Obstructive sleep apnea

Past, present, and future

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Internal Medicine Grand Rounds

University of Texas Southwestern Medical Center

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Title: Obstructive sleep apnea – past, present, and future
From the Pickwick Papers, to CPAP therapy, to home diagnostic testing

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Clinical and Educational Interests:

1. Sleep disordered breathing – obstructive sleep apnea
2. Neuromuscular pulmonary disorders – amyotrophic lateral sclerosis
3. Noninvasive positive pressure ventilation
4. Medical education – simulation training

Purpose & Overview: Obstructive sleep apnea (OSA) is a widely prevalent disease associated with the rising obesity epidemic. OSA has been associated with a number of cardiovascular disorders including hypertension, coronary artery disease, arrhythmias, congestive heart failure, and stroke. Continuous positive airway pressure (CPAP) is the most effective treatment for OSA, but variable adherence fuels research for alternative treatments. Finally, diagnostic testing using home portable monitoring in appropriately selected patients will improve identification of and treatment for this disease.

Educational Objectives:

1. Review the pathophysiology of obstructive sleep apnea
2. Understand polysomnography testing to diagnose sleep disordered breathing
3. Review current treatment options for OSA including CPAP therapy
4. Overview of known adverse cardiovascular implications of OSA
5. Introduce home diagnostic sleep testing procedures and alterative treatments for sleep apnea

I. Introduction and Overview

Obstructive sleep apnea (OSA) is a nocturnal breathing disorder characterized by frequent and repetitive closure of the upper airway (apneas and hypopneas) resulting in hypoxia and sleep fragmentation. In the 1950's, OSA was thought to be an uncommon disease associated with obesity. Now, an abundance of research has uncovered the high prevalence of OSA and identified OSA as an independent risk factor for multiple adverse cardiovascular disorders including hypertension, coronary artery disease, congestive heart failure, arrhythmias, and stroke. Obesity is a major risk factor for OSA, and as rates of obesity increase, the importance of appropriate diagnostic testing for patients at highest risk for OSA has been recognized. While diagnostic polysomnography (overnight attended sleep study) remains the gold standard for diagnosis of OSA, recent research has confirmed that out-of-sleep-center testing (home sleep testing) may aid in the recognition of this disease and facilitate timely, effective treatment. Finally, with variable adherence to effective treatment of OSA by weight reduction and continuous positive airway pressure (CPAP), ongoing research focuses on alternative therapies that may lead to increased patient adherence.

II. Origins of the Pickwickian syndrome. History of obstructive sleep apnea. President Howard Taft.

The first recorded clinical description of sleep disordered breathing came not from medical literature, but instead from a series of fictional novels written by Charles Dickens in 1836 called *The Posthumous Papers of the Pickwick Club* (commonly referred to as *The Pickwick Papers*) – (**Figure 1**). [1] Dickens creates a character named Joe – an obese servant estimated to weigh 280 pounds – with snoring, daytime somnolence, polycythemia, and likely cor pulmonale. Dickens writes "...on the box sat a fat and red-faced boy, in a state of somnolency...." "[he] opened his eyes, swallowed the huge piece of pie he had been in the act of masticating when he last fell asleep..." "Sleep!' said the old gentleman, 'he's always asleep. Goes on errands fast asleep, and snores as he waits at table" [1].

Figure 1. The Posthumous Papers of the Pickwick Club by Charles Dickens[1].

In 1956, C. Sidney Burwell and others at Peter Bent Brigham Hospital published a case report titled "Extreme obesity associated with alveolar hypoventilation – A Pickwickian Syndrome [2]." This paper popularized the term "Pickwickian syndrome", characterized as patients with obesity, somnolence, periodic respiration, polycythemia, and right ventricular dysfunction. The Pickwickian syndrome is now commonly known as the "obesity hypoventilation syndrome (OHS)." OHS is an extreme pathologic form of sleep disordered breathing characterized by patients with a body mass index body mass index (BMI) > 30, the presence of obstructive sleep apnea, hypoventilation resulting in daytime hypercapnia ($PaCO_2$ > 45 mm Hg) not attributable to restrictive or obstructive lung disease, and suggestive signs of right ventricular dysfunction and cor pulmonale [3].

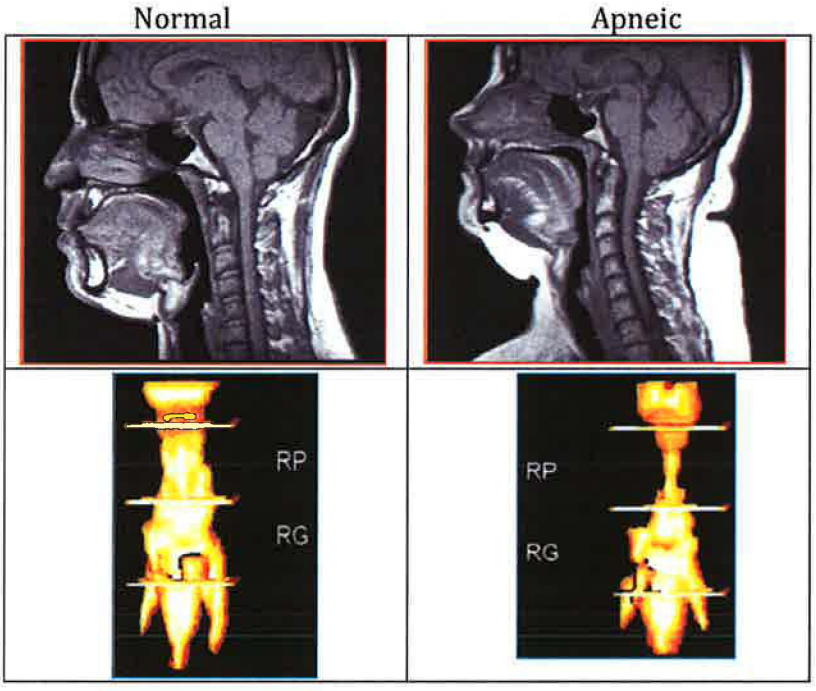
Figure 2: Howard Taft, 27th President of the United States

