

# Cardiovascular consequences of sleep apnea: II-Cardiovascular mechanisms

*Uyku apnesinin kardiyovasküler sonuçları: II-Kardiyovasküler mekanizmalar*

Yelda Turgut Çelen<sup>1</sup>, Yüksel Peker<sup>1,2</sup>

<sup>1</sup>Sleep Medicine Unit, Department of Neurology and Rehabilitation Medicine, Skaraborg Hospital, Skövde,

<sup>2</sup>University of Gothenburg, Gothenburg, Sweden

## ABSTRACT

Obstructive sleep apnea (OSA) is a common disorder with serious cardiovascular consequences. The pathogenesis in this context is likely to be multifactorial process including large negative swings in intrathoracic pressure, intermittent hypoxemia and hypercapnia, increased sympathetic nervous system activity, vascular endothelial dysfunction, oxidative stress, systemic inflammation, excessive platelet activation as well as metabolic dysregulation. Although there is scientific support for a considerable impact of OSA on vascular structure and function, it is likely that development of cardiovascular diseases is determined by multiple genotypic and phenotypic factors. The current article focuses on the available research evidence addressing the cardiovascular mechanisms in this context. (*Anadolu Kardiyol Derg 2010; 10: 168-75*)

**Key words:** Obstructive sleep apnea, cardiovascular diseases

## ÖZET

Obstrüktif uyku apnesi (OSA), sık karşılaşılan ve ciddi kardiyovasküler sonuçları olan bir hastalıktır. Kardiyovasküler hastalıkların gelişimi, negatif intratorasik basınçta büyük dalgalanmaları, intermitan hipoksi ve hiperkapniyi, sempatik sinir sistemi aktivitesinde artışı, vasküler endotelial disfonksiyonu, oksidatif stresi, sistemik inflamasyonu, aşırı trombosit aktivasyonunu ve metabolik disregülasyonu içeren multifaktöryel süreçtir. Obstrüktif uyku apnesinin tek başına vasküler yapı ve fonksiyonları üzerine olumsuz etkisi olduğunu destekleyen bilimsel veriler olmasına karşın, OSA hastalarında kardiyovasküler hastalık gelişimi çok sayıda fenotipik ve genotipik faktörlere bağlı olması muhtemeldir. Bu makalede OSA'da kardiyovasküler hastalık gelişim mekanizmalarını inceleyen araştırmaların verilerine odaklanılmıştır. (*Anadolu Kardiyol Derg 2010; 10: 168-75*)

**Anahtar kelimeler:** Obstrüktif uyku apnesi, kardiyovasküler hastalıklar

## Introduction

The clinical and population-based epidemiological studies regarding the relationship between obstructive sleep apnea (OSA) and cardiovascular diseases (CVD) has been recently reviewed (1). The pathogenesis in this context is likely to be multifactorial process including large negative swings in intrathoracic pressure, intermittent hypoxemia and hypercapnia, increased sympathetic nervous system activity, vascular endothelial dysfunction, oxidative stress, systemic inflammation,

excessive platelet activation as well as metabolic dysregulation (Fig. 1). In the current review, we aim to analyze available literature addressing these mechanisms involved in the cardiovascular consequences of sleep apnea.

## General cardiovascular mechanisms

### Acute hemodynamic changes during OSA

The hemodynamic changes associated with OSA have been intensively discussed in a variety of comprehensive reviews (2).

