# Cardiovascular diseases in obstructive sleep apnea

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***ÖZET***

***Obstrüktif uyku apnede kardiyovasküler hastalıklar***

*Obstrüktif uyku apne (OSA) orta yaştaki erişkinlerde yaklaşık olarak erkeklerin %15'ini, kadınların %5'ini etkiler ve istenmeyen sağlık sonuçlarıyla ilişkilidir. Kardiyovasküler bozukluklar OSA'nın en ciddi komplikasyonlarıdır. Bu komplikasyonlar, kalp yetersizligi, sol/sağ ventrikül disfonksiyonu, akut miyokard infarktüsü, aritmiler, inme, sistemik ve pulmoner hipertansiyonu içerir. Tüm bu kardiyovasküler komplikasyonlar OSA'nın morbidite ve mortalitesini arttırmaktadır. Çeşitli epidemiyolojik çalışmalarda, uykuyla ilişkili solunum bozukluklarının, olasılıkla uykuda tekrarlayan hipoksi ve hiperkapniler, arousaller, artmış sempatik aktivite ve bozulmuş barorefleks kontrolü mekanizmalarıyla oluşan hipertansiyon için bağımsız bir risk faktörü olduğu gösterilmiştir. Sol ventrikül disfonksiyonunun bağımsız belirleyicileri olan arteryel hipertansiyon, obezite, diabetes mellitus ve koroner arter hastalığı (KAH) sıklıkla OSA'ya eşlik eder. Özellikle diyastolik disfonksiyonu olan ciddi OSA hastaları, diyastolik ve sistolik disfonksiyon birarada bulunabildiğinden, kalp yetersizliği için artmış riske sahiptir. Kalp yetersizliği ve ölüme ilerleyişi önlemek için, ventrikül disfonksiyonunun erken tanı ve uygun tedavisi önerilmektedir. Belirgin kalp yetersizliği olmaksızın özellikle apne ve hipoksemisi olan akut miyokard infarktüslü hastalar, uyku bozuklukları açısından değerlendirilmelidir. KAH olan hastalar OSA ve OSA'lı hastalar da KAH açısından değerlendirilmelidir. OSA'nın erken tanı ve tedavisi kardiyovasküler fonksiyonları düzeltebilir. Nazal CPAP uygulaması, hastalığın tedavisi ve komplikasyonlarının önlenmesinde halen altın standart yöntemdir.*

***Anahtar Kelimeler:*** *Kardiyovasküler hastalıklar, obstrüktif uyku apne, hipertansiyon, metabolik sendrom, CPAP.*

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*SUMMARY*

***Cardiovascular diseases in obstructive sleep apnea***

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*Obstructive sleep apnea (OSA) affects approximately 5% of women and 15% of men in the middle-aged adults, and associated with adverse health outcomes. Cardiovascular disturbances are the most serious complications of OSA. These complications include heart failure, left/right ventricular dysfunction, acute myocardial infarction, arrhythmias, stroke, systemic and pulmonary hypertension. All these cardiovascular complications increase morbidity and mortality of OSA. Several epidemiologic studies have demonstrated that sleep related breathing disorders are an independent risk factor for hypertension, probably resulting from a combination of intermittent hypoxia and hypercapnia, arousals, increased sympathetic activity, and altered baroreflex control during sleep. Arterial hypertension, obesity, diabetes mellitus and coronary artery disease (CAD) which are independent predictors of left ventricular dysfunction, often have coexistince with OSA. Especially severe OSA patients having diastolic dysfunction might have an increased risk of heart failure, since diastolic dysfunction might be combined with systolic dysfunction. Early recognition and appropriate therapy of ventricular dysfunction is advisable to prevent further progression to heart failure and death. Patients with acute myocardial infarction, especially if they had apneas and hypoxemia without evident heart failure should be evaluated for sleep disorders. So, patients with CAD should be evaluated for OSA and vice versa. Early recognition and treatment of OSA may improve cardiovascular functions. Continuous positive airway pressure (CPAP) applied by nasal mask, is still the gold standard method for treatment of the disease and prevention of complications.*

