

Oxidative stress inflammation and endothelial dysfunction in obstructive sleep apnea

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1. ABSTRACT

Obstructive sleep apnea syndrome (OSA) is a breathing disorder in sleep. In recent years, this entity has emerged as a major public health problem due to its high prevalence and the profound impact on patients' health and quality of life. A large body of evidence identified OSA as an independent risk factor for cardiovascular morbidity and mortality. Also an association was demonstrated with additional cardiovascular risk factors. This has led to intensive research on the mechanisms involved. The main characteristics of OSA are the recurrent pauses in respiration which result in intermittent hypoxia (IH) and hypercapnia, accompanied by decreased blood oxygen saturation and arousals during sleep. The associations of OSA with cardiovascular morbidities rely on the cyclic nature of the IH, and implicate the apnea related multiple cycles of hypoxia/reoxygenation with increased production of reactive oxygen species (ROS), thereby initiating inflammation. This review summarizes the main findings in oxidative stress/inflammation in the context of OSA and its consequences to possible cardiovascular outcomes through the development of endothelial dysfunction and early clinical signs of atherosclerosis.

2. INTRODUCTION

In the last decade it has become increasingly evident that obstructive sleep apnea (OSA) is a major public health problem due to its high prevalence and its profound impact on patients' health and quality of life (1, 2). The prevalence is high; at least 4% of adult men and 2% of adult women are diagnosed with OSA and its characteristic symptoms (1, 3). It is higher in the male gender but also due to central obesity, smoking and in post-menopausal women. In non-symptomatic men not displaying day time somnolence, the prevalence may rise up to 24% and in the obese and elderly to 60% (1-4).

The main features of OSA are the recurrent pauses in respiration, which cause cyclic decreases in blood oxygen saturation, resulting in intermittent hypoxia (IH), hypercapnia, and brief arousals from sleep because of obstruction or collapse of the upper airways (5). The severity of OSA is defined by two primary measures. The most commonly used measure relies on the number of breathing cessations throughout the sleeping period – the number of apneas and hypopneas. Dividing the number apneas-hypopneas by the hours of sleep gives the apnea-hypopnea index (AHI). Normal AHI values are considered