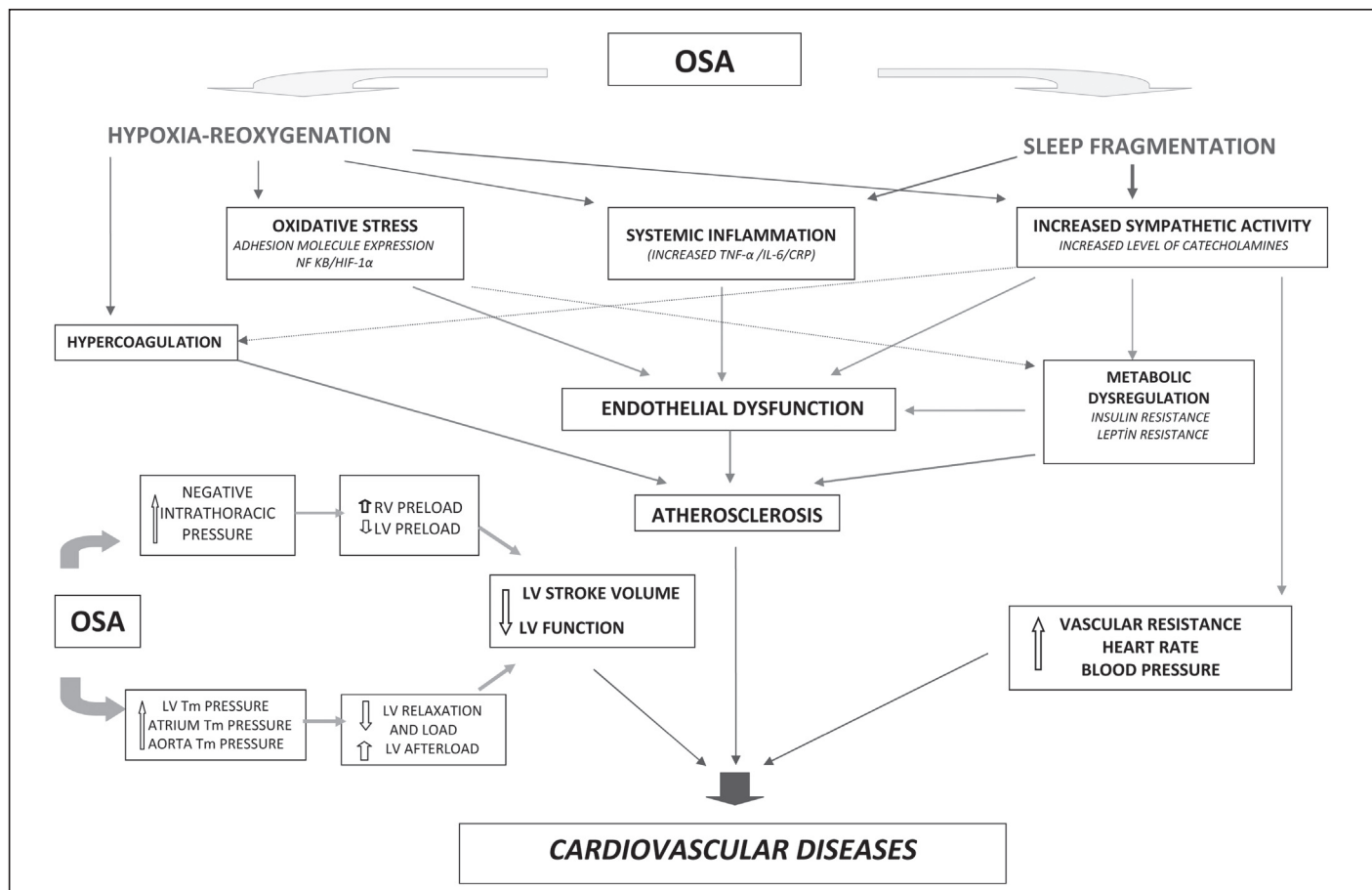
**Address for Correspondence/Yazışma Adresi:** Yüksel Peker, MD, University of Gothenburg & Sleep Medicine Unit Department of Neurology and Rehabilitation Medicine Skaraborg Hospital, SE-541 85 Skövde, Sweden Phone: +46 500 431000 Fax: +46 500 431897 E-mail: yuksel.peker@lungall.gu.se

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**Figure 1. The mechanisms involved in the cardiovascular consequences of obstructive sleep apnea**

LV - left ventricular, OSA - obstructive sleep apnea

Large swings in the systemic and pulmonary arterial pressures during obstructive apneic events were described. It has been revealed that there is an initial decrease in blood pressure (BP) and bradycardia during the early period of apnea. During the second phase of apnea, arterial oxygen saturation ( $\text{SaO}_2$ ) decreases, pleural pressure swings increase as well as heart rate (HR) and BP rise. During the third phase, after apnea termination and arousal,  $\text{SaO}_2$  starts to rise, pleural pressure swings are reduced compared to the second phase, HR further increases, and BP is sharply elevated to reach a peak within the first immediate postapneic breaths. The initial depressor effect has been related to an increased parasympathetic activity resulting in a decreased HR. Left ventricular (LV) stroke volume is reduced due to the negative intrathoracic pressure, i. e., increased LV afterload, as well as decreased pulmonary venous return, i.e., decreased LV preload, accounting for a decrease in cardiac output.