***Key Words:*** *Cardiovascular diseases, obstructive sleep apnea, hypertension, metabolic syndrome, CPAP.*

Obstructive sleep apnea (OSA) affects approximately 5% of women and 15% of men in the middle-aged adults, and associated with adverse health outcomes (1). The obstructive apneic event is associated with considerable breathing efforts against totally or partially occluded upper airway. The apnea is terminated by an arousal and heavy snoring as airflow is restored. Complete collapse of the upper airway for at least 10 seconds with persistent effort to breathe is termed obstructive apnea. Hypopnea, partial collapse of the airway during sleep, is defined as a 50% or greater reduction in airflow and a 3% desaturation. Severity of OSA is described according to total number of apneas and hypopneas per hour of sleep which is named as apnea hypopnea index (AHI). An AHI lower than 5 per hour is normal; an AHI of 5 to 15 is mild disease, 15 to 30 is moderate disease, and greater than 30 is severe disease (2). The most common nocturnal symptom is snoring and this is the key symptom, while the most common daytime symptom is hypersomnolance (3). Sleep apnea might cause several social and public problems by disturbing work performance and driving, and also might be associated with some neuropsychiatric complications, especially like depression (20-56%) (3,4).

Cardiovascular disturbances are the most serious complications of OSA (3,5). These complications include heart failure (HF), left/right ventricular dysfunction, acute myocardial infarction (MI), arrhythmias, stroke, systemic hypertension (SH) and pulmonary hypertension (6-25). All these cardiovascular complications increase morbidity and mortality of OSA. Nowadays, sleep apnea is accepted as one of the identifiable causes of hypertension in Joint National Committee (JNC) 7 report (26). Also, OSA is closely associated with obesity and aging (27,28). In a series of

1620 patients with OSA, Lavie et al. reported that the observed-to-expected mortality ratio was 3.33 in patients younger than 70 years (29).

Continuous positive airway pressure (CPAP) applied by nasal mask, is the gold standart method for treatment of the disease and prevention of complications (30). CPAP therapy is known to maintain upper airway patency during sleep by increasing transmural pressure of upper airways, and treatment of OSA by CPAP improves cardiac function and quality of life (31-35).

**OSA and Cardiovascular Disease (CVD)**

Sleep apnea could be a cause of CVD. It was shown several years ago that OSA is very common in patients presenting with acute MI. Nocturnal ischemia has been shown to be common in patients with both OSA and coronary artery disease (CAD) and similarly, OSA has been found to be very common in patients with nocturnal ischemia (36,37). Furthermore, in a study with a five-year follow up of patients known to have CAD, mortality has been shown to be significantly higher in those with OSA, independent of confounding factors (38).

Cardiovascular events and proposed potential mechanisms of CVD in sleep apnea were summarized in Table 1 and Table 2 respectively. Although the exact cause that links OSA with CVD is unknown, there is evidence that OSA is associated with a group of proinflammatory and prothrombotic factors that have been identified to be important in the development of atherosclerosis (12,39-44). Both atherosclerosis and OSA are associated with endothelial dysfunction, increased C-reactive protein, interleukin-6, fibrinogen, and plasminogen activator inhibitor, and reduced fibrinolytic activity. Leukocyte adhesion and accumulation on endothelial cells are common in both OSA and atherosclerosis (41-43). Also, OSA has been associated with enhanced platelet activity and aggregation (12,43,44).

During an obstructive apnea, large negative intrathoracic pressures are generated during inspiratory efforts, which increase transmural pressures across the myocardium, thus increasing afterload. An increase in preload and pulmonary congestion may also occur due to increased venous return. The presence of hypoxemia decreases oxygen delivery to the myocardium, which may promote angina and arrhythmias. Also, frequent arousals from sleep lead to increase daytime and nocturnal sympathetic activity. Autonomic abnormalities seen in patients with OSA include increased resting heart rate, decreased R-R interval variability, and increased blood pressure (BP) variability (23). Other responsible mechanisms include impaired vagal activity, increased platelet aggregability, insulin resistance, and endothelial dysfunction with reduced endogenous nitric oxide production (6,12,15,16).

