to other clusters but with the lowest metrics of hypoxemia compared with other clusters.[112,118] This cluster had the overall lowest rates of associated comorbidities, and CPAP was generally successful by reductions in ESS and QOL (like Subtype C).

Among PSG metric-based studies, two subtypes appear mostly in males.

Subtype E includes patients predominantly male) with hyper-severe OSA (AHI, 66-84), highest BMIs (33-38 kg/m^2) and most marked hypoxemia T90%, 20%-45%) among the clusters.[116,117] They have the highest ESS scores compared with other PSG clusters, and marked obesity may predispose to hypoxia with respiratory events. These patients exhibit increased risk of incident CVD or death [HR, 1.91].[109,115] CPAP is the recommended treatment for this subtype.

Subtype F is the second common PSG phenotype and includes those with severe OSA

(AHIs 34-68), lower BMIs (28-38 kg/m^2), and notably lowest degrees of hypoxemia for a given AHI.[101,116,117] EES scores (9-10) in this cluster were lower compared with other clusters of similar OSA severity. In a study by Nakayama *et al.*[120] this subgroup exhibited the shortest respiratory event duration. In Zinchus *et al.*'s[101] "arousal and poor sleep" cluster exhibited the lowest rate of regular CPAP use (29%) among clusters with AHI ≥15 and did not exhibit a significant reduction in CVD or death with CPAP use [OR, 0.55; P > 0.05]. Oral appliance therapy and possibly sedative hypnotics and/or acetazolamide and/or supplemental oxygen therapy are considerations for this subtype. Direct comparisons with demographic/symptom/comorbidity-based clusters are difficult; however, both Subtype C (predominant insomnia, a disorder of hyperarousal) and Subtype D (less sleepy, with increased sudden awakenings and lower hypoxemia) may be connected with this polysomnographic subtype.

Residual Excessive Sleepiness in Adults with OSA

Residual excessive sleepiness (RES) in adults treated for OSA may occur even when breathing and oxygenation parameters during sleep are normalized by successful OSA therapy. Pépin *et al.*[112] followed 500 patients with documented CPAP >3 h/night and documented a prevalence rate of RES of 12% (95% CI 9.1-14.8), with patients with RES being younger and sleepier at diagnosis. Residual sleepiness appears to be associated with a higher score on the Epworth Sleepiness Scale calculator and slightly lower AHI on presentation. Baseline severity of OSA does not appear to be a risk factor for residual sleepiness in OSA patients on adequate CPAP therapy.

In one large study, patients with moderate OSA at baseline (defined as AHI between 15-30 events per hour) were twice as likely to complain of residual sleepiness than those with severe OSA (AHI > 30 events per hour). Severe obesity and medical comorbidities such as hypertension and diabetes were not associated with residual sleepiness.[118]

Although the definition of RES is agreed upon, the entity itself is not universally accepted, as some experts feel that the prevalence of EDS in patients with successfully treated OSA simply reflects a prevalent complaint in the general population (i.e., a population of patients with a predisposition to excessive sleepiness). Two studies revealed that approximately 10 percent of the population suffered from severe excessive sleepiness, especially in females. Factors associated with such daytime sleepiness included alcohol dependence (OR: 1.4), bipolar disorder (OR: 2.1), use of over-the-counter sleeping pills (OR: 2.5), narcotic analgesics (OR: 3.4), antidepressants (other than SSRI or tricyclics), and presence of gastro-esophageal reflux disease (OR: 1.5). These sleepy individuals, like those with OSA, were twice as likely, compared to non-sleepy participants, to have had accidents while they were at the wheel of a vehicle during the previous year.[119] Another study also found no difference in the percentage of RES in persons on CPAP (~10 percent) to the percentage of excessive sleepiness (ESS >11) in the general population (~10 percent).[120]

For patients with adequately treated OSA who have persistent burdensome daytime sleepiness, and where alternative causes of daytime sleepiness have been excluded, a trial of a wakefulness-promoting agent may be considered.[121] Available agents include modafinil and its active R-enantiomer armodafinil.[122] Selection of the agent used is often made upon consideration of cost. Modafinil and armodafinil are not approved in Europe for this indication. In the U.S. modafinil and armodafinil are most frequently prescribed, with modafinil sometimes less expensive). Modafinil and armodafinil decrease the effectiveness of oral contraception and are contraindicated during pregnancy.

One meta-analysis of 1479 patients with OSA and residual sleepiness on adequate

CPAP adherence reported that compared with placebo, modafinil and armodafinil resulted in a decrease of the EES score by 2.5 points and 26 percent improvement on the Clinical Global Impression of Change scale.[124] A double-blind crossover trial randomly assigned 157 patients with OSA who had persistent daytime sleepiness despite adequate CPAP therapy to receive modafinil versus placebo, resulting in EDS resolution in 51 percent of modafinil patients versus 27 percent taking placebo, as measured by ESS.[123]

Measurements of CPAP Adherence

The threshold most often used for "adherent" use is >4 hours per night on >70% of nights over a rolling 30-day period. This threshold was based on a very early study of 35 CPAP users that showed a bimodal distribution, which has sense then been adopted as policy for coverage determination.[124–126] Very few studies have examined this relationship, although increasing data suggests disparities exist with CPAP adherence across socioeconomic and racial groups.

