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Obstructive sleep apnea: the new cardiovascular disease. Part I: obstructive sleep apnea and the pathogenesis of vascular disease

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Abstract Obstructive sleep apnea (OSA) is increasingly recognized as a novel cardiovascular risk factor. OSA is implicated in the pathogenesis of hypertension, left ventricular dysfunction, coronary artery disease and stroke. OSA exerts its negative cardiovascular consequences through its unique pattern of intermittent hypoxia. Endothelial dysfunction, oxidative stress, and inflammation are all consequences of OSA directly linked to intermittent hypoxia and critical pathways in the pathogenesis of cardiovascular disease in patients with OSA. This review will discuss the known mechanisms of vascular dysfunction in patients with OSA and their implications for cardiovascular disease.

Keywords Obstructive sleep apnea · Heart failure · Endothelial dysfunction · Intermittent hypoxia · Oxidative stress

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Introduction

Obstructive sleep apnea (OSA) is a respiratory disorder of sleep characterized by recurrent episodes of complete or partial upper airway obstruction. OSA has an estimated prevalence of 9–24% in middle-aged individuals [1, 2] and is increasingly emerging as a cardiovascular risk factor [3–6]. Several etiological factors in OSA overlap with those of cardiovascular diseases creating difficulty in distinguishing the direct cardiovascular consequences of OSA from its role in exacerbating concomitant cardiovascular disease. Nevertheless, an independent role for OSA in cardiovascular morbidity and mortality is now well supported [4–6].

This review will discuss the pathophysiological responses to episodes of obstructive apnea and hypopnea. These responses include sympathetic activation, increased respiratory workload, and intermittent hypoxia in the immediate term. Endothelial dysfunction, oxidative stress, and inflammation are long-term consequences that mediate cardiovascular disease in patients with OSA. A subsequent review in this series will attempt to present the background and evidence for a causative relationship between OSA and cardiovascular disease with focus on hypertension and heart failure.

Presentation and definition of OSA

The term Sleep Disordered Breathing (SDB) encompasses all types of respiratory disturbance during sleep: obstructive, central, and mixed. Typically, patients have predominance of either central or obstructive events, so SDB is divided broadly into two main clinical syndromes, central and obstructive sleep disorders.

In normal conditions, a tenuous balance between constrictor and dilator forces maintains the patency of the upper airway during sleep [7, 8]. Obstructive events occur when this balance shifts toward the constricting forces [9]. One of the important collapsing factors leading to constriction of the upper airway is the extra-luminal pressure from the tissue surrounding the airway [10], a common condition in obesity.

The presence of compatible clinical symptoms, including excessive daytime sleepiness, and at least five obstructive respiratory events, apneas or hypopneas, per hour of sleep defines Obstructive Sleep Apnea Syndrome. Obstructive apneas result from complete collapse of the upper airway resulting in cessation of airflow against which the inspiratory effort persists. Obstructive hypopneas result from a partial collapse of the upper airway causing reduction in, but not cessation of airflow, and are associated with increased respiratory effort.

The most effective treatment for OSA is continuous positive airway pressure (CPAP), which acts as pneumatic splint keeping the airway open during sleep. Discussion of treatment modalities for OSA is elsewhere in this special issue.

The physiological response to episodes of obstructive apnea and hypopnea

A typical patient with OSA may experience anywhere from five to well over one hundred apnea or hypopnea events per hour. Each of these obstructive respiratory events results in an episode of hypoxia. Re-oxygenation occurs when the episode is terminated by an arousal that restores the airway patency (Fig. 1). The recurrence of these respiratory events and their respective recovery phases produces a characteristic pattern of nocturnal intermittent hypoxia that is unique to OSA. Generally, both apnea and hypopnea events produce the same pattern of intermittent hypoxia. Each episode of hypoxia stimulates the carotid chemoreceptors resulting in sympathetic nerve activation [11] and subsequent surge in blood pressure [12]. As a result, patients with OSA spend their sleep period in a state of intermittent hypoxia and a cycling pattern of recurrent surges of sympathetic activity and blood pressure.