**Table 1. Cardiovascular events in sleep apnea.**

| |
|---|
| Coronary heart disease |
| Acute coronary syndrome |
| Angina |
| Hypertension |
| Systemic hypertension |
| Pulmonary hypertension |
| Ventricular hypertrophy and dysfunction |
| Left /right ventricular hypertrophy |
| Left/right ventricular diastolic dysfunction |
| Left/right ventricular global dysfunction |
| Left ventricular systolic dysfunction |
| Congestive heart failure |
| Cardiac arrhythmias |
| Bradycardia |
| Sinus bradycardia |
| Atrioventricular block |
| Tachyarrhythmias |
| Supraventricular tachycardia |
| Ventricular tachycardia |
| Atrial fibrillation |
| Stroke |

De Olazabel et al. were first to report breathing disorders and hypoxia during sleep in patients with CAD (45). Schafer et al. reported OSA in approximately 30% of 223 male patients with angiographically verified CAD compared with in almost 20% of 66 controls without CAD (46). Also, in multivariate analysis, OSA (AHI ≥ 20) was

**Table 2. Proposed potential mechanisms of cardiovascular diseases in sleep apnea.**

| |
|---|
| Endothelial damage and dysfunction |
| Increased endothelin-1 activity |
| Reduced endogenous nitric oxide (NO) production |
| Blunted vasodilation to cholinergic stimulation |
| Increased intercellular adhesion molecule-1 (ICAM-1) |
| Increased vascular cell adhesion molecule-1 (VCAM-1) |
| Increased E-selectin |
| Increased adhesion of leukocytes to vascular endothelium |
| Increased vascular endothelial growth factor (VEGF) |
| Increased platelet derived growth factor (PDGF) |
| Tissue growth factor (TGF) |
| Insulin-like growth factor (ILGF) |
| Increases in inflammatory mediators |
| C-reactive protein (CRP) |
| Interleukin 1 and 6 (IL-1 and 6) |
| Tumour necrosis factor- alfa (TNF-α) |
| Monocyte adhesion molecules (CD15 ve CD11c) |
| Platelet-endothelial cell adhesion molecule (PECAM) |
| Oxidative stress by oxygen free radicals |
| Increases in prothrombotic factors |
| Fibrinogen |
| Platelet activation and aggregation |
| Plasminogen activator inhibitor-1 (PAI-1) |
| Platelet factor-4 (PF-4) |
| Endothelin |
| Tromboxan A2 (TX-A2) |
| Increased sympathetic activity (Exaggerated negative intrathoracic pressure with airway obstruction) |
| Initial inhibition then progressive increase in 24-h sympathetic nervous system activity |
| Increased resting heart rates (HR) |
| Decreased R-R interval variability |
| Increased blood pressure (BP) variability |
| During apnea - BP decreases with varying effect on HR |
| Following apnea - BP and HR increase significantly |
| Increased transmural pressures across the myocardium |
| Increased left ventricular afterload |
| Increased venous return to the right ventricle |
| Decreased left ventricular preload |
| Decreased stroke volume during apnea |
| Increased stroke volume with relief of obstruction |
| Hypoxemia |
| Sympathetic stimulation |
| Ischaemia - reperfusion injury of endothelial cells |
| Decreased oxygen delivery to the myocardium |
| Impaired vagal activity |
| Insulin resistance |

significantly associated with MI with an OR of 2.0. In a recent study, Peker et al. showed that a sleep clinic population had a 4.9 times greater chance of developing CVD during a seven-year follow-up period, independent of age, BMI, systolic and diastolic BPs, and smoking (47). In contrast, the Sleep Heart Health Study showed only a modest association between OSA and CAD in its recent cross-sectional analysis (48). Those in the highest quartile of AHI (AHI > 11) had only a 1.27-fold (95% CI 0.99-1.62) increased risk of self-reported CAD compared with those in the lowest quartile of AHI. It was suggested that patients with acute MI, especially if they had apneas and hypoxemia without evident heart failure might be evaluated for sleep disorders, since OSA patients commonly had coronary risk factors such as hypertension and obesity (11). In conclusion, patients with CAD should be evaluated for OSA and vice versa.

**OSA and Cardiac Arrhythmias**

Several studies have investigated the prevalence of nocturnal arrhythmias in patients with OSA (13,15,16). The prevalence of arrhythmias in two prospective studies was similar to that observed in healthy adults (15,16). However, analysis of electrocardiographic recordings in 458 patients having sleep studies showed a 58% prevalence of arrhythmias in patients with OSA, compared with 42% in nonapneics, most arrhythmias occurring in those with AHI ≥ 40/h (16). The study with the most valid measurement and classification of arrhythmias found no difference between the groups.