Weight loss management for OSA

As obesity is the major condition associated with most cases of OSA, weight loss strategies would seem to be integral to any management strategy of this condition. The most recent ATS clinical practice guideline did show some success in reducing AHI, but the number of participants has been small, and the reported gains were not impressive.[127] One radical approach to achieve weight loss in this population of patients is bariatric surgery, which in one series achieved a 38% weight reduction with a consequent reduction in AHI by 68% in severe OSA patients.[128] But this approach could be recommended only for a minority of patients with severe OSA who could and would afford this high-risk surgery in this population.

In one study of 89 subjects with mean AHI of 41, 49 were randomized to the control group and 40 to the intervention group consisting of 8-week weight loss and lifestyle intervention involving nutritional behavior change, aerobic exercise, and alcohol and tobacco cessation. The intervention group had a 57% reduction in AHI compared to the control group, with 18 of 40 participants (45%) no longer requiring CPAP therapy. The intervention group averaged 7 Kg weight loss. The obvious drawback to the study was the inability of most patients with OSA to access such a rigorous program.[129]

Another study looked at intensive lifestyle intervention (ILI) over 10 years in 125 participants (with the number still participating at 10 years being 67 participants). There was an initial mean 10 Kg weight loss in the first year, but over 10 years the weight loss achieved was only a mean of 5 Kg. They measured a mean decrease in AHI of −4 initially and this fell to a mean of −8 at 10 years.[130]

A case for early use of glucagon-like peptide-1 (GLP-1) receptor agonists in OSA patients with comorbid diabetes and obesity was made by Sultana[131] because of the multiple effects of GLP-1RA had on comorbidities (e.g., hypertension, diabetes, obesity, metabolic syndrome, and atherosclerotic cardiovascular diseases) that commonly co-occur with OSA.

Tirzepatide is a long-acting glucose-dependent insulinotropic polypeptide (GIP) receptor *and* glucagon-like peptide-1 (GLP-1) receptor agonist that selectively binds to and activates both the GIP and GLP-1 receptors. Treatment with Tirzepatide has led to significant reductions in excess body weight, improvements in blood pressure, and reduction in markers of inflammation and vascular endothelial dysfunction. Malhotra *et al.*[132] reported the results of the SURMOUNT-OSA phase 3 trials evaluating the safety and efficacy of tirzepatide for the treatment of adults with obstructive sleep apnea and obesity. They conducted two double-blind, randomized, controlled trials, with the first trial treating subjects not on CPAP and the second trial treating those already on CPAP, both receiving 10mg or 15 mg of tirzepatide vs placebo over 52 weeks. The first

group had a mean AHI of 51.5 events per hour with a mean BMI of 39.1. The second group had a mean AHI of 49.5 events per hour and mean BMI of 38.7. In trial 1, the mean change in AHI at week 52 was -25.3 events per hour with tirzepatide and -5.3 events per hour with placebo, for an estimated treatment difference of -20.0 events per hour (95% CI, -25.8 to -14.2) ($P<0.001$). In trial 2, the mean change in AHI at week 52 was -29.3 events per hour with tirzepatide and -5.5 events per hour with placebo, for an estimated treatment difference of -23.8 events per hour (95% CI, -29.6 to 17.9) ($P<0.001$). Their study concluded that among persons with moderate-to-severe OSA and obesity, tirzepatide reduced the AHI, body weight, hypoxic burden, hsCRP concentration, and systolic blood pressure and improved sleep-related patient outcomes. Up to 50% of persons in both trials achieved a combined key secondary end-point criteria of fewer than 5 AHI events per hour or 5 to 14 AHI events per hour and an ESS of 10 or less.

Mandibular advancement therapy is predominantly used in patients who are unable to unwilling to adhere to treatment with CPAP, but it is not universally efficacious.[133] Upper-airway surgery, including stimulation of the hypoglossal nerve, may be effective but is an invasive option that may be appropriate only for selected patients.

It may be noted by careful readers that no mention of home sleep apnea tests (HSATs) has been mentioned. These devices do not record sleep stages and may unreliably measure desaturations and other important parameters. It is the opinion of this author that these HSAT devices should be considered screening devices, with full polysomnography recommended if moderate and especially severe OSA is detected.

CONCLUSIONS

As is hopefully evident from this article, OSA is a complex disease, with various manifestations (severity of AHI, degree of hypoxemia, sleep disruption, etc.) not universally amenable to a single therapeutic solution. Excellent studies often disagree as to the morbidity or mortality reversibility with CPAP or other interventions. Underwriting evaluation of OSA will require a careful investigation that includes assessment of OSA, sleep stages, degree and duration of hypoxemia, association with PLMS, and hopefully categorization into the various subtypes from cluster analysis, for a fair determination of insurability and ratings. It is this author's opinion that a pharmacologic approach to obesity and OSA using tarazepide, the long-acting agonist for glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor, may currently be the best approach to treating this difficult condition.

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