Hypoxia may influence BP control by a number of different mechanisms (2). The local vascular effect of relatively severe hypoxia tends to reduce arterial BP by vasodilatation. Vasoactive substances derived from the vascular endothelium including nitric oxide (NO), adenosine and eicosanoids may be implicated as early mechanisms in this response. On the other hand, acute

hypoxemia has been found to cause reflex vasoconstriction, increase in HR as well as the activity of the autonomic sympathetic system. The postapneic BP elevation correlates with the severity of hypoxia during apnea. Both spillover and clearance of noradrenaline are increased in healthy volunteers exposed to acute hypoxia. Muscle sympathetic nerve traffic, which reflects peripheral sympathetic activity, is inhibited during the first phase of the obstructive apnea, gradually increases during the second phase followed by a strong inhibition during the last phase. The change in sympathetic nerve traffic is associated with directionally similar changes in vascular resistance and may therefore have implications for the increase in BP observed during the second phase of obstructive apneas. In healthy subjects, Somers and coworkers (3) have demonstrated an approximately 12-fold potentiation of the sympathetic nerve traffic response to hypoxia following voluntary apnea. In addition to hypoxia, hypercapnia has also been reported to contribute to the chemostimulation of the sympathetic system (4).

Arousal from sleep, which occurs during the third phase of an obstructive apneic event, may further elevate total peripheral resistance by increasing sympathetic nerve activity (2). Arousal from normal sleep raises BP to a level similar to that seen during

sleep apnea-induced arousal. Non-respiratory sleep disorders, which cause arousal, such as periodic leg movements, also cause BP rises similar to those in OSA.

Sleep stages, i.e., NREM and REM sleep, also affect changes in BP and thereby also the hemodynamic response to OSA. A higher baseline BP and a more pronounced hemodynamic response to an obstructive apneic event were observed during REM sleep compared with NREM sleep. It is suggested that the higher sympathetic activity may provide a resting condition characterized by increased peripheral vascular resistance during REM sleep.

### **Impact of the cardiovascular mechanisms at intermediate- and long-term**

#### **Negative intrathoracic pressure**

Recurrent forced inspiration against the occluded airway during apnea episodes result in excessive negative intrathoracic pressure. This pressure leads to an increased venous return to the right ventricle (RV) and overload of the RV (5). The excess load forces the interventricular septum to shift to the left that causes reduced left ventricular (LV) filling (5). The transmural pressure of the atrium, LV and aorta is increased due to elevated intrathoracic pressure. Thus, all of these mechanical effects and the contribution of surges in BP end up with diastolic dysfunction (6), reduced stroke volume and cardiac output (CO) in accordance with increased LV preload and afterload (7). The structural and functional consequences of OSA on the heart are found to be accelerated with increasing severity of apnea-hypopnea index (AHI).

#### **Sympathetic overstimulation**

Obstructive apnea is often terminated by an arousal, which is accompanied with an increase in the sympathetic activity (8). Besides, repetitive hypoxia and large swings in intrathoracic pressure due to airway collapse in OSA patients may cause an overactive sympathetic system (9). Strikingly, OSA patients continue to have repetitive bursts of sympathetic activity and increased sympathetic activity even during the day (9), as demonstrated by microneurography and elevated catecholamine levels both in plasma and urine. Indeed, increased and variable HR and BP were demonstrated in OSA patients compared to normal subjects during wakefulness (10). As the altered cardiovascular variability due to the dysfunction of autonomic cardiovascular regulation predicts morbidity and mortality in patients with hypertension (HT), diabetes, heart failure (HF) and coronary artery disease (CAD), this may be the case even for OSA patients with OSA that experience CVD. In this context, obesity has been considered as a main confounding factor. However, it has also been showed that obesity alone, in the absence of OSA, is not accompanied by increased sympathetic activity (11).