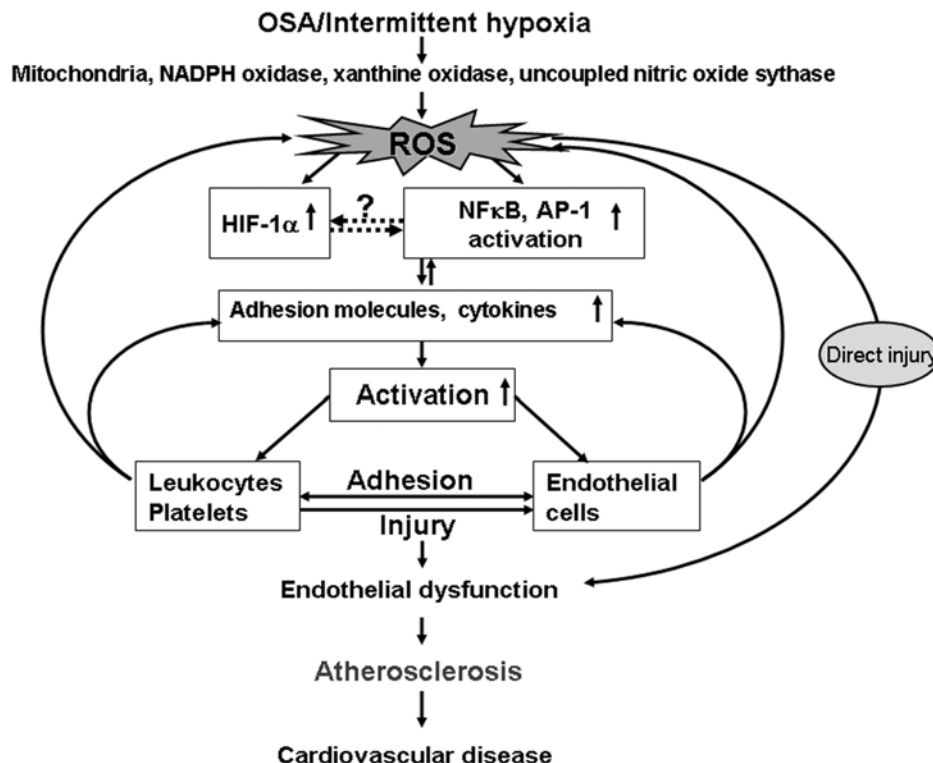


Figure 1. Oxidative stress and inflammation in OSA. The intermittent hypoxia induces ROS formation which in turn activates an inflammatory cascade via activation of transcription factors and downstream genes as inflammatory cytokines and adhesion molecules. These in turn can further activate transcription factors and various blood cells. Activated leukocytes and platelets produce higher amounts of ROS adhesion molecules and pro-inflammatory cytokines exacerbating this oxidative/inflammatory cycle and facilitating endothelial dysfunction which is the prelude to atherosclerosis and cardiovascular morbidity (26).

up to 5 or 10 events per hour. No less important in defining OSA severity is the level of hypoxemia. This is determined by the oxygen desaturation index (ODI) denoting the number of decreases in oxygen desaturation of at least 3%-4%, normalized by the hours of sleep. An alternative measure is the % of sleep time patients spend with arterial oxygen saturation below 90%.

One of the most well studied outcomes of OSA is the profound impact it exerts on the cardio/cerebrovascular system. Over the past few years a great number of large scale cross sectional, prospective, population based and intervention studies, identified OSA as an independent risk factor for cardiovascular morbidity and mortality (6). Hypertension, ischemic heart disease, arrhythmias, chronic heart failure, strokes as well as cardiovascular mortality, were all shown to be associated with OSA (6). These associations are mainly attributed to increased sympathetic discharge and intrathoracic pressure. But more recently also oxidative stress, inflammation and accelerated atherosclerotic processes were shown to participate.

The present review is aimed at describing the current knowledge on two of these underlying mechanisms namely - oxidative stress and inflammation - and their contribution to the development of cardiovascular

morbidities in OSA through endothelial dysfunction and atherosclerosis as illustrated in Figure 1.

3. ASSOCIATION OF OSA WITH CARDIOVASCULAR MORBIDITY

Coronary artery disease or atherosclerotic heart diseases are affected by a great number of factors (7) and characterized by reduced blood supply to the heart. Progressive atherosclerosis may lead to wall thickening and occlusion of the coronary arteries resulting in acute myocardial ischemia (8).

Given that OSA is characterized by nightly IH and decreased oxygen supply, it is likely that it can initiate cardiovascular morbidity. Indeed the association between OSA and cardiovascular morbidity has been long recognized in small scale clinical studies (9). However, cross-sectional and case-control studies further established this association. Moreover, while high rates of OSA were shown in unselected cardiovascular patients, also, higher rates of cardiovascular morbidity were shown in OSA (10, 11). Similar findings were also reported in large scale epidemiological studies as well as prospective studies, which controlled for possible confounding variables. Collectively, these confirmed the independent association between OSA and cardiovascular diseases (12-14). These

associations were further supported by treatment studies (15) and animal models mimicking sleep apnea (16).

Interestingly, the ramifications of OSA on the cardiovascular system are mainly evident in relatively middle aged populations of about 50 years and are less evident in elderly populations (17). Also, it has become increasingly evident that OSA is also associated with additional risk factors characteristic of the metabolic syndrome such as hyperlipidemia, insulin resistance, hypertension, and obesity. These may also contribute and augment cardiovascular risk by acting synergistically with the apneic events (18-20).

