Medical Disorders Impacted by Obstructive Sleep Apnea

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KEYWORDS

• Obstructive sleep apnea • Continuous positive airway pressure
• OSA medical complications

Normal sleeping individuals experience a lower metabolic rate and relative cardiovascular quiescent state with lower heart rate and blood pressure that naturally occurs during sleep compared with the waking state. In patients with obstructive sleep apnea (OSA), this quiescent state becomes disrupted. Research has shown a higher risk for several medical disorders, most ominous being a myocardial infarction or stroke. This article serves as an overview to the cardiovascular, cerebrovascular, metabolic, and gastroesophageal effects of OSA.

OVERVIEW OF PATHOPHYSIOLOGY

Complete pathophysiology and background of disease mechanisms is beyond the scope of this article; however, a brief introduction may be helpful before introducing each medical complication of sleep apnea. Please see **Fig. 1** for a graphical representation[1] of the following succinct explanation.

Most patients with sleep apnea trigger hypoxemic events during the apnea with reoxygenation on recovery from the apnea event, causing oxidative stress. Intermittent hypoxia can potentially lead to reactive oxygen species that can damage biomolecules and alter cellular functions that can contribute to inflammation and endothelial dysfunction.[2] The longer the period of apnea, the more likely transient hypercapnia can also result. It has also been well described that sleep apnea increases sympathetic activation[3] leading to vasoconstriction, a strong factor in cardiovascular consequences of sleep apnea. Inflammation including elevations of C-reactive protein (CRP),[4,5] adhesion molecules, and other cytokines and inflammatory mediators has been shown to be overly active in patients with sleep apnea.[1,6] Although platelet dysfunction and factors of coagulation, such as fibrinogen, are increased in patients

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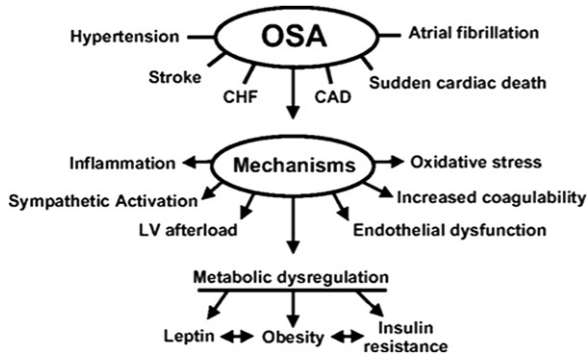

Fig. 1. Association between OSA and cardiovascular disease; partial list of the disease mechanisms associated with OSA considered as possible links to several cardiovascular diseases and metabolic dysregulation. CAD, coronary artery disease; CHF, congestive heart failure; LV, left ventricular. (*Reprinted from* Lopez-Jimenez F, Sert Kuniyoshi FH, Gami A, et al. Obstructive sleep apnea: implications for cardiac and vascular disease. Chest 2008; 133:793–804; with permission.)

with sleep apnea,[7] the clear connection to sleep apnea as a direct cause is not certain and may be linked to other comorbid conditions.

Each obstructive apnea is accompanied by waves of effort against a closed airway that, in turn, causes negative intrathoracic pressure changes. Transmural pressure increases across the heart and great vessels with a ripple effect of increased afterload, atrial size, diastolic dysfunction, and increased cardiac wall stress.[6,8,9]

Leptin, a protein involved in appetite suppression, has been shown to be elevated in patients with OSA at levels higher than in subjects with a comparable body mass index (BMI).[10] Other important metabolic dysregulation has a connection between relative insulin resistance and patients with sleep apnea. This glucose intolerance associated with OSA appears to be independent of BMI.[11–13]