Significant experimental evidence has emerged indicating that intermittent hypoxia is a unique physiological state with a profile of biological consequences that is distinct from other types of hypoxia [13–16]. More importantly, intermittent hypoxia is the critical element accounting for most of the immediate and long-term cardiovascular consequences of OSA including hypertension [17–19].

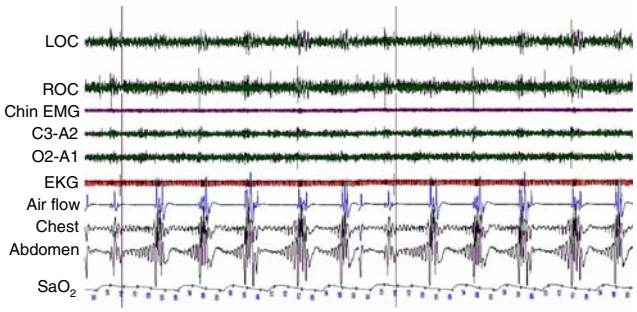

Fig. 1 A fragment from a full night sleep study recording (polysomnography) of a patient with severe OSA. Channels from top: LOC: left eye electrooculogram, ROC: right eye electrooculogram, Chin EMG: Electromyogram of the chin, C3-A2 and O2-A1: recordings of two Electroencephalogram leads used for scoring sleep; EKG: Electrocardiogram, Air flow: measured by nasal pressure cannula; Abdomen and chest effort measured by respiratory inductance plesythmography belts, SaO2: Pulse oximetry. Note the recurrent episodes of cessation of flow with persistent respiratory effort (obstructive apneas). Each episode is associated with hypoxia, and is terminated by an arousal and subsequent restoration of the patency of the airway and airflow

Intermittent hypoxia, sympathetic activation, and the pathogenesis of hypertension

Patients with OSA experience recurrent episodes of sympathetic activation and blood pressure surges throughout the sleep period [20]. This sympathetic activation, along with the increased blood pressure persists during the daytime indicating a link between OSA and the pathogenesis of hypertension [20]. Several studies attempted to explain this blood pressure relation to apnea. Xie et al. reported that a short (20 min) exposure to hypoxia in healthy humans resulted in substantial increase in sympathetic nerve activity, which remained elevated 20 min after withdrawal of the chemical stimulus [21]. In humans exposed to intermittent hypoxia, intact sympathetic pathway was required for the hypertensive response to voluntary apnea [12, 21]. In other experiments, the same investigators, as well as others, confirmed that intermittent hypoxia, and not the respiratory effort associated with apnea, is responsible for the sympathetic activation following episodes of obstructive apnea [11, 22]. Additionally, hypoxia, and not hypercapnea, was critical for the persistence of sympathetic activation following episodes of apnea [23]. Withdrawal of the inhibitory vagal signal associated with inspiration during breath holds was not important for the sympathetic activation and blood pressure surge [24]. In summary, these human experiments confirmed that intermittent hypoxia is the critical stimulus for OSA-associated sympathetic activation [22] and surge in blood pressure following obstructive episodes [12, 21]. The sympathetic response to intermittent hypoxia is associated with a carryover effect in which sympathetic

activation and blood pressure surge persist after hypoxia has resolved [25].

Animal models confirmed the role of intermittent hypoxia-induced sympathetic activation in OSA-related hypertension. In a landmark experiment, Brooks et al. developed a dog model of OSA in which they mimicked the upper airway occlusion of OSA. Again, intermittent hypoxia was the mandatory stimulus for the blood pressure response [19]. Fletcher et al. developed an animal model of OSA in which rats were exposed to a protocol of intermittent hypoxia designed to simulate the pattern of nocturnal hypoxia in OSA [26]. An increase in blood pressure occurred in the rats exposed to this intermittent hypoxia protocol compared to control animals [27]. Carotid body denervation prevented the increase in arterial blood pressure. Additionally, either chemical or surgical sympathectomy prevented the blood pressure response to intermittent hypoxia [17, 28]. Similar to human experiments, these series of experiments demonstrated that chemoreception-induced sympathetic activation mediated the blood pressure response to intermittent hypoxia. In particular, intact renal artery, and medullary sympathetic activity were required for the hypertensive response in this animal model [29]. Moreover, in this rat model, intermittent hypoxia not only resulted in increased basal sympathetic activity, but also facilitated enhanced sympathetic response to subsequent episodes of hypoxia [30–32]. Other investigators, using a similar rat model, confirmed that intermittent hypoxia induces long-term facilitation in the sympathetic activation via an effect on the carotid chemoreceptors [25].