Both tachyarrhythmias and bradyarrhythmias have been implicated as possible causes of cardiovascular morbidity in OSA patients. The risk of arrhythmia with OSA appears to be related to sleep apnea severity. There are several mechanisms which might lead to either brady or tachyarrhythmias in OSA (Table 2). In the initial phase of the apnea there is a predominance of vagal tone, towards the end of the event and following relief of the obstruction there is then a surge in sympathetic nervous system discharge. These neurohumoral factors as well as the mechanical stress on the myocardium from the intrathoracic pressure changes might potentially be arrhythmogenic. Altered autonomic cardiac control is known to predispose individuals to ventricular arrhythmias under several experimental and clinical conditions; increased sympathetic and/or reduced vagal tone may facilitate arrhythmogenesis by a reentrant mechanism, triggered activity and increased automaticity (17,18).

Bradycardia is common during apneas. Indeed, sinus pauses of up to 2 s duration are commonly seen in severe OSA, and are a normal physiological response to apnea without airflow. Severe bradycardia and atrioventricular block are seen frequently in OSA. Transient heart block has been reported in up to 10% of patients with OSA (49). Sinus pause of up to 13 s have been observed. Those most at risk have pre-existing conduction disturbances or are taking negative chronotropic medications. Sustained tachyarrhythmias, such as atrial fibrillation (AF), might also develop as a result of OSA. AF is more likely to occur after coronary artery bypass surgery in patients with OSA than in those without OSA (38). The recurrence of AF at 12 months following successful cardioversion was halved for those with treated compared to untreated OSA. In those without OSA treatment, the risk of AF recurrence was related to the degree of nocturnal desaturation. A more recent study of 151 patients with AF and 312 patients without AF, the odds ratio for the association between OSA and AF was highly significant at 2.2 (50). In a study of 81 males with stable heart failure, incidences of AF and ventricular tachycardia were significantly higher in sleep apnea subjects (AHI ≥ 10/h) than in those without apnea (51). Also, a high frequency of ventricular ectopic beats has been observed in patients with OSA and HF (52).

It was shown that QT interval dispersion (QTd) is increased in patients with moderate-severe OSA when compared with controls. A significant positive correlation was also found between repolarisation inhomogeneity (QTd) and severity of OSA (14). Therefore, it might be suggested that increased QTd in OSA patients is related to the severity of OSA and, thus, to hypoxaemia. So, incre-

ased AHI and desaturation index (DI) in patients with OSA may result in inhomogeneity of repolarisation, favouring a propensity towards ventricular tachyarrhythmias. However, it was shown that CPAP therapy improves the inhomogeneity of repolarization via a significant decrease in QTcd in OSA patients without hypertension (53).

Bradyarrhythmias are probably associated with severity of OSA and are usually reversible with CPAP usage. CPAP therapy has been shown to abolish the majority of bradyarrhythmias and premature ventricular contractions and couplets in OSA patients with normal left ventricular function (52). In a study, atrial pacing reduced the severity of OSA based on AHI (54). However, the mechanism by which this might have been achieved is unclear; reflex effects on upper airway tone represent one possible explanation.

**OSA and Systemic Hypertension (SH)**

A strong relationship between SH and OSA has been pointed out in some epidemiologic studies before that OSA is indeed an independent risk factor for hypertension, although the effect is small to moderate (20-24,55). The Sleep Heart Health Study examined 6424 patients who were already enrolled in cardiovascular risk trials and would undergo polysomnography at home (56). A linear relationship between the severity of sleep-disordered breathing and prevalence of hypertension was found (20). The odds ratio for the most severe group compared with the normal group was 1.37; thus, the overall effect was small to moderate. Also, an independent association with all CVD was also observed in that study (48). The Wisconsin Sleep Cohort Study analyzed the development of hypertension as function of the severity of OSA (22). Of the original group, 709 subjects were followed up for four years, and 184 subjects were followed up for eight years. The unadjusted odds ratio for developing hypertension was 4.5 in the subjects with an AHI greater than 15 compared with the subjects without OSA. When adjusted for age, sex, body habitus, smoking and alcohol intake, the odds ratio for the development of hypertension was 2.9, providing strong evidence that OSA is an independent risk factor for hypertension. Nowadays, OSA is accepted as one of the identifiable causes of hypertension (26).