It is also thought that Howard Taft – president of the United States from 1909 to 1913 and Chief Justice of the Supreme Court from 1921 to 1930, suffered from OSA (**Figure 2**)[4]. During his presidency, Taft weighed more than 300 pounds with a peak BMI of > 45 and also had hypertension. He often demonstrated significant daytime hypersomnolence and fell asleep in various situations – signing documents, playing card games, during conversations with the Speaker of the House, the Chief Justice, and the wife of the French ambassador. He was a loud snorer, although descriptions of observed apneas are not available. President Taft's combination of obesity, large neck circumference of 19 inches, snoring, excessive daytime sleepiness, and hypertension would be consistent with OSA, although he never underwent a diagnostic polysomnogram. The other interesting aspect of President Taft was that with weight loss (especially during his successful tenure as Chief Justice of the Supreme Court), his sleepiness improved: "I have lost that tendency to sleepiness which made me think of the fat boy in Pickwick. My color is very much better and my ability to work is greater[4]."

III. Definition of obstructive sleep apnea. Perioperative screening questionnaires – STOP Bang. Diagnosis of OSA with polysomnography (PSG)

Obstructive sleep apnea is characterized by repetitive episodes of complete (apnea) or partial obstruction (hypopnea) of the upper airway/pharynx during sleep along with preserved respiratory effort to overcome this obstruction. This collapse of the upper airway during sleep leads to transient asphyxia commonly terminating with a cerebral microarousal (sleep fragmentation), carbon dioxide retention (perhaps implicated with morning headaches), and oxygen desaturation, all of which lead to hyperadrenergic nocturnal activity and daytime somnolence[5]. Airway obstruction/closure occurs in the oropharynx at the level of the retropalatal region(behind the soft palate),the retroglossal region, (behind the tongue) or both (**Figure 3**) [6]. Although obesity commonly leads to increased upper airway resistance, even lean patients can have obstructive sleep apnea due to narrowed anatomic features such as retrognathia, micrognathia, or macroglossia [7].

FIGURE 3. Sagital and coronal magnetic resonance imaging of an awake and asleep apneic patient. In this subject, the obstruction affects the retropalatal pharynx (RP) more so then the retroglossal region (RG) [6]



Classic symptoms of OSA include snoring, observed breathing pauses by the bed partner, morning headaches, sleep maintenance insomnia, nocturnal choking or gasping, all resulting in the most common symptom – daytime hypersomnolence. Common risk factors for OSA include obesity, male gender, advanced age, craniofacial abnormalities (retrognathia and macroglossia), menopause, and wide neck circumference (**Table 1**). [8]

TABLE 1: Risk factors for OSA

Obesity
Gender (male > women)
Aging
Menopause
Craniofacial anatomy (retrognathia and micrognathia)
Supine body position
Opioids, benzodiazepines, and ethanol

Several screening tools combine the above clinical features to identify patients at risk for OSA. One of the simplest screening questionnaires is STOP-Bang, developed and validated to recognize sleep apnea preoperatively in elective surgery by Canadian anesthesiologist Frances Chung[9] (**Table 2**)." Three or more positive answers on the STOP-Bang screening test carries a high sensitivity for moderately severe OSA (93% for an AHI > 15) and also has a high negative predictive value (less than 3 positive answers), making it a useful screening tool for postoperative complications. When 7 to 8 questions are answered affirmatively, the sensitivity decreases but the specificity is over 90% for moderately severe sleep apnea [10].

TABLE 2: STOP-Bang Scoring System for OSA screening [9]

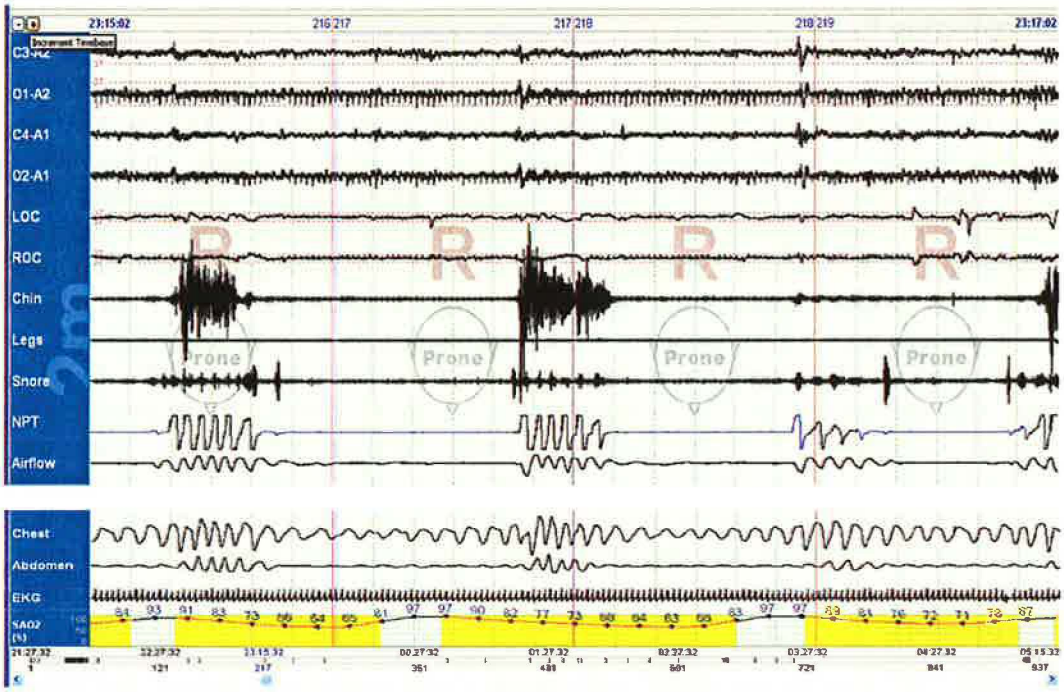
S	Snoring • Do you snore loudly (louder than talking or loud enough to be heard through closed doors)?
T	Tired • Do you often feel tired, fatigued, or sleep during daytime?
O	Observed apneas • Has anyone observed you stop breathing during your sleep?
P	Pressure • Do you have or are you being treated for high blood pressure ?
B	BMI > 35
A	Age > 50 years
N	Neck circumference > 40 cm
G	G – Gender , Male

Despite the above screening questionnaire, the gold standard diagnostic test for OSA remains an attended in-laboratory polysomnogram (PSG) that collects several

variables during sleep. The parameters recorded include EEG (electroencephalogram to determine different stages of sleep and identify epileptiform activity), EOG (electrooculogram – measurement of eye movements), ECG (electrocardiogram to identify arrhythmias), EMG (electromyogram to monitor chin muscle tone and nocturnal limb movements), nasal and oral airflow (to identify apneas and hypopneas), chest and abdominal belts (to identify respiratory effort), and pulse oximetry (to measure oxygen saturation).

