Obstructive sleep apnea and cardiovascular risk

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Abstract: Obstructive sleep apnea (OSA) is a form of sleep disordered breathing characterized by episodes of apnea (during sleep) lasting at least 10 seconds per episode. The apneic periods are associated with arterial hypoxemia and disruption of normal sleep as a result of awakenings. It is increasingly being recognized that OSA is a public health hazard and there is increasing evidence that it is associated with an increase in morbidity (and possibly mortality). Patients with OSA also utilize the healthcare resources at higher rates than control patients long before their diagnosis is confirmed. Early recognition of this condition may lead to earlier treatments (eg, nasal CPAP) with reduction of the risk of cardiovascular diseases such as hypertension, ischemic heart disease, arrhythmias, platelet activation and pulmonary hypertension.

Keywords: obstructive sleep apnea (OSA), apnea-hypopnea index (AHI), polysomnography, overlap syndrome, C-Reactive protein (CRP), sleep disordered breathing (SDB), Cheynes Stokes respiration-central sleep apnea (CSR-CSA)

Epidemiology of OSA

Early observational studies linked snoring to increased cardiac events. However, subsequent studies demonstrated a clear relationship between the presence and severity of obstructive sleep apnea (OSA) with systemic hypertension and increased cardiovascular disease. The initial descriptions of OSA were that of severe apnea in obese, middle-aged male subjects (Block et al 1979). OSA syndrome is a common breathing disorder that affects 2%–4% of the adult population with men being affected almost twice as much compared to women (Young et al 1993). In a later study, women accounted for one third of OSA patients (Edwards et al 1998).

Pathophysiologic mechanisms of cardiovascular disease in OSA

Pathophysiology of OSA

Obstructive sleep apnea is the most common form of sleep disordered breathing (SDB) and characterized by repetitive partial or complete closure of the upper airway during sleep. Acute physiologic stresses occur during these episodes of asphyxia, including arterial oxygen desaturation, surges in sympathetic activity, and acute hypertension.

Obstructive sleep apnea results in hypoxemia and hypercapnea and contributes to arousals which are frequently associated with it and leads to an increase in myocardial oxygen demand. The hypoxemia and hypercapnea as well as the associated arousals, activate the sympathetic nervous system and increases catecholamine release which further aggravates the myocardial oxygen demand. The ensuing hypertension and associated cardiac ischemia and hypertrophy, lead to a propensity for arrhythmias and an increase in LV wall tension and consequently, congestive heart failure. In a study by Dursunoglu et al (2005) of 67 patients without previous cardiac and pulmonary disease who were diagnosed as having mild, moderate or severe OSA, LV hypertrophy and LV mass index, on echocardiographic criteria, was higher in those with moderate

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to severe OSA compared with those with mild sleep apnea. However, in this study hypertension was also more prevalent in those with moderate and severe OSA.

Patients also develop a hypercoagulable state as a result of platelet activation which further aggravates the heart failure (Bradley and Floras 2003).

OSA, COPD and pulmonary hypertension

The prevalence of OSA in predominantly mild COPD patients is not greater than in the general population, but the two conditions frequently coexist. This association is thought to occur by chance and is not pathophysiologically linked (Sanders et al 2003). The association of OSA with COPD ('overlap syndrome') is also significant in that a large epidemiologic study by Sanders et al have demonstrated greater reductions in nocturnal oxygen saturations than either alone. Conventional domiciliary oxygen therapy (daytime and nocturnal) is indicated in COPD patients with marked daytime hypoxemia ($PaO_2 < 55$–60 mmHg) and there is insufficient data on the use of nocturnal O_2 therapy in COPD patients with nocturnal desaturation without daytime hypoxemia ($PaO_2 > 60$ mmHg) (Weitzenblum and Chaouat 2004).

Alveolar hypoxemia is also the most important mechanism leading to pulmonary vasoconstriction, pulmonary vascular remodeling and pulmonary hypertension. Some evidence suggests that patients with OSA and COPD are at greater risk of pulmonary hypertension than patients with sleep apnea alone (Chaouat et al 1995; Hawrylkiewicz et al 2004).