CARDIOVASCULAR

Systemic Hypertension

Important information to understand the link between systemic hypertension and patients with sleep apnea has been evident in several studies. The Wisconsin Sleep Cohort Study showed a dose-response relationship between OSA and blood pressure elevations independent of age, sex, BMI, and other factors.[14] It is interesting to note that the Sleep Heart Health Study did not show a statistical difference once BMI was factored out, with the implication that the development of hypertension was more related to obesity itself rather than purely OSA.[15] There were enough differences in study design, for example, using a different score for apnea-hypopnea index (AHI), so as not to discount a link with systemic hypertension; however, there are likely other associated factors.[16] Nonetheless, the seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure stated the importance of OSA as a risk factor for systemic hypertension.[17]

Intermittent nocturnal hypoxia not only sets off oxidative stress and other factors introduced earlier, but also activates the renin-angiotensin system. This then increases endothelin-l, an amino acid peptide produced by vascular endothelial cells and an important vasoconstrictor in the pathway leading to systemic hypertension.[18] Angiotensin II, a bioactive product of the renin-angiotensin system, is a potent arteriole

vasoconstrictor and triggers release of aldosterone that can lead to fluid accumulation and further airway resistance.[18–20]

Continuous positive airway pressure (CPAP) has been shown to improve blood pressure control in hypertensive patients. A recent small study revealed that CPAP therapy in a small group of hypertensive subjects reduced sympathetic activity during the daytime and reduced vascular resistance.[21] Another larger prospective controlled study showed data to suggest that OSA is associated with increased arterial stiffness that was independent of age, gender, BMI, antihypertensive medications, and hypertension and that CPAP therapy significantly reduced arterial stiffness.[22] If a patient with elevated blood pressure cannot tolerate CPAP, oral appliances have also recently been shown to improve hypertension in small studies.[23,24]

Myocardial Ischemia and Infarction

There is evidence of a greater prevalence of OSA in patients with coronary artery disease than those who do not have coronary artery disease. As mentioned earlier, intermittent hypoxia as a result of sleep apnea in the face of a reduction of stroke volume in combination with cardiac transmural pressure elevation in susceptible patients with coronary artery disease can lead to increased risk of myocardial infarction and sudden death. Other factors include blood pressure surges with the sympathetic activation and intrathoracic pressure swings, systemic inflammation, and endothelial dysfunction.[5,6,25] **Table 1** lists the process from pathophysiology to subsequent disease.

When patients with OSA were compared with control subjects, there were more episodes of cardiac arrhythmias and nocturnal ST-segment depression.[26] Peker and colleagues[27] reported, on a study of 182 men with and without OSA over 7 years, an increased risk of developing cardiovascular disease that was independent of age, BMI, blood pressure, and smoking. A larger study of participants followed over a 10-year period showed a significant increase in both fatal and nonfatal cardiovascular events in patients with severe OSA who were on no therapy compared with healthy controls.[28] CPAP therapy for patients with OSA with ischemic heart disease has been shown to lessen the severity of ST-segment depression.[29] Despite growing evidence of nocturnal cardiac ischemia in patients with OSA, a small study of patients with coronary artery disease with moderate or severe OSA did not show detectable myocardial injury by cardiac troponin T assay.[30] Another study also mentioned that cardiac troponin assay remained unchanged; however, CRP served as a useful cardiac biomarker. CRP correlated with improved systolic and diastolic cardiac function and overall cardiovascular remodeling in patients with OSA on CPAP therapy.[31]

Table 1
Mechanisms of myocardial ischemia and infarction in patients with sleep apnea

Underlying Pathophysiology	Signs and Symptoms	Disease Progression
Profound intermittent hypoxia	Nocturnal angina (symptoms of chest discomfort)	Coronary artery disease
Sympathetic vasoconstriction	Nocturnal ST depression on electrocardiogram	Ventricular arrhythmias
Cellular level acidosis		Myocardial ischemia
Blood pressure elevation		Myocardial infarction
Endothelial dysfunction		Sudden cardiac death[a]
Systemic inflammation		
↑Cardiac transmural pressure		

[a] Sudden cardiac death timing is traditionally between the hours of 6 and 11 AM; however, in those with OSA, this shifts over to traditional sleeping periods, most pronounced between 12 midnight and 6 AM.[94]