Sympathetic overactivity appears to be the critical link between OSA and hypertension [20, 33]. The mechanism by which sympathetic activation contributes to the pathogenesis of hypertension in patients with OSA is not yet fully understood. Parallels do exist in the current understanding of the pathogenesis of essential hypertension, in which sympathetic activity is central [34, 35]. Increased sympathetic tone exerts systemic changes that promote the persistence of elevated blood pressure [36, 37] and augment the response to subsequent sympathetic stimuli [38]. Young patients with early essential hypertension have increased cardiac sympathetic tone compared to age matched controls [39]. In a population-based study, increased heart rate, a manifestation of sympathetic activation, correlated with future development of hypertension [40]. The sympathetic interaction with the renin-angiotensin system may be another important element in the pathogenesis of hypertension [36, 41, 42]. In turn, angiotensin II potentiates the vasoconstrictor effects of sympathetic activation via post-ganglionic effects [43–45]. In the previously mentioned rat model of intermittent hypoxia, Fletcher et al. showed that intermittent hypoxia-induced hypertension was mediated by renal sympathetic nerve activity [17, 46] and that intact renin-angiotensin system was critical for this blood pressure response to intermittent hypoxia [47].

Another important link between OSA and hypertension is the resetting of the baroreflex. Patients and animal models of hypertension demonstrate changes in their autonomic regulation of blood pressure (baroreflex) consistent with adaptation of the baroreceptors to a higher blood pressure set point [48, 49]. This adaptation was reported in patients with OSA both with and without changes in the sensitivity of the baroreflex [50, 51]. Adaptation of the baroreflex in hypertension requires reactive oxygen species (ROS) [52]. Also, long-term facilitation of sympathetic activation in animal models of intermittent hypoxia required ROS [53], establishing another important link with OSA, that is oxidative stress.

Finally, sympathetic activation-mediated vasoconstriction may induce long lasting structural changes in resistance vessels that contribute to the persistence of hypertension [54]. Animal models of intermittent hypoxia demonstrate early structural and functional changes [55], along with impaired vasodilator response to hypoxia [56]. These local effects of increased sympathetic tone on the vascular wall and structure may be mediated by endothelial factors. In the rat model of intermittent hypoxia, endothelin-1 was critical for the sustained increase in blood pressure in response to intermittent hypoxia [57, 58].

In summary, sympathetic activation is central to the pathogenesis of hypertension in OSA. Intermittent hypoxia-induced sympathetic activation and blood pressure increases in patients with OSA persist through the day and mediate a cascade of changes that set the stage for persistent hypertension, probably similar to the conditions of initial stages of essential hypertension [33].

Respiratory effort and the mechanical consequences of OSA

When an obstructive apnea occurs, an increase in the respiratory effort against the closed airway ensues. This inspiratory effort is a result of increased respiratory drive stimulated by the associated hypoxia [59] and results in a profound increase in negative intrathoracic pressure with each inspiration. Interest in the mechanical effects of this negative pressure on cardiac function has been long present. However, the available data suggest that hypoxia and not the respiratory effort is responsible for most of the cardiovascular response to respiratory events [60]. Nevertheless, the effect of this respiratory effort may be more important in patients with existing cardiac dysfunction [61, 62] than in otherwise healthy individuals with OSA. Negative intrathoracic pressure augments the gradient between the intraventricular pressure and the intrathoracic pressure

resulting in increased left ventricular work and wall stress during systole [61]. Also, this negative intrathoracic pressure may affect the balance of forces governing the transudation of fluid into the interstitial space resulting in pulmonary edema [63]. Finally, increased venous return to the right ventricle is likely [64], which may cause an increase in preload. Alternatively, some sources suggest that the negative intrathoracic pressure may cause a reduction in venous return and preload and subsequently would reduce stroke volume [61]. It is well established that patients with heart failure and OSA experience immediate improvement in their cardiac work index with elimination of OSA events [65, 66].