#### **Oxidative stress**

Obstructive sleep apnea is characterized by apnea-related multiple cycles of hypoxia/reoxygenation which is accepted to promote the formation of reactive oxygen species (ROS) and induce oxidative stress (12). The imbalance between oxidant-producing systems and antioxidant defense mechanisms determine oxidative/nitrosative stress, which results in excessive formation of ROS or reactive nitrogen species (RNS). Ordinarily, maintenance of homeostasis is provided by this tightly regulated balance (redox balance) system. The superoxide anion radical is the predominant ROS molecule. In particular, importance in the vasculature is the reaction of superoxide with the powerful vasodilator NO, which promotes the formation of peroxynitrite while diminishing the bioactivity and bioavailability of NO. This activity is a major contributor of oxidative/nitrosative stress in the vasculature, hence, greatly affecting endothelial function, vascular inflammation and atherosclerosis.

#### **Inflammation**

Inflammation occurs in the vasculature as a response to injury, lipid peroxidation and oxidative stress and plays a significant role in the pathogenesis of atherosclerosis (13). Observational studies demonstrated an association between inflammation and various vascular disorders (13, 14). The recognized cardiovascular biomarkers in these context include intercellular adhesion molecule-1 (ICAM-1) and selectins (cell adhesion molecules), tumor necrosis factor alpha (TNF- $\alpha$ ) and interleukin 6 (IL-6, cytokines), interleukin 8 (IL-8, chemokines) and C-reactive protein (CRP) (14). A large number of studies reported elevated levels of cytokines including IL-6 and TNF- $\alpha$ , matrix metalloproteinases, acute phase proteins, as well as endothelial adhesion molecules such as ICAM-1 and vascular cell adhesion molecules (VCAM) in patients with OSA (15-17). Among these inflammatory markers, TNF- $\alpha$  and CRP seem to have particular importance as prospective studies showed that both are significant predictors of coronary events in healthy males and females (18, 19). Elevated CRP levels were found to be associated with a two-fold increase in the risk of cardiovascular events in OSA patients (20). However, it should be noted that determinants of these markers are, beside OSA, also influenced by multiple circumstances including comorbid risk factors for CVD, lifestyle, environmental factors and genetics.

#### **Endothelial dysfunction**

Vascular endothelium is the major regulator of vascular homeostasis, which sustains the balance between vasodilatation and vasoconstriction. Vascular tone, cellular growth, coagulation and the modulation of the activity of various blood components such as platelets and monocytes by secreting a variety of vasoactive substances are maintained by the endothelium. If vasoconstriction predominates and this homeostasis gets

impaired for a while, endothelial dysfunction can occur and cause damage to the arterial wall. Cardiovascular risk factors initiate this process and precede endothelial dysfunction and atherosclerosis, consequently (21). Endothelial dysfunction is often seen in patients with HT, hyperlipidemia, diabetes and smoking, all of which are independent cardiovascular risk factors. However, there is also evidence suggesting impaired endothelial function in OSA both in middle aged (22, 23) and older adults (24) independent of HT (23). Impairment of endothelium-dependent vasodilatation was suggested as the main determinant of endothelial dysfunction in OSA patients (25). As mentioned in the previous section, endothelial dysfunction in OSA is believed to be initiated mainly by hypoxia, inflammation or oxidative stress. Vascular function found to be more deteriorated in desaturating OSA patients compared to non-desaturators, supporting the hypothesis that endothelial dysfunction develops as a response to oxidative stress. Moreover, the AHI and desaturation frequency were demonstrated to be inversely correlated to peak vasodilatation with both acetylcholine and sodium nitroprusside in OSA patients (26). However, reduction in production and activity of major vasodilator substance released by the endothelium, namely NO, together with impaired endothelial mediated vasodilatation is also accepted to be associated with endothelial dysfunction in OSA (26). On the other hand, an endogenous NO antagonist, asymmetric dimethylarginine (ADMA) is found to be higher in OSA patients (27). Moreover, vasoconstrictor substances, such as endothelin and angiotensin II, were also found to be elevated in OSA patients (28), suggesting that mechanisms regulating not only vasodilatation but also vasoconstriction play an important role in the development of endothelial dysfunction.