Cardiac Arrhythmias

Some cardiac arrhythmias can occur during sleep in healthy individuals, including premature atrial contractions, premature ventricular contractions, and sinus pauses. Patients with OSA have been shown to have premature ventricular contractions, nonsustained ventricular tachycardia, bradyarrhythmias, sinus arrest, and second-degree atrioventricular block.[17,32,33] **Fig. 2** shows examples of various electrocardiographic (ECG) rhythms during sleep.[34]

Patients with OSA can have more arrhythmias that cause adverse health consequences than patients who do not have OSA. Atrial fibrillation (AF) has a higher

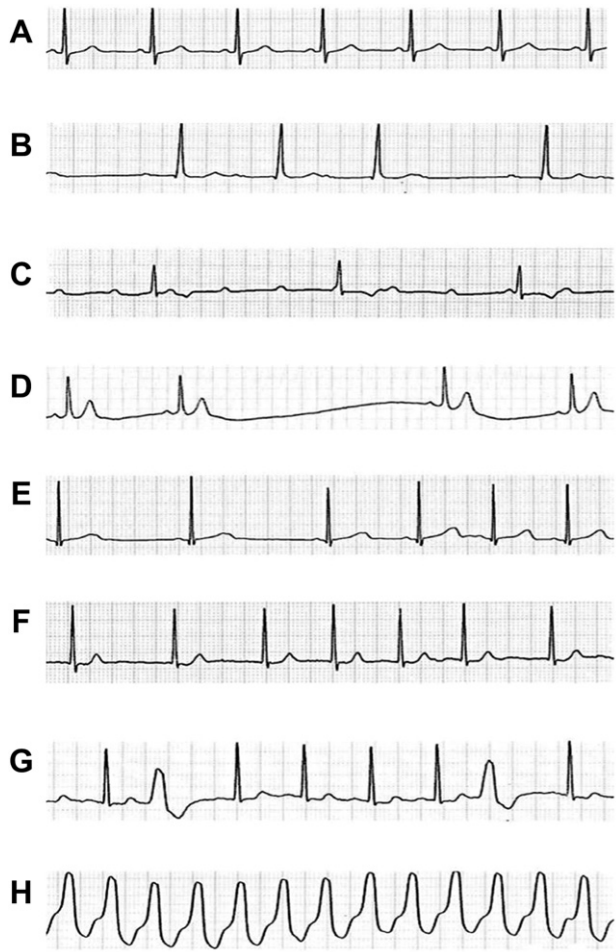

Fig. 2. Examples of various ECG rhythms that might be seen during sleep. (*A*) Normal sinus rhythm. (*B*, *C*) Atrioventricular conduction block: P wave is not followed by the QRS complex. (*D*) Sinus pause. (*E*) Atrial fibrillation: no P waves are visible. (*F*) Sinus arrhythmia. (*G*) Isolated extrasystoles. (*H*) Ventricular tachycardia. Note that the QRS complex is narrow in the supraventricular arrhythmias differentiating them from ventricular arrhythmias (in the absence of preexisting bundle branch block). (*Reprinted from* Hanak V, Konecny T, Somers VK. Cardiovascular pathophysiology of sleep apnea. In: Avidan AY, Barkoukis TJ, editors. Review of sleep medicine. Philadelphia: Elsevier-Saunders; 2011; with permission.)

incidence in patients with OSA. AF has a very high risk of recurrence after cardioversion unless the patient is on adequate OSA therapy.[35] Even after catheter ablation of AF, there is a 25% greater risk of recurring AF in patients with OSA than in those with no OSA.[36]