In patients with severe COPD a reduction in oxygen saturation during sleep was twice as much as that during maximal exercise (Mulloy and McNicholas 1996). Patients with obstructive sleep apnea as well as COPD ('overlap syndrome') are associated with a greater risk of pulmonary hypertension. It has been observed that patients with COPD who are hypoxemic during wakefulness are at greater risk of hypoxemia during sleep and usually more profound during REM sleep (Wynne et al 1979). These desaturations are not only present during REM sleep, but also during the earlier stages of non-REM sleep (Stages 1 and 2), and are not as severe (Kurtz et al 1987; Mulloy and McNicholas 1996). In a small study of 40 patients by Vos et al (1995) to determine predictors of nocturnal desaturations in COPD, only a small number of patients with mild to moderate daytime hypoxemia (PaO_2 60–80 mmHg) had nocturnal desaturations with mean arterial O_2 saturations below 90%. These patients also had a lower hypercapneic ventilatory response, and no patients with daytime $PaO_2 > 80$ mmHg had nocturnal desaturations (Vos et al 1995).

Earlier reports have hypothesized that COPD patients with moderate hypoxia (PaO_2 56–69) were at risk of nocturnal oxygen desaturations and subsequent pulmonary hypertension. In a study published by Chaouat et al (1997) of 94 patients with COPD randomized to saturators (group 1) and desaturators (group 2 : O_2 saturation >30% of time less than 90%,) it has been concluded that there are no individual variables or combination of variables (except $PaCO_2$ which was higher in the desaturators) that predicted the presence of pulmonary hypertension, and that the mean pulmonary artery pressure did not correlate with the degree and duration of nocturnal hypoxemia (Bradley et al 1990; Chaouat et al 1997).

The two mechanisms responsible for the worsening of hypoxemia during sleep are alveolar hypoventilation and ventilation-perfusion (V/Q) mismatching. Apneas generally do not occur in COPD patients unless they are associated with OSA. Transient hypoxemia which may occur during sleep in patients with COPD has been stated not to be a sleep apnea syndrome (Chatterhall et al 1983).

Pulmonary hypertension in patients with COPD has traditionally been explained on the basis of hypoxic pulmonary vasoconstriction. Christensen et al (2004) studied 17 patients with COPD of varying severity with no or mild hypoxemia at rest and during their exercise equivalent of their activities of daily living (ADLs). In their study, they have demonstrated that exercise-induced pulmonary hypertension occurred in 65% of patients, and that the increase in pulmonary artery pressure was negatively correlated with arterial oxygen tensions. In addition, patients with exercise-induced pulmonary hypertension were not invariably accompanied by hypoxemia and not all patients with exercise-induced hypoxemia had pulmonary hypertension. Their study also demonstrated a negative correlation between pulmonary vascular resistance index (PVRI) and arterial oxygen tension during exercise, but also an elevated PVRI occurred in 35% of patients without exercise-induced hypoxemia. The authors concluded that mechanisms other than hypoxemia, such as arterial remodeling due to inflammation may contribute to pulmonary hypertension in these patients (Christensen et al 2004).

With reference to the association of OSA and pulmonary arterial hypertension (PAH), the American College of Chest Physicians has provided clinical practice guidelines in an evidence-based approach. Based on the available evidence the following recommendations have been made:

1. In the evaluation of patients with PAH, an assessment of sleep disordered breathing (SDB) is recommended

using polysomnography if OSA is suspected either by high clinical suspicion or if a screening test result is positive.
2. In the management of patients with OSA, the routine evaluation for the presence of PAH is not recommended.
3. In patients with both OSA and PAH, treatment of OSA with positive pressure ventilation should be provided with the expectation that the pulmonary pressures may be reduced but not normalized, especially in patients with more severe PAH (Atwood et al 2004).