The prevalence of OSA has been found higher (20-30%) in hypertensive population than normotensive subjects in several studies (57-59). This prevalence is also higher in the non-dipper than the dipper hypertensive group (24). Moreover, risk of developing SH increases according to the severity of OSA (22,60,61). In addition, it was suggested that BP will be decreased with the optimal treatment of OSA (62). Recent placebo-controlled trials have revealed reductions of up to 10 mmHg in systolic and diastolic BPs with CPAP therapy (63-65). However, in a study, it was shown that CPAP therapy in OSA patients with hypertension did not decrease BPs and heart rates acutely, but reduced the variability of these parameters during sleep (33).

The causal correlation between SH and OSA was investigated firstly by Hedner et al (66). They showed that nocturnal hypoxemia increase sympathetic stimulation and this might cause SH. On the other hand, Arabi et al. had proved that SH development in hypoxic situation in normotensive cases, and furthermore they showed a decrease in the adrenergic mediators in patients having CPAP therapy for OSA (67). Also, strong relations were established between severity of SH and AHI, DI, minimum nocturnal oxygen saturation in several studies (22,61,68,69).

**OSA and Left Heart**

Arterial hypertension, obesity, diabetes mellitus (DM) and CAD which are independent predictors of left ventricular dysfunction, often have coexistince with OSA. Early recognition and appropriate therapy of ventricular dysfunction is advisable to prevent further progression to HF and death (70,71).

It is well known that OSA contributes to the development of left ventricular hypertrophy (LVH). The proposed causes include associated changes in left ventricular afterload, intermittent hypoxemia, and recurrent arousals during sleep. LVH is a major independent risk factor for morbidity and mortality from CVD (72-74). It was shown that many subjects with LVH have normal BP, suggesting that factors other than hemodynamic overload may contribute to the hypertrophy (75). Patients with OSA often have coexis-

ting disorders which have been associated with increased left ventricular mass (LVM) and diastolic dysfunction such as obesity, hypertension, and DM (76-78). Hedner and colleagues reported that OSA causes LVH in a study that compared 61 men with OSA and 61 male control subjects (79). The OSA group were heavier and 50% had SH. They reported that LVM was approximately 15% higher among normotensive OSA patients than in normotensive control subjects, despite comparison of subjects with matching body mass index (BMI). More recently, Noda et al. reported echocardiographic evidence of LVH in 50% of patients with an AHI > 20/h compared with 21.4% in those with an AHI < 20/h. In contrast, Davies et al. did not find a significant difference in LVM, determined by echocardiography, between 19 patients with OSAS, 19 non-apneic snorers, and 38 control subjects matched for age, sex and BMI (80,81). It was shown that severe and moderate OSA patients had higher LVM and LVM index, and also had left ventricular global dysfunction with an increased myocardial performance index (MPI) (8). A significant positive correlation between MPI and severity of OSA was also shown in that study, and it was concluded that especially severe OSA patients having diastolic dysfunction might have an increased risk of HF, since diastolic dysfunction might be combined with systolic dysfunction. On the other hand, it was shown that in male patients with severe OSA, CPAP therapy significantly decreases left ventricular wall thickness and improves global function even with six months of usage (35).

The proposed causes of LVH in OSA include associated changes in left ventricular afterload, intermittent hypoxemia, and recurrent arousals during sleep (Table 2). Left ventricular afterload increases during sleep in patients with OSA because of the combined effects of increased negative intrathoracic pressure, associated with attempted breathing against an occluded upper airway, and increased systemic BP associated with elevated sympathetic nervous system activity, hypoxemia, and arousal from sleep (82,83). Forced inspiration against increased airway resistance during wakefulness (Mueller maneuver) raises aortic transmural pressure, thereby increasing aortic stiffness and left ventricular systolic load (84). Isovolumic relaxation time of the left ventricle has also been shown to increase in the presence of either hypertension-related or age-dependent increase in aortic stiffness (85).

Sleep apnea could worsen or contribute to left ventricular dysfunction. Hypertension is an important risk factor for cardiac failure and, as has been seen, OSA is a cause of hypertension. However, OSA itself might affect cardiac function more directly. The exaggerated negative intrathoracic pressure and hypoxia that occur in OSA have significant adverse haemodynamic effects (Table 2). It is possible that if these effects are repeated over months or years (as occurs in OSA), then susceptible individuals could develop sustained left ventricular dysfunction. Decreased cardiac output as a result of congestive HF can lead to ventilatory instability with periods of apnea followed by excessive hyperpnea - the classic central apnoeas of Cheyne-Stokes respiration. This instability in ventilatory drive (known as loop gain) can also lead to upper airway collapse in those susceptible to OSA (86).