Endothelial dysfunction

Endothelial dysfunction generally denotes impairment in endothelium-dependent vasodilation, a function mediated by nitric oxide. Endothelial dysfunction is an important vascular abnormality that precedes the clinical manifestations of cardiovascular disease including hypertension [67, 68]. Dysfunction promotes atherosclerotic changes and arterial lesion development with subsequent clinical complications [69]. Flow-mediated dilation (FMD) is nitric oxide-dependent vasodilation [70] that results from shear-mediated activation of endothelial nitric oxide synthesis in response to an acute increase in blood flow [71]. Measurement of flow-mediated dilation by non-invasive methods provides an assessment of endothelial function and can help in the evaluation of cardiovascular risk [72].

Endothelial dysfunction was demonstrated repeatedly in patients with OSA and in animal models of intermittent hypoxia providing an important link between OSA and cardiovascular diseases. Kato et al. described impaired endothelial-mediated vasodilation in a group of newly diagnosed patients with OSA compared to matched controls [73]. Later, Ip et al. evaluated flow-mediated dilation in a group of OSA patients who were otherwise free of clinically known cardiovascular disease. These investigators also found baseline impairment in endothelial function, which improved after treatment of OSA [74]. A correlation existed between the apnea hypopnea index and the impairment in flow-mediated dilation in both studies. A similar correlation between baseline vascular diameter and oxygen desaturation index was also reported in a large population based study of patients with sleep apnea and cardiovascular disease further supporting a cause-effect relationship [75].

In animal models of intermittent hypoxia, endothelial dysfunction occurred without a change in the levels of endothelial nitric oxide synthase (eNOS) [76]. To date, however, the levels and function of eNOS have not been directly measured in patients with OSA. Circulating levels of nitric oxide (NO) in patients with OSA were reduced at baseline and improved with treatment with CPAP [77]. Oxidative stress plays a major role in disorders of endothelial dysfunction and NO bioavailability [78–81]. Recently, two important studies demonstrated an improvement in endothelial dysfunction in patients with OSA with antioxidant treatment [82, 83], suggesting a similar role for oxidative stress in the mechanism of reduced NO availability in patients with OSA. This provides parallels to other cardiovascular diseases in which oxidative stress-induced endothelial dysfunction is important [84, 85].

Several mechanisms have been proposed to explain the oxidative stress-mediated reduction in NO in patients with OSA. Hypoxia-mediated reduction in molecular oxygen, a substrate of eNOS, in the endothelial cell is one possible mechanism. The increase in free radical production in OSA may cause superoxide-mediated scavenging of NO generating peroxynitrite. Svatikova et al. measured circulating nitrotyrosine as an indicator of peroxynitrite formation in the vascular environment in humans with OSA and found no increase in nitrotyrosine levels [86]. This study, however, does not rule out the accumulation of peroxynitrite in the endothelial cells. Tetrahydrobiopterin (BH4) is a cofactor critical for NO production by eNOS [87, 88]. When this cofactor is depleted in conditions of increased oxidative stress, eNOS produces superoxide instead of NO resulting in endothelial dysfunction [89]. Ascorbate is suggested to replete BH4 [90]. In a relevant study, Grebe et al. showed an improvement in endothelial dysfunction in OSA patients after supplementation with vitamin C, lending support to this pathway [82, 83]. Sources of ROS in the vascular environment are numerous and include mitochondria, xanthine oxidoreductase (XOR), NADPH oxidase, eNOS, Cytochrome P450 enzymes, and the arachidonic acid pathway enzymes lipoxygenase and cyclooxygenase. ROS generated from xanthine oxidoreductase activity during ischemia reperfusion injury [91, 92] are implicated in endothelial dysfunction [93, 94] and hypertension [95, 96]. XOR inhibitors have already been shown to improve endothelial function in humans with other forms of endothelial dysfunction [97–99]. Recent evidence also shows improvement in endothelial dysfunction with xanthine inhibitor treatment in patients with OSA [83].