### **Hypercoagulation**

Coagulopathy and abnormal platelet activity play important roles in the pathogenesis of atherothrombotic disease by predisposing to clot formation. The contribution of prothrombotic state to the elevated cardiovascular risk in patients with OSA was suggested. The impact of OSA on the development of hemostasis and thrombosis is debated; as it may be due to endothelial dysfunction, raised nocturnal catecholamine levels or be simply a response to apneic episodes (29). Nevertheless, increases in whole blood and plasma viscosity were shown in OSA (30). Furthermore, studies indicated the elevated levels of hemotocrit (31), plasma fibrinogen and activated coagulation factors (32). Increased platelet activation as well as shorter aggregation half-time was also demonstrated in OSA patients (33). Finally, studies have reported an increased D-dimer level and positive correlation with the severity of nocturnal hypoxemia in OSA (34).

### **Metabolic dysregulation**

Metabolic syndrome comprises central obesity, insulin resistance, glucose intolerance, dyslipidemia and HT which are the

manifestations of altered total body energy regulation and a cluster of risk factors that promote atherosclerotic CVD. As discussed above, OSA-related factors such as increased sympathetic activity, sleep fragmentation and intermittent hypoxia are demonstrated to contribute to the development of metabolic dysregulation in terms of insulin resistance (IR) and leptin resistance (LR) (35).

### **Glucose intolerance**

The mechanisms of impaired glucose tolerance in OSA syndrome particularly involve IR. While the effect of obesity in this relationship has been widely discussed, high insulin levels or IR in non-obese OSA patients was also reported and shown to be worsened with increasing AHI and orthostatic dysregulation (OD) levels (36). In another study, compared with obese and non-obese groups, OSA patients were found to have the highest IR and visceral fat (37). Thus, obesity appears to be a part of the link rather than the sole mechanism. In OSA, sleep fragmentation and intermittent hypoxia appear to induce elevated sympathetic nervous system activity, altered hypothalamic pituitary adrenocortical axis function as well as increased oxidative stress and activation of inflammatory pathways. Such mechanisms alone or in concert could clearly be implied in a reduced pancreatic  $\beta$ -cell function and development of insulin resistance (38). Both human (39) and animal studies (40) demonstrated the correlation and causative effect of intermittent hypoxia on glucose intolerance.

### **Leptin pathway and dyslipidemia**

Leptin is an adipocyte-derived hormone that regulates body weight and fat distribution through the control of appetite and energy expenditure. Hence, obesity is significantly associated with increased leptin levels and a state of LR. Moreover, leptin may predispose to platelet aggregation and has been regarded as an independent cardiovascular risk factor particularly for CAD (41). Increased leptin levels in association with sympathetic overdrive were demonstrated in OSA patients (35).

### **Atherosclerosis**

Atherosclerosis is recognized as the precursor stage of CVD. Hyperlipidemia, HT, smoking and diabetes are the well-established risk factors for these arterial lesions. Immuno-inflammatory cells induced by oxidative stress dominate early atherosclerotic processes, with the secretion of several proinflammatory molecules that accelerate the progression of the arterial lesions and also elicit atherosclerotic plaque rupture, precipitating clinical events such as acute myocardial infarction (MI) and stroke. Moreover, carotid intima-media thickness (IMT), the presence of atherosclerotic plaque, occurrence of carotid plaques, arterial stiffness (evaluated by carotid-to-femoral pulse wave velocity (PWV)), coronary calcifications are all closely associated with the severity of generalized atherosclerosis, therefore, recog-

nized as markers of preclinical atheroma and a potent predictor of MI or stroke (42). Increased carotid IMT, PWV and plaque occurrence was reported in OSA patients without any other significant comorbidity compared to matched controls (43). Moreover, both plaque occurrence or volume as well as and the thickness were directly related to the extent of OD (44). The study by Minoguchi et al. (43) showed a positive correlation between IMT and CRP, IL 6 and IL 8 levels on one hand and the degree of nocturnal hypoxia on the other and suggested that OSA-related hypoxia and systemic inflammation might be associated with the progression of atherosclerosis (43).