OSA and sytemic hypertension

There is increasing evidence that hypertension is associated with sleep apnea syndromes. Both case control and cross-sectional studies have demonstrated a higher prevalence of hypertension in patients with OSA (50%–90%). Dhillon et al (2005) in an observational review of 180 consecutive charts from 1995 to 2002, studied patients with OSA from an urban and a rural sample, who were either hypertensive or normotensive. Their study demonstrated that 28% (50/180) of patients were hypertensive and that treatment with CPAP for an average of 12 months was associated with significant reduction in systolic and diastolic blood pressures (11 mmHg vs 6 mmHg respectively) and consequently a reduction in cardiovascular risk. This study confirms the relationship of sleep apnea and hypertension and the benefit of CPAP as reported in other studies (Dhillon et al 2005). Other studies have also demonstrated that CPAP treatment of OSA patients with hypertension, have led to a lowering of blood pressures resulting in a reduced cardiovascular risk (Tilkian et al 1976; Millman 1991).

Subjects with an apnea-hypopnea index (AHI) $>$ 5 have a higher incidence of systolic and diastolic hypertension. Sleep apnea has been shown to occur frequently in patients with essential hypertension (22%–62%) (Lavie et al 1984). In a study of 23 patients treated for essential hypertension, using a questionnaire for symptoms of sleep apnea, and a sleep study, the prevalence of sleep apnea was 48% (11/23). Of these patients, one third (7/11) were found to have severe oxygen desaturations defined as at least a 4% reduction or saturations $<$ 90% (average 87%) during sleep as a result of apnea (Williams et al 1985).

In some of the earlier studies or surveys, there had been no objective data on breathing during sleep and it is not clear if the association was due to the inclusion of apneic individuals among snorers. Inconsistencies in the association of sleep apnea and hypertension have been demonstrated, with some studies showing a strong association and others not. These inconsistencies were probably related to differences in definitions of hypertension and apnea, as well as the inability to control for factors associated with hypertension such as obesity and diabetes. In one of the largest cohort of 6,132 subjects (Sleep Heart Health Study), it has been clearly demonstrated that sleep disordered breathing is associated with systemic hypertension in middle-aged and older-aged individuals of different sexes and ethnic backgrounds even after adjusting for variables such as body mass index (BMI), neck circumference, waist-to-hip ratio, alcohol intake and smoking. In the unadjusted arm of the study, the prevalence rates of hypertension increased according to the severity of the apnea (43% (AHI $<$ 1.5), 53% (AHI 1.5–4.9), 59% (AHI 5–14.9), 62% (AHI 15–29.9) and 67% with an AHI $>$ 30. When adjusted for other demographics, the odds of hypertension increased in a graded response according to the severity of the AHI (Nieto et al 2000). In another large cohort of 709 patients (Wisconsin Sleep Study) it has been demonstrated that there was a dose-response association with hypertension and the severity of sleep apnea according to their AHI, even after adjusting for other factors such as BMI, alcohol and tobacco use (Peppard et al 2000).

A cross-sectional community based study of 147 male and female patients (30–60 years) selected from the Wisconsin Sleep Cohort Study looked at the association of blood pressure during sleep and wakefulness in patients with and without sleep apnea. In this study, the mean blood pressures were significantly elevated in patients with sleep apnea during wakefulness (131/80 ± 1.7/1.1 mmHg) compared to 122/75 ± 1.9/1.2 mmHg in those without sleep apnea. In addition the mean blood pressures in sleep apnea patients during sleep were also significantly elevated (113/66 ± 1.8/1.1 mmHg, compared to 104/62 ± 2/1.3 mmHg, $P < 0.05$). The study also demonstrated the variability of the blood pressure during sleep was significantly greater in participants with sleep apnea or a history of snoring compared with those without. The variability in mean arterial blood pressure in non-snorers with an AHI $<$ 5 was 7.5 mmHg compared to 8.5 mmHg in snorers with an AHI $<$ 5 and 8.9 in apneic patients with AHI $\geq$ 5 ($P < 0.05$). Even after controlling for obesity, gender and age, the prevalence of hypertension was significantly associated with sleep apnea (OR 2.0 to 5.0 for AHI 5–25) (Hla et al 1994).