Obstructive apneas are defined by complete or near-complete cessation of airflow lasting at least 10 seconds. Obstructive hypopneas are characterized by at least a 30% reduction in airflow, lasting for at least 10 seconds, associated with a minimum 4% oxygen desaturation; alternatively, hypopneas are defined as a 50% reduction in airflow leading to an EEG arousal or 3% oxygen desaturation [11]. (Figure 4).

Figure 4: Obstructive apneas are demonstrated in the nasal pressure transducer (NPT) and airflow tracing. These last > 30 seconds leading to EEG arousals and profound oxygen desaturations (as low as 63%). Also note the significant reoxygenation following each recovery breath (resaturation to > 93%).



In sleep medicine literature, apneas and hyponeas are equally pathologic and clinically important, therefore the apnea-hypopnea index (AHI) is used to determine severity of disease. The AHI is calculated by dividing the number of apneas and

hypopneas by the number of hours of sleep. The American Academy of Sleep Medicine (AASM) categorizes the severity of OSA in **table 3** [12].

Table 3: Severity of sleep apnea based on AHI.

Severity of sleep apnea	AHI (apnea/hyponea index)
Normal	< 5
Mild	5-15
Moderate	15-30
Severe	> 30

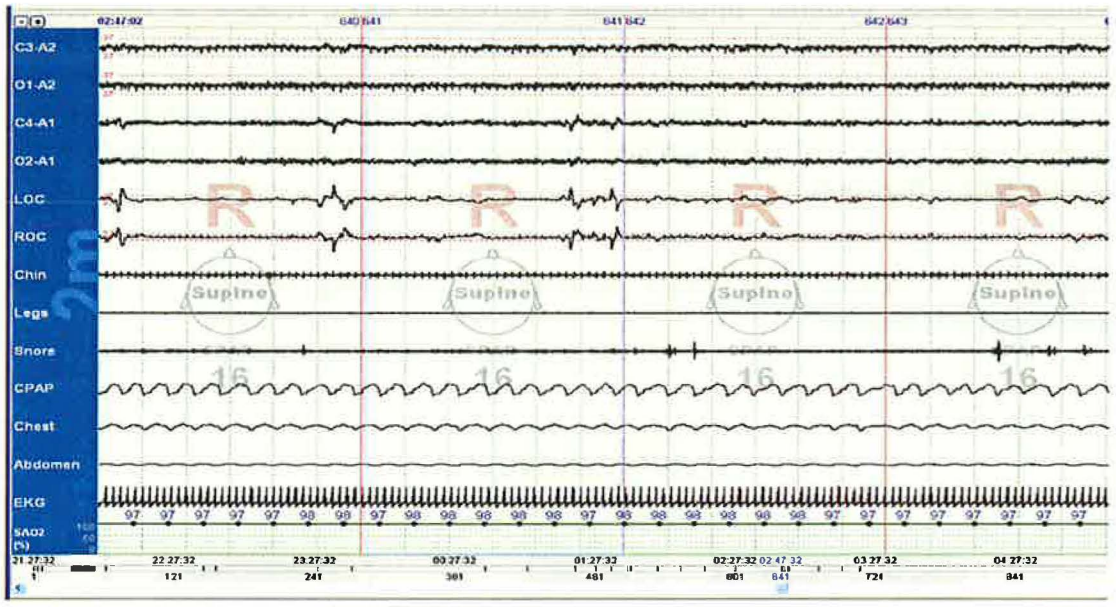
IV. Treatment of sleep disordered breathing: Upper airway surgery (tracheostomy and uvulopalatopharyngoplasty), continuous positive airway pressure (CPAP), and alternative treatments.

Tracheostomy was one of the first surgical interventions used to treat severe OSA by bypassing the functional upper airway obstruction[13]. It is effective in reducing daytime hypersomnolence, resolution of snoring, resolving hypercapnia in most patients, but is disfiguring and an extreme surgical intervention [14]. Other treatment modalities for OSA include uvulopalatopharyngoplasty (UPPP), maxillomandibular advancement (MMA) surgery, progesterone (to stimulate respiration), positional therapy (to prevent airway obstruction from a posteriorly falling tongue), oral appliances for sleep apnea (to anteriorly advance the lower jaw/tongue), and weight reduction [15].

In April 1981, Australian pulmonologist Colin Sullivan published the first landmark paper in *Lancet* describing continuous positive airway pressure (CPAP) therapy for OSA[16]. He created a CPAP blower by modifying a vacuum cleaner motor with variable speed control, molded a mask together using Silastic paste/glue, and fortunately had a willing subject (a construction worker did not want to undergo tracheostomy). Dr. Sullivian writes, "we were very tentative going into this, not knowing what would happen, how the patient might respond, or even if we might 'blow the patient up[17]." Five patients were described with a mean non REM AHI of 62 (severe OSA) with oxygen desaturations down to a mean nadir of 84%. In all 5 patients, the application of CPAP (range from 4.5 to 10 cm H2O) resolved sleep disordered breathing. Each patient awoke feeling more alert and the hypersomnolence was resolved – one patient was able to watch television for several hours, something that he had been unable to do for years. Not only is the *Lancet* publication notable for the description of CPAP, but it also clarified that physiologically obstructive events were passive and could be overcome with positive pressure.