Sleep apnea is also strongly associated with systolic HF in human studies. In the Sleep Heart Health Study the largest cardiovascular risk from OSA was seen for a history of HF (48). Those with an AHI > 11/h had a relative risk of 2.4 for reporting a history of congestive HF compared to those with an AHI < 1.4. In many studies beneficial effect of CPAP on cardiac functions have been shown (31-35,87,88). These may include several factors, such as improved myocardial oxygen delivery, decreased sympathetic activity, left ventricular transmural pressure, and afterload. In a study, Cloward et al. showed a regression of LVH by six months of CPAP therapy, but not in the left and right atrial enlargement (89). A recent randomized controlled trial has shown improvements in left ventricular ejection fraction (LVEF) from 25% to 34% plus falls in BP and left ventricular chamber size following treatment of OSA with CPAP in those with systolic HF (90). A more recent Australian study has shown similar results with an improve-

ment in LVEF from 38% to 43%, plus a fall in catecholamine renal excretion and improved quality of life in the CPAP treatment group (91). It has been shown that OSA might be improved by measures to increase cardiac output, such as atrial overdrive pacing in patients with paroxysmal bradyarrhythmias or tachyarrhythmias (53).

OSA is also associated with diastolic HF, but the link is not so clear-cut. Negative intrathoracic pressure causes increased right ventricular filling with a subsequent shift of the intraventricular septum into the left ventricular cavity. This reduces left ventricular diastolic compliance. Hypoxemia leads to delays in ventricular relaxation and tachycardia both of which also impair diastolic function. Chronically, OSA is associated with hypertension and increased left ventricular wall thickness, which might lead to left ventricular diastolic dysfunction (89).

**OSA and Right Heart**

The relation of OSA to right heart structure and function is controversial. The prevalence of right ventricular hypertrophy (RVH) by echocardiography in sleep apnea was ranged from 0 to 71% (92). It has been argued that concomitant chronic pulmonary disorders are required for sleep apnea to cause right HF (93-97). However, Sanner and colleagues demonstrated that sleep apnea was independently associated with depressed right ventricular ejection fraction by radionuclide ventriculography after adjusting for lung function, age, BMI, sex, blood gas analysis, pulmonary artery pressure, and LVEF (98). Hanly and colleagues found no difference in right or left ventricular dimensions between nonapneic snorers and subjects with OSA (99). It was shown that patients with moderate-severe OSA had right ventricular global dysfunction; and CPAP therapy significantly decreased right ventricular free wall thickness and improved global dysfunction with a significantly decreased MPI even if six months of CPAP usage (9,34). Right atrial and ventricular diameters of the OSA patients without hypertension were in normal limits at baseline, and none of them significantly have changed by CPAP usage in that study.

The reasons for the disparate conclusions of the prior studies examining RVH, systolic function, and right ventricular enlargement are not certain. In a study, right atrial and ventricular dimensions, and right ventricular systolic function were not found to be significantly different between subjects with sleep-disordered breathing and the low respiratory disturbance index subjects, but this study indicated that sleep-disordered breathing was associated with increased right ventricular wall thickness in a general population (100).

**OSA and Metabolic Syndrome (MBS)**

MBS, which is closely linked to insulin resistance, is recognized as raising the risk of CVD. The new National Cholesterol Education Program (NCEP) guidelines (Adult Treatment Panel: ATP III) recognized MBS as a secondary target of risk-reduction therapy and selected to define MBS when three or more of the following certain five risk determinants are present: abdominal obesity (waist circumference > 102 cm in men, > 88 cm in women), hypertriglyceridemia (≥ 150 mg/dL), a decresase in high density lipoprotein cholesterol (HDL-C < 40 mg/dL in men, < 50 mg/dL in women), hypertension (systolic BP ≥ 130 or diastolic BP ≥ 85 mmHg or taking antihypertensive medication), and DM or fasting blood glucose ≥ 110 mg/dL (101).