Asymmetrical dimethylarginine (ADMA) and NG-monomethyl-L-arginine(L-NMMA) are structural analogues of L-Arginine, a substrate for eNOS, and can function as competitive inhibitors for eNOS when their levels accumulate in the vascular environment. Only one human study so far suggests a change in the level of ADMA in patients with OSA with treatment. This reduction of ADMA correlated with the improvement in FMD in these OSA

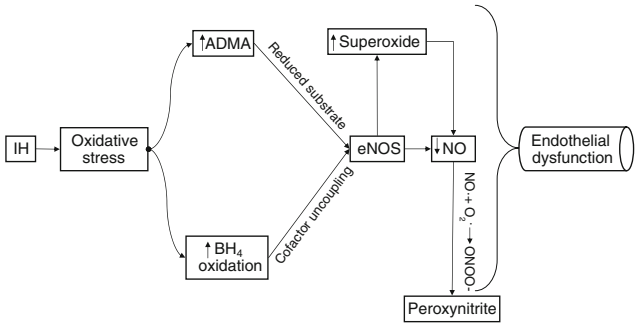

Fig. 2 A schema of potential mechanisms of oxidative stress-mediated endothelial dysfunction. IH: intermittent hypoxia, ADMA: asymmetrical dimethlarginine, BH4: tetrahydrobiopterin, eNOS: endothelial nitric oxide synthase, NO: nitric oxide, O2: oxygen ONOO-: peroxynitrite

patients [100]. Figure 2 summarizes some of the mechanisms of oxidative stress-mediated endothelial dysfunction that may play a role in endothelial dysfunction in patients with OSA.

Intermittent hypoxia and oxidative stress

Oxidative stress describes an imbalance between the production of ROS and the antioxidant capacity of a biological system. Oxidative stress occurs in conditions of ischemia reperfusion typical to many disease states. Oxidative stress can be assessed directly by measurement of ROS in biological systems, or indirectly by measurement of oxidation products such as lipids, proteins, or DNA. Additionally, increased oxidative stress can be quantified by measuring the available in vitro antioxidant capacity of a biological system as an indicator of existing oxidative stress. Given the significant influence of environmental factors on oxidative activity, large sample sizes, very meticulous techniques, and sophisticated measurements are usually required to evaluate the role of oxidative stress in a particular disease process [101].

The resemblance between the pattern of intermittent hypoxia associated with OSA and ischemia reperfusion patterns leads to the postulation that OSA would also be associated with oxidative stress. Potential mechanisms for oxidative stress in OSA may be related directly to intermittent hypoxia in a fashion similar to ischemia reperfusion injury, or indirectly via inflammatory response. The increased sympathetic tone and elevated catecholamine levels, a hallmark of OSA, might also be associated with increased ROS production.

Despite the biological plausibility, several earlier studies provided conflicting information regarding the presence of increased oxidative stress in patients with OSA [102–105]. In some of these studies, the negative results may have been due to inadequate controlling, small sample size or use of less-refined techniques than what is available currently [102–104]. Recent studies, particularly ones that involved larger numbers of patients, were able to demonstrate that OSA is indeed associated with increased markers of oxidative stress. Lavie et al. [106] measured plasma levels of thiobarbituric reactive substances (TBARS), a marker of lipid peroxidation, and the levels of paraxonase-1, a marker of antioxidant capacity, in 114 OSA patients and a group of normal controls. The investigators found an increase in lipid peroxidation and a reduction in antioxidant capacity in patients with OSA, which correlated with the severity of their OSA, and subsequently improved with treatment. Similarly, Barcelo et al. [107] found increased lipid peroxidation (oxidized LDL) in patients with OSA compared to controls. Treatment with CPAP reduced the susceptibility of LDL to oxidation.