The earliest CPAP machines were cumbersome and noisy and options for mask interfaces were limited. In 2012, CPAP machines are compact and quiet, and there is a wide variety of mask interfaces designed to fit even the most challenging facial anatomy. Importantly, CPAP therapy ameliorates obstructive breathing events, reduces sleepiness, and improves quality of life. **Figure 5.**

Figure 5: In this example, CPAP of 16 cm H2O resolves obstructive respiratory events, resulting in consolidated sleep (REM rebound), resolution of arousals, and normalization of oxygen saturation.



V. OSA and cardiovascular disorders

There is a strong association between sleep apnea and a number of cardiovascular disorders including hypertension, coronary artery disease, arrhythmias, congestive heart failure, stroke, and cardiovascular morbidity and mortality [18]. Furthermore, there are a number of compelling studies revealing the reduction in these morbidities with the consistent use of CPAP therapy. However, several important considerations and limitations must be highlighted when evaluating the relationship between OSA and cardiovascular disorders[18]:

- There is a close association between obesity and OSA. It is difficult to distinguish the impact of obesity, the impact of OSA, and the effect of the combination of the two on cardiovascular conditions since it is known that obesity has a large impact on development of cardiovascular disorders.
- Sleep apnea patients often have comorbidities, including cardiovascular disease, metabolic syndrome and diabetes confounding whether OSA alone has an independent effect on incident coronary disorders.
- Randomization of therapy for OSA is challenging as it is difficult to perform double blind placebo studies comparing CPAP to sham CPAP. Furthermore, in those OSA patients with severe daytime sleepiness it may be unethical to withhold CPAP therapy.

Mechanism: Obstructive apneas frequently lead to intermittent hypoxemia, hypercapnia, and microarousals at the end of apneic events. This leads to increased sympathetic nervous system activity thereby causing vasoconstriction, tachycardia, and systemic hypertension [5]. Repetitive hypoxia and reoxygenation leads to oxidative stress, systemic inflammation (increased CRP), release of vasoactive substances (endothelin 1), thrombosis (platelet activation), and insulin resistance which ultimately lead to endothelial dysfunction, atherosclerosis and associated cardiovascular disease [18-20]. Patients with OSA have elevated sympathetic activity, resting heart rates, and resting blood pressure when compared to controls with similar BMI [21] **Figure 6.**

Figure 6: Mechanism of sleep disordered breathing leading to adverse cardiovascular disease[22]

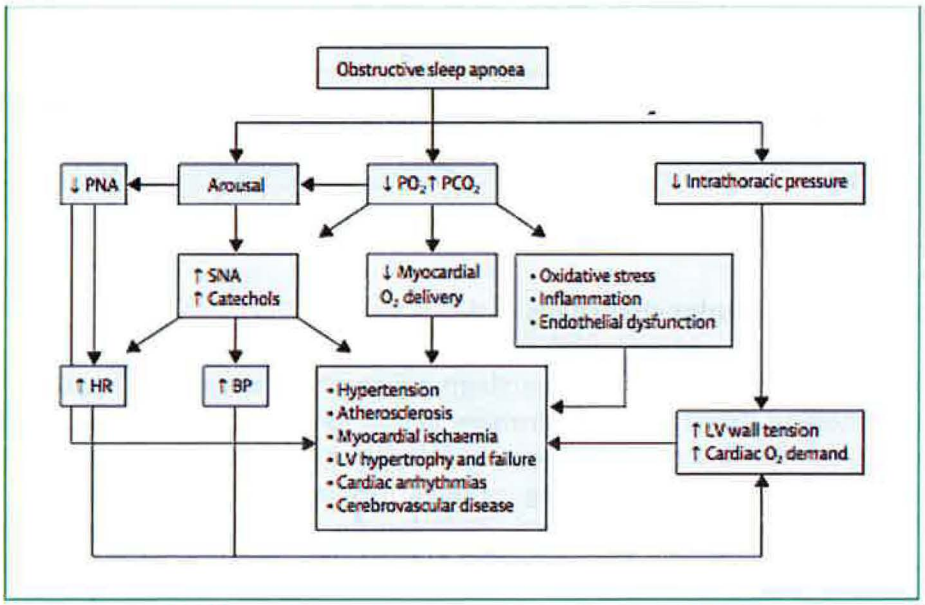


Figure: **Pathophysiological effects of obstructive sleep apnoea on the cardiovascular system**
PNA=parasympathetic nervous system activity. PO_2=partial pressure of oxygen. PCO_2=partial pressure of carbon dioxide. SNA=sympathetic nervous system activity. HR=heart rate. BP=blood pressure. LV=left ventricular.

Much of what we know about the relationship between OSA and cardiovascular disorders comes from The Sleep Heart Health Study (SHHS), the Wisconsin Sleep Cohort, and Spanish Sleep and Breathing Network.

- The SHHS is a community-based prospective cohort study supported by the NIH/NHLBI since the 1990's seeking to understand the impact of OSA on coronary heart disease, stroke, hypertension, and all cause mortality.

- The Wisconsin Sleep Cohort is a longitudinal population study of Wisconsin state employees to evaluate the consequences and natural history of sleep apnea.
- The Spanish Sleep and Breathing Network is clinic-based observational study. The subjects in this group were referred to a sleep clinic. Many of these patients were offered CPAP therapy and followed longitudinally. Although these studies are at risk for referral bias, the advantage of this cohort is that it closely mimics actual clinical practice.

Hypertension and OSA: Many patients with OSA have hypertension and many hypertensive patients have OSA therefore, establishing causality is challenging due to shared risk factors [23]. Nevertheless, epidemiologic, clinic-based, cross sectional, and longitudinal studies provide strong supportive evidence that OSA contributes to the development of hypertension [19]. Peppard et al (Wisconsin Sleep Cohort) showed in a longitudinal prospective population study the dose response impact of OSA on incidence of hypertension over a 4 year period. OSA – when controlled for age, body habitus, baseline hypertension, alcohol, and smoking – emerged as an independent risk factor for incident hypertension. [24]

However, multiple studies have shown that CPAP therapy results in only a modest decrease in mean blood pressure of 2-5 mm Hg[25]. A 4 year longitudinal study of CPAP therapy in nonsleepy patients (low Epworth sleepiness scale) failed to show any statistically significant decrease in incidence of hypertension or adverse cardiovascular events, except in the subgroup of patients who used CPAP for > 4 hours consistently[26]. A recent prospective longitudinal study (median of 12.2 years) by Marin confirmed that patients with OSA who were not adherent to CPAP therapy had a higher incidence of developing hypertension, in a graded fashion similar to the above Peppard study [27]. Importantly, those who were adherent to CPAP therapy had a significantly reduced incidence of developing hypertension.