Pulmonary Hypertension

Pulmonary hypertension in subjects with OSA is likely attributable to hyper-reactivity to hypoxia, pulmonary arteriole remodeling, and impaired left ventricular diastolic function and enlarged left atria.[37] Although there are multiple pulmonary artery pressure elevations with OSA events, daytime sustained pulmonary hypertension as a result of sleep apnea has been less clearly linked. Patients with pulmonary hypertension and OSA tend to have more profound nocturnal hypoxemia, but may also have daytime hypoxemia as well, such as in obesity-hypoventilation syndrome or in patients who also have chronic obstructive pulmonary disease (COPD). Those patients with OSA with more predominant hypoxemia are at greater risk, as hypoxemia induces pulmonary artery pressure elevation. Despite controversy as to whether OSA is a primary cause of persistent pulmonary artery hypertension, CPAP has been shown to lower pulmonary artery pressure.[6,22,31,38]

STROKE

Stroke is a condition of acute injury to central nervous system tissue arising either from ischemia, which is more common, or hemorrhage. Transient ischemic attack (TIA) is a transient neurologic dysfunction secondary to focal ischemia but without infarction; however, it does increase the risk for stroke.[39] Stroke is a major health care problem in the United States, leading to many deaths, as well as functional impairment in survivors.[40] Both snoring and OSA have been linked to an increased incidence of stroke, and the risk for developing stroke increases with increased severity of sleep apnea at baseline.[41,42] The increased incidence is most likely secondary to interplay of various factors (see **Fig. 1**). OSA is known to contribute to increased risk for hypertension, cardiac arrhythmia, increased platelet adhesions, and dysfunction of vascular endothelium.[43,44] In fact, heavy snoring and OSA have been associated with increased risk for carotid atherosclerosis and arterial intima-media thickening.[45,46] Interestingly, stroke and TIA are risk factors for developing obstructive and central apneas as well. About half of patients who had an acute stroke have sleep apnea, and improvement is expected, more with central than obstructive apnea events, in only about half of patients in subsequent months.[47,48] Studies suggest that presence of moderate to severe OSA after stroke may lead to worse functional outcome and increase the risk for early death.[49,50] There are limited and conflicting data on outcome of positive airway pressure therapy for sleep apnea following stroke.[51,52]

DIABETES MELLITUS

There is a growing body of evidence from numerous human and animal studies that suggests an association between OSA and insulin resistance, glucose intolerance, and type 2 diabetes mellitus (DM2). Deficient insulin action lies at the heart of the problem in diabetes mellitus, which leads to hyperglycemia as a result of inadequate insulin secretion or diminished action on peripheral tissues, or both. The American Diabetes Association has established criteria to properly diagnose DM2 based on plasma glucose or hemoglobin A1C levels (**Box 1**).[53] An intermediate category is also recognized that puts an individual at risk for developing diabetes in the future. Prediabetes is the term often used to describe a clinical scenario where glucose levels

Box 1
American Diabetes Association criteria for diagnosing diabetes mellitus type 2

Hemoglobin A1C ≥6.5%

OR

Fasting plasma glucose ≥126 mg

OR

2-hour plasma glucose ≥200 mg/dL during oral glucose tolerance test

OR

Random plasma glucose ≥200 mg/dL plus classic symptoms of hyperglycemia

are higher than normal but less than that used for diagnosing diabetes. Impaired fasting glucose and impaired glucose tolerance fall under this category (**Box 2**).[53,54]