### Cardiovascular mechanisms of CAD in OSA

Apneic events and arousal episodes are frequently associated with low oxygen supply to coronary arteries due to lack of ventilation as well as with increased cardiac oxygen demand due to acute changes in HR and increase in afterload (45). Thus, increased oxygen demand and reduced oxygen supply (i.e., hypoxemia) during night may trigger an attack of myocardial ischemia and nocturnal angina. As discussed above, OSA-related phenomena, including hypoxemia, reoxygenation, BP surges due to sympathetic over-activation, acute imbalance of vasoactive hormones, endothelial dysfunction, procoagulant state and recurrent vascular wall may lead to atherosclerosis and consequently CAD at long-term. For instance, OSA related hypoxemia and markers of increased sympathetic tone and sleep fragmentation (arousal index) and daytime epinephrine levels were found to be related to both daytime and nocturnal ischemic ST-segment depression in the absence of CAD (46). It is generally believed that mechanical stress on atherosclerotic plaque are greatest early in the morning due to sudden increase in HR and BP, which occurs on awakening from sleep. However, the cycle variations in HR and BP are dramatic in OSA and far more than the hemodynamic stress in daily life, occurring during sleep, a time when HR and BP are lowest in normal subjects. Moreover, an independent association between AHI and the median coronary artery calcification score was found in OSA patients who were free of CAD symptoms (47). Indeed, a significant relationship was demonstrated between the coronary atherosclerotic plaque volume and AHI as well as sleep fragmentation in OSA patients with stable CAD (48).

### Cardiovascular mechanisms of cardiac arrhythmias in OSA

Supraventricular bradyarrhythmias and tachyarrhythmias were suggested to develop predominantly due to sympathetic activation whereas ventricular arrhythmias were linked to hypoxemia in OSA patients (49). During the episodes of apnea/

hypopneas the occurrence of hypoxemia, carbon dioxide retention, sympathetic activation, BP surges, transmural pressure changes and systemic inflammation may act as a part of the mechanism of the facilitative effects of OSA for incident atrial fibrillation (AF) (50). An earlier study by Shepard et al. (51) suggested that the lowest hypoxemia level which was necessary to trigger a ventricular ectopy was as low as 60%. Moreover, Alonso-Fernandez et al. (44) found a significant relationship between minimum arterial oxygen saturation and nocturnal sinus bradycardia and supraventricular tachycardia along with the ST-segment depression episodes in OSA patients.

### Cardiovascular mechanisms of HF in OSA

As another consequence of the mechanisms discussed above, OSA also promotes poorly controlled HT, coronary events and AF, which in turn can lead to acutely decompensated HF (52). Moreover, as myocardial oxygen demand increases at times of recurrent hypoxia, this metabolic mismatch could directly reduce myocardial contractility (45). Recurrent sudden depression of cardiac functions during obstructive apneas may lead to cardiac structural remodeling as well as cardiac muscle weakness, contractile dysfunction, myocardial ischemia, ventricular dilation and consequently, cause HF at long term (52). Presumably, the most likely mechanism by which OSA might promote LV systolic dysfunction is via systemic HT during both daytime and sleep. However, there are reports demonstrating LV dysfunction even in normotensive OSA patients (53), which highlights that other mechanisms are also involved in the development of HF in OSA. As extensively discussed above, the increased levels of cytokines, catecholamines, endothelin and other growth factors in OSA may also contribute to the development of LV hypertrophy independent of HT. On the other hand, the mechanisms leading to diastolic dysfunction in OSA are less clear. Nocturnal OD is reported to be an independent predictor of impaired ventricular relaxation during diastole (54). The rise in afterload and a reduction in fractional shortening that occur during intrathoracic pressure swings may lead to impaired relaxation. Of note, increased LV thickness and hypertrophy can also precipitate impaired relaxation in OSA patients. It is also known that right ventricular (RV) function is substantially influenced by RV afterload, which is mainly determined by pulmonary vascular resistance, and closely related to the breathing pattern and hypoxia. As hypoxia and pulmonary HT are associated with OSA, right heart failure is likely to establish. Accordingly, attenuated RV contractility as well as impaired RV ejection fraction and hypertrophy have all been demonstrated in OSA patients in the absence of concomitant chronic obstructive pulmonary disease and HT (55).



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