Taken together, the above studies support that obstructive sleep apnea is causal in development of hypertension, especially in those with severe OSA. Also, it is likely that consistent nightly adherence to CPAP therapy (> 4 hours) results in attenuation of this risk. Based on above, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 has recommended screening for sleep apnea as a causal factor for developing incident hypertension [28].

Cardiovascular disease and OSA: Two large observational trials from the Spanish Sleep Cohort reveal the impact of OSA and use of CPAP on incident cardiovascular disease. The first study by Marin et al published in 2005, was a large prospective observational study of 1387 Spanish men referred to a sleep clinic over 10.1 years. Those men with untreated severe sleep apnea (AHI > 30; n=235) had higher fatal and nonfatal cardiovascular events and all-cause mortality when compared with those with mild-moderate disease and healthy controls[29]. Importantly in this study, the consistent use of CPAP for more than 4 hours (n=372) over this 10-year time

period resulted in significantly reduced cardiovascular event rates similar to the control group. The second observational study by Campos-Rodriguez, published in 2012, showed similar findings in women[30]. This was a prospective observational cohort study of 1166 women referred to a sleep clinic for suspected sleep disordered breathing and were stratified based on an AHI above or below 10. When comparing these two groups, women with an AHI less than 10 (control arm) had a lower cardiovascular mortality compared to the OSA group (AHI > 10). When controlling for other variables (age, BMI, hypertension, diabetes, previous cardiovascular events), severe untreated OSA (AHI > 30) was an independent predictor of cardiovascular mortality (HR = 3.5 when compared to control group). Similar to the Marin trial, those women who were consistently compliant with CPAP therapy did not differ from the control group in rates of cardiovascular mortality.

Both of these large observational studies provide evidence that consistent CPAP therapy may lower the risks of cardiovascular morbidity and mortality in men and women with severe sleep apnea (AHI > 30).

Similar findings were confirmed from the Sleep Heart Health Study (prospective community based cohort) on 1927 men and 2495 women, age > 40, and without baseline heart disease [31]. They used portable home sleep studies to diagnose OSA and then evaluated incident coronary heart disease (myocardial infarction, coronary heart disease death, coronary revascularization procedure, and congestive heart failure) with a median follow up of 8.7 years. A small percentage was treated with CPAP therapy and did not impact the outcome. After adjustment for multiple risk factors, the study concluded that OSA was a predictor for incident coronary heart disease in those who were men, less than 70 years of age but surprisingly not in women. When comparing men with an AHI > 30 to those with an AHI < 5, the more severely affected group was 68% more likely to develop coronary heart disease and 58% more likely to develop congestive heart failure. The gender outcome differences in these studies are important and may be due to: different study designs (less women with severe OSA in the SHHS may under-power this subgroup), age of presentation of OSA (women present with OSA older than men and may have less cumulative exposure of OSA), differences in response to obstructive events (men may be more likely to have worsened desaturations), or other unmeasured variables and deserve future studies.

Congestive heart failure and sleep disordered breathing: Studies have reported the prevalence of OSA in patients with heart failure (most with diastolic dysfunction) ranging from 10 to 35% [18]. Although there is an association between OSA and heart failure, causality has yet to be determined. The most likely mechanism linking OSA and congestive heart failure relates to the impact of hypertension on induction of left ventricular remodeling. Also, repetitive nocturnal obstructive apneas can lead to cyclical nocturnal oxygen desaturation events, carbon-dioxide retention, and higher sympathetic nervous activity, all leading to increased ventricular afterload and myocardial consumption during diastole and systole [22]. Additionally, it has been suggested that fluid retention conditions during

heart failure can lead to upper airway congestion and further destabilization of pharyngeal integrity, particular in those patients in the recumbent position[18].

Studies have shown that CPAP therapy results in a modest improvement in left ventricular function, decrease in blood pressure, and decreased sympathetic catecholamines, however reduction in long term mortality have not been demonstrated[22]. Finally, Cheyne-Stokes is a crescendo-decrescendo respiratory pattern and has been associated with severe systolic heart failure and is a marker for higher mortality[32].

Cardiac arrhythmias: Several arrhythmias have been associated with OSA including atrial fibrillation, nonsustained ventricular tachycardia, complex ventricular ectopy, and bradyarrhythmia (due to diving reflex)[5,18] One Mayo cardiology clinic-based prevalence study revealed that 49% of patients with atrial fibrillation had coexisting OSA[33]. A randomized study showed that the treatment of coexisting OSA in patients with heart failure by CPAP for 1 month caused a 59% decrease in the frequency of ventricular premature beats during sleep[34]. Finally, Kanagala and colleagues found that patients undergoing elective cardioverson for atrial fibrillation with untreated OSA had a significantly increased risk of failure rate when compared to those OSA patients compliant with CPAP therapy (83% chance of converting back to atrial fibrillation vs. 42%)[35].

Stroke: Several studies have implicated OSA as a risk factor for development of stroke [36]. Recently, data from the SHHS of more than 5000 subjects followed over a median of 8.7 years showed a positive correlation between incident ischemic stroke and OSA, particularly in men with the highest AHI quartile. This was also found in women with an AHI quartile great than 25[37]. Overall, this data showed that men with modest to severe OSA were at 3 times the risk of ischemic stroke.

VI. Perioperative recognition and management of OSA

The prevalence of mild OSA in patients undergoing elective surgery at a large academic institution was 22%[38], similar to prevalence rates in the general population[8]. Several studies describe perioperative complications implicated with OSA including hypoxemia, arrhythmias, myocardial injury, unanticipated transfer to the intensive care unit, and even sudden cardiac death [39] (**Table 4**).