Patients with concomitant OSA and DM2 are frequently encountered in clinical practice. Clinic-based cross-sectional studies have examined the relationship between polysomnography (PSG)-diagnosed OSA and glucose metabolism. Most studies have demonstrated impaired glucose tolerance, higher fasting glucose, and insulin resistance in patients with OSA compared with patients without OSA irrespective of weight, presence of visceral fat, and age.[55–57] In a clinic-based study of 595 men, OSA was diagnosed in 494 patients and 30.1% of these were found to have DM2, when diagnosed on the basis of 2-hour oral glucose tolerance test.[58] There are also population-based cross-sectional studies linking OSA to altered glucose metabolism and DM2. Some of these studies have used surrogate markers of OSA, such as snoring and witnessed apneas,[59–63] whereas others have diagnosed OSA by PSG.[12,64,65] A more robust association between OSA surrogate markers and DM2 has been shown by longitudinal studies. A 10-year follow-up study of 2668 Swedish men showed self-reported diabetes in 5.4% of habitual snorers at baseline compared with 2.4% without (P<.001). In addition, the occurrence of incident diabetes in obese snorers was 7 times more likely than nonobese snorers.[66] Likewise, in the US Nurses' Health Study involving 69,852 women where presence of DM2 was confirmed by composite clinical and laboratory criteria, there was a twofold increase in the risk of developing diabetes in habitual snorers at a 10-year follow-up even when adjusted for age, BMI, smoking history, number of sleep hours, history of hypertension, or family history of diabetes.[67] These studies suggest a causal relationship between OSA and diabetes mellitus, but are severely limited by the lack of PSG data. The available data on studies with OSA diagnosed by PSG is conflicting and limited by number of years of follow-up. Although one observational cohort study with a mean duration of

Box 2
Prediabetes criteria

Impaired fasting glucose: fasting plasma glucose 100–125 mg/dL

OR

Impaired glucose tolerance: 2-hour plasma glucose 140–199 mg/dL oral glucose tolerance test

OR

Hemoglobin A1C 5.7–6.4%

follow-up of 2.7 years found an independent association between sleep apnea and incident diabetes,[68] the other did not show any association after 4-year follow-up.[69]

OSA may not only increase the risk of dysfunction in glucose metabolism, but also affect glycemic control in patients who already have diabetes. There is a suggestion that OSA severity may play a role in conferring the degree of dysfunction. In an observational cross-sectional study of 52 patients, increased hemoglobin A1C (HbA1c) levels were associated with increased severity.[70] This was independent of age, gender, BMI, duration of diabetes, and insulin dose; however, a plateau effect was noted from moderate to severe OSA levels.

Intermittent hypoxemia and recurrent arousals from sleep are thought to play an important role in pathophysiologic mechanisms leading to altered glucose homeostasis in patients with OSA (**Fig. 3**). Both mice and human studies have shown diminished insulin sensitivity after exposure to intermittent hypoxemia.[71–73] Patients with OSA have elevated blood levels of leptin, an appetite-suppressing adipokine secreted by adipose tissues, largely contributed by oxygen desaturations during sleep.[74,75] Prolonged hyperleptinemia may lead to leptin resistance.[10,76] Patients with OSA also have elevated circulating inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-6.[77,78] The other 2 possible mechanisms are thought to be activation of the sympathetic nervous system, which can cause upregulation of regulatory factors that have anti-insulin activities, and dysfunction of the hypothalamic-hypophyseal-adrenal axis, which can increase cortisol levels. All of these may contribute to insulin resistance.[10,13,79]

If OSA is associated with insulin resistance, then treatment is expected to improve insulin sensitivity. Nonrandomized trials using CPAP therapy for treating OSA have shown improvement in insulin sensitivity, sleeping glucose levels, and HbA1C, especially in nonobese and nondiabetic patients with OSA.[80–82] The duration of CPAP therapy and the hours of usage per night seem to affect the outcome. The insulin sensitivity improved within 2 days of initiating CPAP therapy in nondiabetic patients who were also not obese, but improvement at 3 months also was seen in patients