Studies have also shown higher sympathetic activity in sleep apnea patients when awake, with further increases during sleep. The greatest increase in sympathetic activity is at the end of the apnea period, after arousal. With resumption of normal breathing, there is a decrease in sympathetic activity and blood pressure. The mechanism(s) of increased

sympathetic nervous activity is unclear but may be determined by factors such as age, sex, obesity, oxygen desaturation and hypercapnea. Continuous positive airway pressure (CPAP) has been shown to attenuate the apneic episodes as well as the increased sympathetic activity and hypertensive responses during sleep. However, this attenuated response is not complete to the levels seen during normal sleep in normal subjects (Somers 1993, 1995).

The arousal mechanism has been considered a stimulant of sympathetic activity and catecholamine levels have been shown to be increased after arousal. Carotid body stimulation appears to be pivotal to this sympathetic nervous activity and the development of increases in blood pressure. Oxygen attenuates the sympathetic nervous system responses to apnea, but does not completely inhibit it. In a more recent study in hypertensive patients with OSA who are hypersomnolent compared with those that are non-hypersomnolent, there has been no significant difference in the mean 24-hour BP when CPAP treatment was compared to sham treatment (suboptimal CPAP) (Robinson et al 2006).

Sleep disordered breathing (SDB) has also been linked to the development of stroke. Until recently there have been no prospective studies that have confirmed the association of SDB with stroke. In a cross-sectional and longitudinal study published by Arzt et al (2005), subjects with SDB were compared with those without SDB in the general population and followed for 4 years for the development of stroke. Of 1475 subjects studied in the cross-sectional analysis, 22 suffered a first-ever stroke over the next 4 years and none of these had atrial fibrillation. The percent prevalence rates for stroke according to AHI's of <5, 5 to <20 and >20 were 1.2%, 0.8% and 6.1% respectively. After adjustment for age, sex, body mass index, smoking and alcohol consumption, the odds ratio for developing a stroke in the SDB group was still elevated (O.R. 4.3 for AHI $>$ 20, 95% C.I 1.32–14.24). When hypertension was added as a confounding variable, the odds ratio was 3.87 (95% C.I. 1.19–12.63) and remained significant. In the group with mild to moderate SDB (AHI 5.0 – $<$20.0) the odds ratio for the prevalence of stroke was not significantly different from the reference group (AHI $<$ 5.0). This study however, does demonstrate an association with SDB and the development of stroke even after adjusting for confounding factors (Artz et al 2005).

OSA and ischemic heart disease

Increasing evidence is emerging that indicate that OSA is a risk factor for cardiovascular disease, independent of other commonly associated conditions such as age, sex, obesity, diabetes and hypertension. Earlier epidemiologic studies, using snoring as a surrogate for OSA, suggested a higher prevalence of hypertension and ischemic heart disease in snorers (Yates 1987; Markku et al 1985; Norton and Dunn 1985).

Hung et al studied 101 unselected male survivors ($<$65yrs) of acute myocardial infarction (MI) and another 53 male subjects of similar age without evidence of ischemic heart disease. The apnea index was 6.9 in the MI group compared to 1.4 in the control subjects. The relative risk for MI between the highest and lowest quartiles of the apnea index was 23.3 (95% CI 3.9–139.9) (Hung et al 1990).

In a cross-sectional substudy of the Sleep Heart Health Study, of the association of SDB with cardiovascular disease by Shahar et al (2001) it has been demonstrated in 1,023 participants, using multivariable adjustments, that sleep disordered breathing was more strongly associated with self-reported heart failure and stroke than coronary artery disease. In this study the relative odds (95% CI) of heart failure, stroke and coronary artery disease for AHI values that were considered normal or only mildly increased, were 2.38 (1.22–4.62), 1.58 (1.02–2.46) and 1.27 (0.99–1.62) respectively and therefore suggesting only a modest to moderate effect on cardiovascular disease.