Several studies evaluated direct or indirect measurements of increased ROS production in patients with OSA. Christou et al., in a series of experiments, evaluated the presence of oxidative stress in blood samples of patients with OSA [108–110]. In one experiment, they measured levels of Diacron reactive oxygen metabolism (D-ROM). Diacron indicates the ability of metals to catalyze the formation of free radicals in the presence of peroxide. They found increased levels of reactive oxygen metabolites which correlated with the severity of OSA [108]. In a later study, the same group found a reduction in this measure of oxidative stress (D-ROM) after treatment with CPAP. Carpagnano et al. found increased levels of 8-isoprostane in exhaled breath condensate and blood of patients with OSA compared to controls [111, 112]. Isoprostane is another measure of lipid peroxidation that may be linked to the pathogenesis of atherosclerosis [113–115]. Tan et al. recently described a link between the lipid abnormality in OSA and atherosclerosis. These investigators found that HDL was dysfunctional in preventing LDL oxidation in patients with OSA [116]. Other investigators evaluated products of oxidized DNA as a measure of increased ROS production. These investigators found increased oxidized DNA products in patients with OSA which correlated with the desaturation index [117]. Takahashi et al. evaluated thioredoxin levels in patients with OSA. Thioredoxin is a protein that is released from cells in response to oxidative stress and may be implicated in myocardiac injury [118] and atherosclerosis. The investigators found increased levels of thioredoxin and a correlation between these levels and severity of OSA [119].

Other studies evaluated cellular antioxidant capacity in patients with OSA. This antioxidant capacity can change in the presence of significant oxidative load and is a potential measurement or marker of existing oxidative stress in the system. Using Trolox Equivalent Antioxidant Capacity assay, Christou et al. found that the antioxidant capacity in

the blood of patients with severe OSA was reduced in comparison to normal controls [109]. Another study also found that the antioxidant capacity of the serum in 47 patients with OSA was reduced compared to normal controls and improved with treatment of OSA [120]. Together, these studies indicated an impairment in the protective system from oxidative stress in patients with sleep apnea.

In summary, oxidative stress in patients with OSA is central to the cardiovascular morbidity of OSA. Most recent studies in patients with OSA and animal models of intermittent hypoxia confirm that OSA is associated with oxidative stress, which generally correlated with the severity of sleep apnea, and improved with treatment. The conflicting results of some of the earlier human studies are likely a result of methodology or control of patient variables. Meticulous controlling for environmental and circadian factors along with the controlling of subjects is required for evaluation of oxidative stress in OSA patients. The mechanism of increased oxidative stress in patients with OSA and its consequences remains incompletely understood. Oxidative stress provides an important link in understanding the cardiovascular consequences of OSA. Reactive oxygen species are required for the memory effect of the sympathetic activation in animal models of intermittent hypoxia. Increased oxidative stress in the vascular milieu is involved in the pathogenesis of endothelial dysfunction [82, 121]. Furthermore, cognitive impairment [122, 123], inflammation [124, 125], atherosclerosis [116], hypertension [126]and myocardial injury [118] may all be direct consequences of the oxidative stress in OSA.

OSA and inflammation

A link between OSA and inflammation is an intriguing and increasingly likely component of the pathophysiology of OSA. Several studies suggested that systemic inflammation may be involved in the increased ROS production in OSA [111, 124]. Schulz et al. [124] reported a marked increase in neutrophil superoxide generation in OSA patients when compared to controls. Enhanced superoxide generation by neutrophils decreased with CPAP treatment. The neutrophil chemokines, IL-8 and granulocyte chemotactic protein-2, were significantly higher in OSA patients compared to healthy controls [105].

Htoo et al. assessed nuclear factor kappa B (NF-kappaB) activity in OSA patients compared to control subjects. They determined that neutrophils in OSA patients demonstrate several fold increase in NF-kappaB binding activity compared with control subjects. There was a positive correlation between the degree of NF-kappaB activation and indices of OSA severity. CPAP treatment decreased neutrophil NF-kappaB activation to control levels [127].