The prevalence and the excess CHD risk of the MBS and its components were investigated in the Turkish Adult Risk Factor Study by Onat A et al. (102). Prospective analysis was based on 2398 men and women (mean age at baseline 49.1 ± 13 years) and 27% of men and 38.6% of women were found to have MBS at baseline examination. It was estimated that MBS was the culprit in just over half the cases of CHD in Turkey. The MBS has not escaped from the interest of the sleep medicine community OSA. Early reports by Davies et al. and Stoohs et al. documented an increased prevalence of insulin resistance in small groups of subjects with OSA, but differences in BMI accounted for the entire relationship (103,104). Similarly, Levinson and colleagues published a small study in 1994 that failed to detect a relationship between central obesity using waist-to-hip ratio (WHR) and severity of OSA, although patients did tend to have higher WHR when compared to normative values (105).

Although each of the components of the MBS individually has been identified as risk factors for CVD, an individual with three or more components is at particularly high risk. For instance, Wilson et al. have reported a prospective analysis of the Framingham Offspring Study looking for cardiovascular events in 2.406 men and 2.569 women between the ages of 18 to 74 years (106). Clusters of three or more risk factors occurred in 17% of the subjects. Fully 20% of the cardiovascular events in men and 48% of the events in women could be attributed solely to the clustering of three or more factors.

The relationship between hypertension and heart disease is well established and the JNC has emphasized the importance of maintaining low BP for prevention of heart disease and stroke (26). The prevalence of OSA is increased fourfold in patients with obesity (107). It's well known that obesity plays a major part in the development of the MBS, the prevalence of MBS in nonobese individuals is 10%, while in obese subjects it is more than 50% (108). It has been recognized that the type of regional fat distribution (abdominal-visceral vs. gluteal-femoral) plays an important role in the development of the MBS (109,110). Not only increased body weight but fat distribution plays a major role in the development of OSA. Visceral (central) obesity has been recognized to be associated more often with OSA than other forms of obesity (111). The best surrogate of visceral adiposity across a wide age range is waist circumference, in a population in which MBS prevails.

Strohl et al. were able to demonstrate an association between hyperinsulinemia (as well as BP) and AHI independent of BMI in 386 men referred for polysomnography, and more recently, two relatively large prospective studies demonstrated a relationship between OSA severity and insulin resistance that was independent of BMI (112). In a study, Ip and colleagues studied 270 consecutive nondiabetic patients (73% men) who had been referred for evaluation of suspected OSA and found such a quantitative relationship for both AHI and minimum oxyhemoglobin saturation with insulin resistance (113). Central obesity also was correlated with OSA severity. Not unexpectedly, given the previous discussion, hypertension was significantly related to insulin resistance in their subjects. Punjabi and associates recruited 150 men with no history of diabetes, cardiac disease, or pulmonary disease and subjected them to polysomnography, oral glucose tolerance testing, and measurement of fasting insulin and lipid levels (114). They found a surprisingly high prevalence of OSA, ranging from 40 to 60% depending on the value of AHI score used to define a case. Impaired glucose tolerance and insulin resistance were associated with OSA severity, as represented by both AHI and the degree of oxyhemoglobin desaturation.

MS and also OSA may increase cardiovascular morbidity and mortality. Peker et al. showed that the risk of developing CVD was increased in middle-aged OSA subjects independently of age, smoking, BMI and BPs (47). Doherty et al. performed a long-term (7.5 years) follow-up study of 168 patients with OSA, and compared the cardiovascular outcomes of those patients who were intolerant of CPAP (untreated group, 61 patients) with those continuing CPAP therapy (107 patients) (115). Deaths from CVD were more common in the untreated group than in the CPAP-treated group during follow-up (14.8% vs. 1.9%, respectively; $p < 0.009$), but no significant differences were found in the development of new cases of hypertension, cardiac disorder, or stroke. Total cardiovascular events (ie, death and new cardiovascular disease combined) were more common in the untreated group than in the CPAP-treated group (31% vs. 18%, respectively; $p < 0.05$). They concluded that their results support a protective effect of CPAP therapy against death from CVD in patients with OSA.