Table 4: Perioperative complications associated with OSA.

Study Study design	Number of patients	Types of surgery	Higher incidence of events in OSA group
Liao et al. Can J Anaesth. 2009 Retrospective matched cohort	240 OSA 240 matched controls	▪Cardiothoracic ▪Gastrointestinal ▪Gynecologic ▪Orthopedic ▪Otolarnygology ▪Plastics ▪Urology	▪Respiratory complications ▪Oxygen desaturations ▪Prolonged oxygen therapy ▪Need for additional monitoring ▪More ICU monitoring
Gupta et al Mayo Clin Proc. 2001 Retrospective case control study	101 OSA 101 matched controls	▪Orthopedic - Hip replacement - Knee replacement	▪Unplanned ICU transfers ▪Cardiac events ▪Longer hospital length of stay
Hwang et al Chest. 2008 Prospective case control study	74 OSA 98 without OSA	▪Cardiothoracic ▪Gastrointestional ▪Gynecologic ▪Orthopedic ▪Otolaryngology ▪Urologic	▪Respiratory ▪Cardiovascular ▪Gastrointestional bleeding ▪Longer postanesthesia recovery stay
Kaw et al J Cardiovas Surg. 2006 Retrospective case control study	37 OSA 185 matched control	▪Cardiothoracic	▪Encephalopathy ▪Postoperative infections (mediastinitis) ▪ICU length of stay

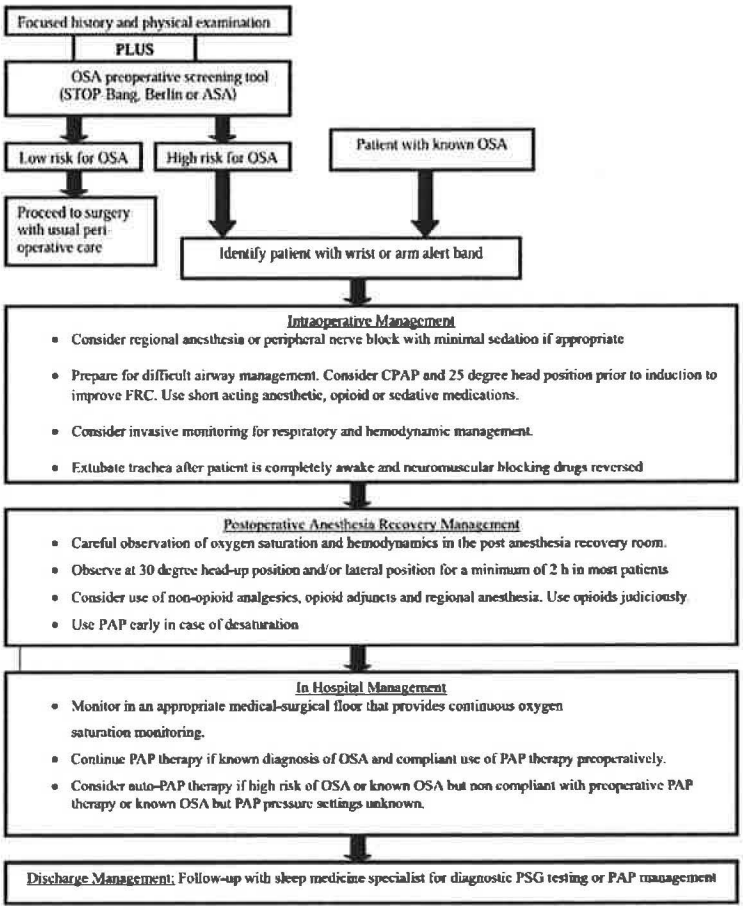
The adverse events are attributed to the exacerbating effects of perioperative analgesics and sedatives on obstructive respiratory events. Anesthetics, sedatives, and opioids can blunt the protective arousal at the end of obstructive events, leading to prolonged apneas and worsened desaturation. In addition, since many OSA patients are obese with other comorbidities such as hypertension, congestive heart failure, pulmonary hypertension or arrhythmias, it follows that appropriate and timely recognition, optimal intraoperative management, and postoperative monitoring could result in reduced adverse events.

Several guidelines and algorithms exist that outline a comprehensive and careful management approach preoperatively, intraoperatively, and postoperatively [39-41] **(Figure 8)**.

- Preoperatively, the importance of utilizing screening questionnaires with a high sensitivity and high negative predictive values are important, such as STOP-Bang. High risk undiagnosed and untreated patients may require formal evaluation by a sleep specialist and initiation of CPAP therapy.
- Intraoperatively, anesthesiologists should anticipate a difficult airway for intubation due to destabilization of the upper airway in obese patients at high risk for OSA. Regional anesthesia should be considered. Extubation parameters should be optimized including upright positioning (supine position can worsen upper airway collapse) and full reversal of neuromuscular blocking agents.

- Postoperatively, careful observation for hypoxia and hypercapnia should be performed in the post-anesthesia care unit. One protocol described the incorporation of recording apneas, bradypnea, hypoxia requiring oxygen, and pain/sedation mismatch in the post operative care unit to identify those at highest risk for oxygen desaturations in the hospital [42]

Figure 8. Proposed algorithm for perioperative management of patients with or at high risk for obstructive sleep apnea in elective surgery[39].



VII. Epidemiology of sleep apnea. Portable monitoring. Alternatives to CPAP therapy.

Epidemiology. Obesity has emerged as a worldwide epidemic. As obesity is clearly implicated as a risk factor for OSA, physicians will encounter patients with this disease. Several large population based studies in different geographic regions confirm a prevalence rate of ~ 24% men and 9% of women with at least mild OSA (AHI > 5) and a prevalence rate of ~4% of men and ~2% of women with OSA syndrome (OSA and excessive daytime sleepiness) [8].

Table 5: Population based studies reporting the prevalence of OSA and OSA syndrome[8].