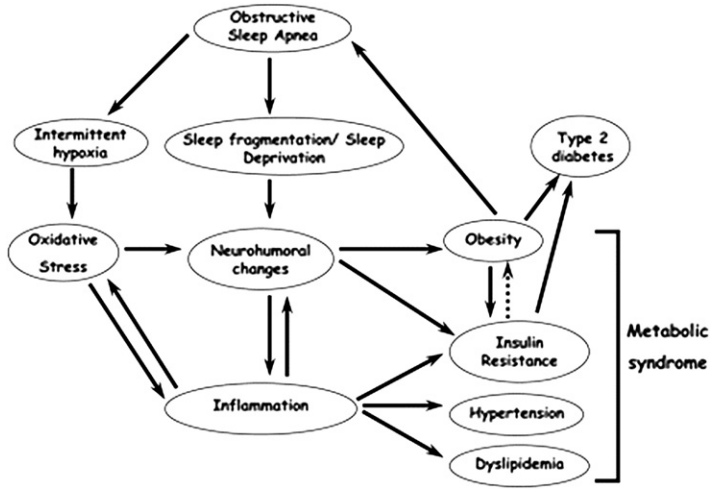

Fig. 3. Possible mechanistic links between OSA, DM2, and metabolic syndrome. Dyslipidemia includes both hypertriglyceridemia and low HDL-cholesterol. (*Reproduced from* Tasali E, Ip MS. Obstructive sleep apnea and metabolic syndrome: alterations in glucose metabolism and inflammation. Proc Am Thorac Soc 2008;5:212; with permission.)

with diabetes irrespective of weight.[80,83] Likewise, a progressive improvement in HbA1C was seen over time with CPAP therapy, but only when CPAP was used for more than 4 hours per night[81]; however, a placebo-controlled CPAP trial did not show any significant improvement in HbA1C and insulin resistance in obese patients with DM2.[84] There is indeed a need for larger controlled trials of longer duration of follow-up to study long-term effects of therapy on glucose metabolism.

METABOLIC SYNDROME

Metabolic syndrome is a constellation of risk factors that are metabolic disturbances in themselves, and predicts an increased risk for future DM2 and cardiovascular diseases. The National Cholesterol Education Program Adult Treatment Panel III has developed criteria consisting of 5 variables (abdominal obesity, triglycerides, high-density lipoprotein cholesterol, blood pressure, and fasting glucose) with set threshold values.[85,86] The presence of 3 or more variables out of 5 qualifies for the diagnosis of metabolic syndrome (**Box 3**). It is hard not to notice that some of the variables, such as obesity, alteration in glucose homeostasis, and hypertension, are associated with OSA as well. In fact, studies have shown that OSA is independently associated with metabolic syndrome,[65,87,88] and that unrecognized OSA is common in patients with metabolic syndrome.[89] Chronic intermittent hypoxemia and sleep fragmentation, as discussed previously, are thought to be involved in the overall pathophysiology (see **Fig. 3**). There is some evidence of OSA therapy improving some of the individual parameters that comprise metabolic syndrome and are discussed elsewhere in this article, but data are scant on the effect of treatment on the whole metabolic syndrome entity and its cardiovascular and diabetic consequences. One study that followed 89 subjects for a period of 12 to 32 months found that metabolic syndrome did not increase the risk of cardiovascular events in CPAP-treated patients with OSA.[90]

GASTROESOPHAGEAL REFLUX DISEASE

During sleep, swallowing frequency decreases and production of saliva ceases. This leads to impaired esophageal acid clearance, thereby increasing acid-mucosa contact time. Gastroesophageal reflux commonly occurs and is noted in sleep as well, and occurs more frequently in patients with gastroesophageal reflux disease. Nocturnal reflux symptoms are increased in patients with OSA.[91] The pathophysiology of this association is not clearly understood, although the pressure gradient across the lower esophageal sphincter that develops during the upper airway collapse is thought to favor reflux. CPAP therapy has been shown to improve not only reflux symptoms in

Box 3
Metabolic syndrome criteria: 3 or more variables out of 5 qualify for the diagnosis of metabolic syndrome

- Waist circumference >40 inches in men and 35 inches in women
- Serum triglycerides level $\geq$150 mg/dL
- Serum high-density lipoprotein cholesterol level <40 mg/dL in men and <50 mg/dL in women
- Blood pressure $\geq$130/85 mm Hg
- Fasting glucose level $\geq$100 mg/dL

patients with and without OSA, but also has been shown to improve lower esophageal sphincter function.[92,93]

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