**OSA and Pulmonary Hypertension (PH)**

Acute pulmonary hemodynamic changes during obstructive apneas have been well defined that pulmonary artery pressure rises immediately in response to hypoxemia in patients with OSA. However, there is no general consensus that OSA alone may cause daytime PH, since most early studies did not adequately control for the presence of underlying cardiac or pulmonary disease. Diurnal PH in patients with OSA has be-

en found to correlate more with a lower daytime $PaO_2$ and higher $PaCO_2$ than with severity of OSA (25). However, several recent studies showed a prevalence of diurnal PH of 20% to 41% in patients with OSA in whom underlying lung disease had been excluded (116,117). No correlation was found in these studies between the severity of PH and AHI. Nocturnal desaturation was linked with daytime PH. On the other hand, a reduction in pulmonary artery pressure was shown in patients treated with CPAP (118). As a result, daytime PH occurs frequently in patients with OSA, improves with CPAP, and is more closely associated with BMI and daytime $PaO_2$ than with severity of OSA.

**OSA and Stroke**

Sleep apnea is very common in stroke patients, with a reported prevalence of up to 60% (20). Obstructive sleep apnea was shown to occur more frequently in patients admitted to the hospital with stroke than in controls (119-121). The prevalence of OSA is the same for both completed stroke and transient ischaemic attack (121). Given that there is no lasting neurological damage with a transient ischaemic attack, this suggests OSA is likely to have preceded the stroke. Stroke patients have OSA, suggesting it may increase the stroke risk beyond direct effects on blood pressure level and variability. The factors that might be involved in the pathogenesis of CAD in patients with OSA might also lead to cerebrovascular disease. Hypertension is known to be a prominent risk factor for stroke and might also be a pathway through which OSA can lead to cerebrovascular disease.

There are increasing clinical data supporting an independent association between OSA and stroke. In the Sleep Heart Health Study, OSA was associated with a small but significant increase (1.58 fold) in the prevalence of stroke (48). Other studies have shown a higher than expected incidence of OSA in patients with stroke Palomaki et al. observed an odds ratio of 8.0 for stroke in individuals with a history of OSA after adjustment for hypertension, obesity, alcohol consumption, and coronary heart disease (119,122-124). Spriggs et al. reported that a history of snoring was associated with a relative risk of 3.2 for stroke (124). On the other hand, OSA is associated with a less favorable clinical outcome one year after stroke compared with stroke without OSA (125).

In the largest series, 31% of strokes were present on awakening from sleep (126). The early morning hours are associated with rapid eye movement sleep, during which time apneas are most likely to be the longest and associated with the most significant oxyhemoglobin desaturation. Sleep apnea is associated with the occurrence of stroke and may be associated with a less favorable outcome and evidence to suggest abnormal cerebral blood flow and hemodynamics. Cerebral blood flow has been shown to fluctuate in response to apneas. A significant increase in intracranial pressure and a decrease in cerebral perfusion during obstructive apneas have been shown in several studies (127-129). The ischaemic brain is highly susceptible to further injury from hypoxia, such as can occur in OSA. This could lead to more extensive cerebral damage or it could impair neurological recovery. In a study using transcranial Doppler ultrasonography, middle cerebral artery blood flow was reduced 15% to 20% during obstructive apneas (130). Furthermore, after apnea termination, cerebral blood flow increased 15%, followed by a 23% reduction compared with baseline, and cerebral autoregulation of blood flow was abnormal in patients with OSA (131). Also, it was shown that there is diminished cerebral vasodilator response to hypercapnia that reverses with CPAP treatment (132).

## CONCLUSION

Several epidemiologic studies have demonstrated that sleep related breathing disorders are an independent risk factor for hypertension, probably resulting from a combination of intermittent hypoxia and hypercapnia, arousals, increased sympathetic activity, and altered baroreflex control during sleep. Additionally, arterial hypertension, obesity, DM and CAD which often have coexistince with OSA are independent predictors of left ventricular dysfunction. Early recognition and appropriate therapy of ventricular dysfunction is advisable to prevent further progression to HF and death. Especially severe OSA

patients having diastolic dysfunction might have an increased risk of HF, since diastolic dysfunction might be combined with systolic dysfunction. On the other hand, patients with acute MI, especially if they had apneas and hypoxemia without evident HF might be evaluated for sleep disorders. So, patients with CAD should be evaluated for OSA and vice versa.

Sleep apnea is a common disorder that, if not recognized and treated, leads to significant morbidity and increased mortality. Early recognition and treatment of OSA may improve cardiovascular functions. Nowadays, CPAP usage is still the gold standart method for treatment of the disease and prevention of complications.

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