OSA and cardiac dysfunction

Earlier studies have demonstrated an association with LV dysfunction and OSA. These have been explained largely on the decreases in intrathoracic pressure during inspiration in patients with OSA. It has been demonstrated that large and sustained decreases in intrathoracic pressures as a result of OSA, may affect LV function not only as a result of changes in LV filling but also as a result of changes in afterload. Decreases in intrathoracic pressure results in increases in left ventricular transmural pressure (LVPtm) during systole, which in turn increases afterload (diastolic dysfunction) (Buda et al 1979). In addition, increases in negative intrathoracic pressure swings increase right-sided filling causing right ventricular distention with a leftward shift of the interventricular septum resulting in decreased left-sided filling. These observations have therapeutic implications as positive end expiratory pressure and continuous positive airway pressure may be a factor in improving pulmonary compliance and LV function in these patients (Suter et al 1979). In two outpatient studies of patients with stable and asymptomatic congestive heart failure, approximately 40%–50% of the patient population had OSA or Cheyne Stokes respiration with central sleep apnea Naughton and Bradley (1998). In

a recent randomized study of 258 patients with congestive heart failure and central sleep apnea by Bradley et al (2005) (CANPAP Trial) assessing the benefits of longer term CPAP on morbidity and mortality, CPAP reduced the frequency of apneas and hypopneas, increased the minimal and mean nocturnal oxygen saturations, and increased ejection fractions and six-minute walk distance. However, there has been no effect on morbidity and mortality as measured by the heart transplant-free survival between the CPAP group versus the control.

With reference to OSA and the different forms of cardiac dysfunction, in a study of 68 patients with polysomnographically confirmed OSA, published by Fung et al it has been observed, that an abnormal relaxation period on echo Doppler as evidence for diastolic dysfunction, was present in 37% of patients. In those with diastolic dysfunction there was also an association with increasing age, hypertension and a lower minimal oxygen saturation during sleep. However, using multivariate analysis, is has been observed that a lower oxygen saturation during sleep was an independent predictor of an abnormal relaxation period irrespective of age or hypertension. In addition, diastolic dysfunction was more prevalent in those with severe OSA (AHI $>$ 40 vs $<$ 40) (Fung et al 2002).

In a prospective study of 169 consecutive OSA patients, by Laaban et al (2002) on the association of LV systolic dysfunction and OSA, using radionuclide studies, it has been observed that only 7.7% (13/169) patients had systolic dysfunction, defined as having an LVEF $<$ 50%. In this study, patients with known cardiac disease were excluded and there was no differences in age, body mass index, AHI, nocturnal desaturations or the prevalence of systemic hypertension in those with LVEF's of $>$50% or $<$50%. It was also shown that in about 50% of patients who had been reassessed after treatment of their OSA, their LVEF's had normalized. The authors of this study concluded that systolic dysfunction was an uncommon/rare consequence of OSA, and that multiple potential mechanisms contributed to this, including LV strain related to chronic daytime LV dysfunction, hypoxemia and impairment of myocardial contractility and possibly nocturnal hypertension and catecholamine surges.

Both OSA and Cheyne-Stokes-Respiration with Central Sleep Apnea (CSR-CSA) occur in patients with congestive heart failure. Unlike in OSA and patients with CHF, CSR-CSA tends to be a consequence, rather than a cause of the CHF. In patients with an increase in pulmonary venous congestion, there is an increase in pulmonary vagal afferents, resulting in hyperventilation. This hyperventilation results in a reduction in the arterial $PaCO_2$ below the apnea threshold resulting in recurrent central apneas. Although the former mechanism is controversial, it is believed that an increase in sympathetic nervous system activation may stimulate hyperventilation resulting in hypocapnea. The apneas are terminated when the $PaCO_2$ rises to the ventilatory threshold (Heistad et al 1972; Datta et al 1991; Bradley and Phillipson 1992).

CSR-CSA in patients with CHF appears to be a marker of increased mortality, and this has been demonstrated in at least one study published by Hanley et al who showed in a study comparing patients of similar degrees of functional status and LV ejection fraction, with and without CSR-CSA, that the mortality was 56% in those with CSR-CSA compared to 11% in those without. The most likely mechanism to explain this was an increase in sympathetic nervous system activity (Hanly and Zuberi-Khokhar 1996).

In a study of 47 asymptomatic patients with LV dysfunction (LVEF $<$40%), the prevalence of CSA was much higher than OSA (55% vs 11%). In addition, the severity of CSA was not associated with the severity of hemodynamic impairment (Lanfranchi et al 2003).