Study	Number of subjects	AHI ≥ 5	AHI ≥ 15	OSA syndrome	Methodology
Wisconsin, U.S.A.† 1993 [20]	Men: 352 Women: 250 (age 30–60)	Men: 24% Women: 9%	Men: 9% Women: 4%	Men: 4% Women:2%	Attended PSG (oronasal airflow and respiratory inductance plethysmography)
Pennsylvania. U.S.A.¶ 1998, 2001 [22,23]	Men: 741 Women: 1000 (age 20–100)	Men: 17% Women: 5%	Men: 7% Women: 2%	Men: 3.3% Women:1.2%	Attended PSG (oronasal thermocouple)
Spain ¶ 2001 [21]	Men: 325 Women: 235 (age 30–70)	Men: 26% Women:28%	Men: 14% Women:7%	Men: 3.4% Women:3%	Attended PSG (oronasal thermister)
Australia ‡ 1995 [24]	294 men (age 40–65)	Men: 25.9%	Men: 10% (AHI ≥ 10)	Men: 3.1% Women: n/a	MESAM IV portable monitoring (snoring and oximetry)
Hong Kong, China ‡ 2001, 2004 [25,26]	Men: 153 Women:106 (age 30–60)	Men: 8.8% Women: 3.7%	Men:5.3% Women: 1.2%	Men: 4.1% Women:2 1%	Attended PSG (oronasal thermister, thoracic and abdominal impedance belts)
Korea ‡ 2004 [27]	Men: 309 Women: 148 (age 40–69)	Men: 27% Women: 16%	Men: 10.1% Women: 4.7%	Men: 4.5% Women:3.2%	In laboratory or home PSG (oronasal thermister)
India ‡ 2004 [28]	250 men (age 35–65)	Men: 19.5%	Men: 8.4%	Men: 7.5% Women: n/a	Home PSG (oronasal thermister)
India ‡ 2006 [29]	Men: 88 Women: 63 (age 30–60)	Men: 19.7% Women: 7.4%	n/a	Men: 4.9% Women:2.1%	Attended in laboratory PSG

† Studies that did not use EEG microarousal as part of the definition of hypopnea

‡ OSA Syndrome defined as: AHI ≥ 5 + EDS

¶ OSA Syndrome defined as: AHI ≥ 10 + EDS

MESAM IV: Madaus Medizin-Elektronik – Freiburg, Germany; PSG: Polysomnography

Out of center sleep testing/portable home monitoring. It is estimated that more than 80% of men and women are undiagnosed with OSA[43], therefore improved access and reduced costs for diagnostic testing is essential. Although attended polysomnography (level 1) is considered the gold standard diagnostic test for OSA, barriers to its use include prolonged wait times (depending on local availability), high expense, and patient inconvenience. Because of these limitations, a renewed interest in the use of portable home sleep testing (level 3) has emerged. Level 3 monitors provide the minimal amount of data necessary to recognize nocturnal hypoxia, airflow limitation, and heart rate irregularities. **Table** 6

Table 6: Classification of levels of studies used to evaluate sleep disorders [44]

	Level 1 Attended PSG	Level 2 Unattended PSG	Level 3 Modified portable sleep apnea testing	Level 4 Continuous single or dual bioparameter recording
Measurement variables	Minimum of 7 channels * EEG, EOG, chin EMG, EKG, airflow, respiratory effort, oxygen saturation	Minimum of 7 channels * EEG, EOG, chin EMG, EKG, airflow, respiratory effort, oxygen saturation	Minimum of 4 channels * ventilation (respiratory movement and airflow), heart rate/EKG, and oxygen saturation	Minimum of 1 channel * oxygen saturation, airflow, or chest movement
Body position	Documented or objectively measured	Possible	Possible	No
Limb movements	EMG	Optional	Optional	No
Personnel	Yes	No	No	No

There is growing recent scientific evidence that supports the use of portable monitoring, especially when appropriate high-risk patients are studied (**Table 7**). In most studies, a positive portable study with high clinical features of sleep apnea has a high specificity and high positive predictive value.

In 2012, a large multicenter randomized trial of 373 patients (7 different academic sleep centers) compared portable sleep studies and auto CPAP therapy versus traditional laboratory based polysomnography. The investigators showed no difference between the two strategies in terms of effectiveness of therapy and adherence rates at 1 and 3 months [45]. It is important to highlight that studies endorsing use of portable home monitoring involve tertiary centers with expert decision-making and management by clinical experts in the practice of sleep medicine, therefore these favorable results may not apply in general practice.

Table 7: Recent trials comparing home diagnostic testing to laboratory testing

Study Study design	Number of patients	Methods	Outcomes Time points
Berry RB et al Sleep. 2008 31(10): 1423-1431. Randomized, prospective Single center	53 patients - LAB 53 patients - HOME	LAB - attended diagnostic and CPAP titration studies HOME - Type 3 device - WatchPAT100 (peripheral arterial tone, heart rate, pulse oximetry, actigraphy)	No difference in nightly CPAP adherence, sleepiness severity, quality of life, CPAP satisfaction at 6 weeks
Skomro RP et al Chest 2010 138(2): 257-263. Randomized, prospective Single center	51 patients - LAB 51 patients - HOME	LAB - attended diagnostic and CPAP titration study, split study if indicated HOME - level 3 home test, followed by 1 week of auto CPAP	No difference in sleepiness scores, quality of life, blood pressure, or CPAP adherence at 4 weeks
Kuna ST et al AJRCCM. 2011. 183(9): 1238-1244 Randomized, prospective Two centers	148 patients - LAB 148 patients - HOME	LAB - attended diagnostic and CPAP titration study, split study if indicated HOME - level 3 home test	No difference in functional outcomes of sleep questionnaire, CPAP adherence at 3 months
Rosen CL et al. SLEEP. 2012;35(6): 757-767 Randomized, open-label, parallel group, unblinded, multicenter trial Seven centers	186 patients - LAB 187 patients- HOME	LAB - attended diagnostic study and CPAP titration study HOME - home sleep testing and home auto CPAP titration	No difference - acceptance of PAP therapy, titration pressures, effective titrations, time to treatment 3 month PAP adherence was higher in the HOME arm