In an animal model of OSA, Nácher and colleagues determined that recurrent airway obstruction leads to rapid endothelial cell activation. They noted endothelial cell activation and systemic leukocyte recruitment in the microcirculation, with the apnea group having significantly increased flux of leukocyte activation when compared with the sham groups. P-selectin, an adhesion molecule found in endothelial cells and activated platelets, which plays an essential role in leukocyte recruitment, was up-regulated only in the apnea group [128].

Other studies established that patients with OSA have elevated levels of tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine that plays an important role in neutrophil activation [129, 130]. Vgontzas et al. also demonstrated that Interleukin-6 (IL-6), another pro-inflammatory cytokine, was elevated in OSA patients compared to normal controls. The primary factor influencing TNF-α levels was the degree of sleep disturbance, and the main factor affecting IL-6 levels was body mass index (BMI) [129]. In a recent study, patients with OSA were found to have elevated serum levels of neopterin, a pro-inflammatory marker for macrophage activation, which plays a role in the pathogenesis of cardiovascular disease. In this study, the elevated levels of neopterin also correlated with the severity of the underlying severity of sleep apnea and with the degree of sleep disruption [131].

Expanding literature connecting both IL-6 and C-Reactive Protein (CRP) to OSA is very important, as both of these inflammatory markers are risk factors for cardiovascular disease, including atherosclerosis and coronary heart disease [132–137]. Shamsuzzaman et al. reported that plasma CRP levels were significantly higher in OSA patients compared to age and weight matched controls. In their study, multivariate analysis demonstrated that CRP levels were independently associated with the severity of OSA [138]. In a study assessing adolescents (ages 13–18 years, and free of known cardiovascular disease), an AHI $\geq$ 5 was associated with increased levels of CRP. The authors concluded that OSA in adolescents confers additional cardiovascular risk beyond that of obesity [139]. Another study examining 69 men who were free of cardiovascular disease demonstrated a strong association between the severity of OSA and CRP levels [131]. Monocyte production of IL-6 was higher in patients with OSA compared to obese control subjects. In those patients with OSA, the factors influencing CRP levels were OSA severity and BMI, and the factors affecting IL-6 levels were BMI and nocturnal hypoxia. Treatment with nasal CPAP significantly decreased levels of CRP and production of IL-6 [140].

Activated leukocytes play an important role in the inflammatory response to injury resulting from hypoxia/reoxygenation that may set off the atherogenic processes

[141]. Dyugovaskaya et al. investigated the link between certain adhesion molecules expression on leukocytes and their ability to generate ROS in OSA patients. They found that OSA was associated with increased expression of the adhesion molecules CD15 and CD11c by monocytes, increased adherence of monocytes in culture to human endothelial cells, and increased intracellular ROS production in some monocyte and granulocyte subpopulations. Nasal CPAP reversed most of these inflammatory activities. Minoguchi et al. examined carotid intima-media thickness (IMT) along with inflammatory markers associated with cardiovascular disease (CRP, IL-6, and IL-18). Carotid IMT correlated with serum CRP levels, IL-6, and IL-18, duration of OSA-related hypoxia, and severity of OSA. The primary factor influencing carotid IMT was duration of hypoxia during total sleep time [142]. These findings indicate that patients with OSA are exposed to atherogenic insult nightly [143].

Therefore, OSA appears increasingly linked to cardiovascular morbidity via a distinct inflammatory response. This response is complex and includes several humoral and cellular pathways that are only minimally understood so far. This inflammatory response directly links OSA with the pathogenesis of atherosclerosis.

Summary

In otherwise healthy individuals, OSA constitutes a significant risk factor for the development of cardiovascular disease or the progression of existent cardiovascular disorders toward heart failure, stroke, or death. OSA exerts its negative cardiovascular consequences through its unique pattern of intermittent hypoxia. Endothelial dysfunction, oxidative stress, and inflammation are all consequences of OSA directly linked to intermittent hypoxia and critical pathways in the pathogenesis of cardiovascular disease in patients with OSA.

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