OSA and arrhythmias

Both bradyarrhythmias and tachyarrhythmias occur in patients with OSA. Bradyarrhythmias are said to be more common than tachyarrhythmias, and evidence supports the presence of hypoxemia for bradyarrhythmias to occur. Apnea without hypoxemia does not result in bradyarrhythmias. Hypoxemia causes tachycardia during wakefulness and during all stages of sleep. The longer the duration of apnea and the more severe the oxygen desaturation, the greater the association with bradycardia. Further observations by Zwillich et al have demonstrated that breath-holding whilst breathing air with low oxygen concentrations than room air resulted in bradyarrhythmias (Zwillich et al 1982). The effect of hypoxemia and lung inflation on heart rate appears to be under vagal control, and observations by Zwillich et al have confirmed that pre-treating subjects with atropine before breath holding and breathing lower concentrations of oxygen, prevented bradyarrhythmias.

During normal sleep the body is in a state of hemodynamic and autonomic "quiescence" resulting in a decrease in myocardial workload. In patients with OSA, the "arousals" punctuate this state of autonomic quiescence resulting in increased sympathetic activity and increases in blood pressure and heart rate. Most arrhythmias occur in those with AHI $>$ 40/hour (Hoffstein and Mateika 1994).

In a cohort of patients from the Sleep Heart Health Study, individuals with severe sleep-disordered breathing have two- to fourfold higher odds of complex arrhythmias than those without sleep-disordered breathing even after adjustment for potential confounders. This sub-study however, did not find a significant association between OSA and bradyarrhythmias (Mehra et al 2006).

In a study of patients with OSA and atrial fibrillation, those patients cardioverted for AF but untreated for OSA, there was a doubling of 1 year recurrence rate of their atrial fibrillation compared to those patients receiving CPAP therapy (Kanagala et al 2003).

OSA, platelet activation, endothelial dysfunction and serum biomarkers

Platelet activation is known to be associated with an increase in risk of cardiovascular death (Tofler et al 1987).

Increased platelet activation and aggregation has been shown to occur during sleep in patients with OSA, and this effect has been shown to be reduced by nasal CPAP (Bokinsky et al 1995). Another study confirmed increased in-vitro platelet aggregability in patients with OSA which was reduced by long term treatment with nasal CPAP. This therapy also restored the physiologic diurnal pattern of platelet aggregability (Sanner et al 2000).

In a review of the evidence for an increase in cardiovascular and cerebrovascular disease, many studies have also indicated an increase in hemostatic alterations and a pro-coagulant state in patients with OSA. Some of the mechanisms include an increase in plasma fibrinogen, platelet activation and reduced thrombolytic activity (Von Kanel and Dimsdale 2003).

In the Mayo Clinic Proceedings, OSA, as in atherosclerosis, has been shown to be associated with an increase in CRP, interleukin 6, fibrinogen and plasminogen activator inhibitor and reduced fibrinolytic activity. In addition, there has also been leukocyte adhesion and accumulation on the endothelial cells (Parish and Somers 2004). Although there are no serum markers for OSA, there is evidence of an increase in serum homocysteine and C-Reactive Protein (CRP) which may be used as a predictor of long term prognosis for cardiovascular disease and response to treatment of OSA (Wright et al 1997).

There is increasing evidence to suggest that repeated apnea-related hypoxic events similar to hypoxia and reperfusion injury, may lead to oxidative stresses which in turn result in free radical production and activation of a number of cytokines, adhesion molecules and transcription molecules such as endothelin-1, vascular endothelial growth factor (VGEF), and NF-kappa-B (Lavie 2003; Cummins et al 2006; Zamarron-Sanz et al 2006).

Conclusion

Obstructive sleep apnea is a common condition with major public health implications. It is commonly associated with recognized cardiovascular risk factors such as obesity, hypertension, diabetes and hyperlipidemia. Some studies have suggested that OSA may be an independent cardiovascular risk factor. However, many epidemiologic studies have failed to demonstrate a causal relationship.

Attention to the treatment of the associated co-morbid conditions such as obesity, diabetes, hypothyroidism and COPD, as well as treatment with nasal CPAP have been associated with a reduction in mortality associated with this condition.

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