The AASM has published clinical guidelines to guide clinicians on the appropriate use of portable technology which includes[46]:

- Appropriate selection of patients with high pretest probability for OSA to undergo diagnostic testing
- Exclusion of patients with underlying cardiopulmonary disorders that may hinder recognition of hypoxia due to sleep apnea and not studying patients with alternative non-sleep breathing related diseases (ex: parasomnias, periodic limb movement disorders, etc)
- Interpretation of these studies by experienced board certified sleep physicians trained in reviewing the raw data in detail, and not relying on computer generated interpretations
- Providing effective longitudinal care for those diagnosed with sleep disordered breathing
- Integration of laboratory/attended sleep studies to diagnose more complex sleep breathing disorder patients and to provide optimal PAP titrations

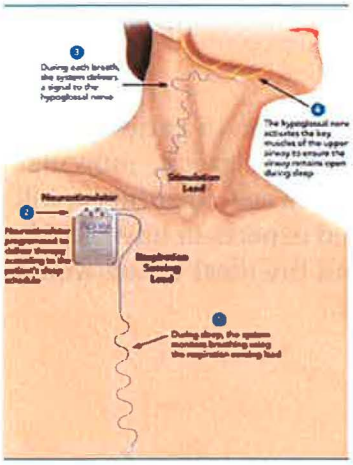
Finally the cost effectiveness of a portable sleep study program needs to be evaluated. This is a complicated calculation and should take into account costs of equipment (lab vs. home), personnel needed to facilitate both, testing strategies for failed/non-diagnostic tests, decision on CPAP titration (lab vs. auto CPAP), impact

on wait time, costs of longitudinal care, and tracking CPAP adherence rates.

Alternatives to CPAP therapy. It has been reported that 5-37% of patients abandon CPAP after initial use and other studies show that up to 50% of patients with mild OSA refuse to undergo CPAP titration[47]. Some studies predict a compliance rate of only 40 to 60%, therefore the advent of alternative technology to treat sleep apnea is important. Barriers to CPAP therapy include lack of subjective improvement of daytime sleepiness, intolerance to the equipment, sleep maintenance insomnia exacerbated by CPAP, and general intolerance to the entire process. Alternative treatments to CPAP include weight loss, positional therapy, oral appliance therapy, and upper airway surgery (uvulopalatopharyngoplasty, maxillomandibular advancement surgery, or tracheostomy). All have variable success rates and challenges of monitoring adherence to therapy, particularly positional therapy and oral appliances.

One recent advance is hypoglossal nerve stimulation (HGNS) to activate the genioglossus muscle, an upper airway dilator muscle, during inspiration during obstructive apneic events[48]. Stimulation of this muscle leads to tongue protrusion and stiffening of the anterior pharyngeal wall. A study showed that 21 subjects' AHI improved from 43 down to 19.5 (>50% reduction) at 6 months. Another recent advance is the use of nasal EPAP, applied to each nostril with an adhesive. Nasal EPAP is a mechanical valve with very low inspiratory resistance but high expiratory resistance, and splints the upper airway throughout exhalation. In a randomized, double-blind, sham-controlled study over 3 months, 77 subjects saw a median AHI decrease from 14.4 to 5.6. There was also oxygenation improvements, improved subjective daytime sleepiness scores, no serious adverse events and reported adherence rates of 88% [49]. Although both are promising alternatives to CPAP therapy, larger longitudinal studies confirming effectiveness and safety are important. **Figure 9.**

FIGURE 9: Hypoglossal nerve stimulator and nasal EPAP – both recent alternative treatments for OSA[48,49].



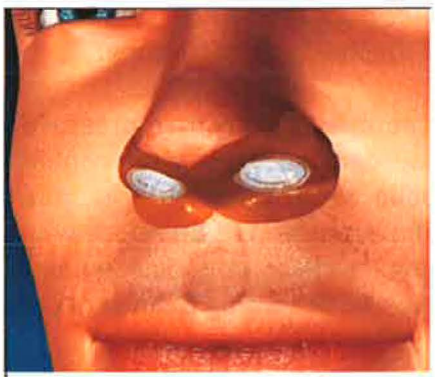


Figure 1—Nasal EPAP device. Single use valves are inserted into ea nostril and sealed with adhesive.

VIII. Conclusion and sleep medicine management in the future.

- With the rising obesity epidemic, the prevalence of OSA will only increase. Since OSA is clearly associated with a wide variety of cardiovascular disorders and perioperative complications, screening for OSA in both outpatient and perioperative settings will be of utmost importance. Screening for OSA will emerge as an important part of primary and secondary disease prevention.

- The utilization of home portable monitoring will emerge as an important diagnostic tool to provide more cost effective and convenient access to increase the diagnosis. To ensure success of this practice, appropriate patient selection (high pretest probability) and appropriate review of raw data by experienced board certified sleep physician will be crucial. Complementary utilization of laboratory sleep studies to diagnose those patients with false negative home studies, management of complex breathing patterns, titration of CPAP and other advanced breathing devices, and to diagnose other non-breathing related disorders such as parasomnias, limb movements, or narcolepsy is paramount.

- The emergence of larger "Sleep Centers" will continue to be successful in sleep medicine management because of the overall increased emphasis on management of sleep apnea as a chronic disease, along with emphasis on longitudinal CPAP management. To be successful, multidisciplinary care will need to emerge: physicians trained in sleep medicine, physician extenders (nurse practitioners and physician assistants), and expert ancillary staff (registered polysomnography technologists, respiratory therapists, and nurses).

- With the continued suboptimal adherence to CPAP therapy, more research on alternative treatments will emerge. In the meantime, optimization of improved mask interfaces, auto CPAP devices, and longitudinal management will continue to be the mainstay of therapy.

- Finally, the use of noninvasive positive pressure ventilation in patients with neuromuscular disorders such as amyotrophic lateral sclerosis, muscular dystrophy, post-polio syndrome, scoliosis, and diaphragm disorders will continue to be of importance. We therefore will need experts in bilevel PAP, advanced ventilation, tracheostomy management and the ideal venue would be a combined Sleep and Breathing Disorders Center.

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