3.1. Prevailing mechanisms

Several mechanisms were proposed to clarify the association between OSA and cardiovascular morbidity. Increases in the activation of the sympathetic nervous system, swings in intrathoracic pressure and altered blood coagulability in OSA were described in earlier studies. Indeed these were shown to contribute to the development of endothelial dysfunction, atherosclerosis and cardiovascular morbidity in OSA through intermittent hypoxia and arousals (21). Moreover, these measures were all shown to increase with the severity of the syndrome while treatment with nasal continuous positive airway pressure (nCPAP) that ameliorated the apneas, moderated some of these measures (22, 23). However, more recent studies implicate also oxidative stress and inflammation in contributing to this association.

Both oxidative stress and inflammation are recognized as two fundamental mechanisms associated with various pathological settings. In OSA, oxidative stress is mainly attributed to the reduced oxygen availability which is followed by a period of reoxygenation in which the flux of radicals is usually generated (24, 25). It is suggested that once oxidative stress is initiated, it promotes inflammation and in turn, inflammation promotes oxidative stress (26). These two components create a vicious cycle of oxidative stress and inflammation augmenting each other and by that promoting endothelial dysfunction and consequently atherosclerosis (Figure 1).

4. OXIDATIVE STRESS IN OSA

4.1. Consequences of oxidative stress

Oxidative stress has gained widespread attention in the last two decades as being a fundamental mechanism, affecting a variety of conditions and morbidities (24). Yet, in each disease the outcome may differ depending on the organ or the cellular function most affected.

Oxidative stress is defined as a disruption in the balance between oxidant producing systems, and anti-oxidant defense mechanisms. Overproduction of the former through excessive production of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) induces oxidative stress. However, decreased antioxidant capacity can also contribute to oxidative stress. Thus, maintaining a stringent cellular oxidation-reduction (redox) balance is essential for normal cellular function (25, 27).

Overproduction of free radicals could largely affect a variety of cellular activities and functions by damaging biomolecules such as lipids, proteins, DNA and carbohydrates (25). However, oxidant molecules are also vital regulators of normal cellular function and act as second messengers in a plethora of signaling transduction pathways (28). Both these consequences of increased ROS formation; damage to vital macromolecules and altered signaling pathways, are major contributors to the development of cardiovascular morbidities.

4.2. Reactive oxygen species (ROS) and their Sources

Free radicals or ROS represent a class of atoms or molecules with a unique ability to chemically react with each other or with other atoms or molecules. They possess one unpaired electron in the outer orbit which allows for transferring or receiving an electron and thus producing a new molecule (25). When two free radicals react with each other, a new non-radical molecule is formed. But when a radical reacts with a non-radical molecule a new radical is formed. Such interactions of radicals with non-radicals initiate and propagate free radical chain reactions.

The superoxide anion ($O_2^{\bullet -}$) is the most abundant ROS molecule. Although it is considered a relatively weak radical, by reacting with other molecules, it gives rise to a variety of ROS molecules such as hydrogen peroxide (H_2O_2) which is a weaker radical than superoxide, and hydroxyl radical (OH^{\bullet}) which is a very potent oxidant. Another crucial and potent oxidant molecule is peroxynitrite ($OONO^{\bullet}$). Peroxynitrite, a nitrogen reactive species (RNS), largely contributes to impair endothelial function. It is formed when nitric oxide (NO) interacts with superoxide, thus increasing oxidative stress in the endothelial milieu. As a result, NO availability is diminished and the relaxing capacity of the endothelium deteriorates (29).

The mitochondria are a major source of cellular ROS and oxidative stress. It is estimated that at least 3-5% of the oxygen consumed during normal aerobic respiration is converted to superoxide anion. In hypoxic conditions mitochondria become dysfunctional and produce even higher amounts of ROS (25). There are also several enzymatic systems which produce superoxide. The NADPH oxidase is one of the main sources. It is primarily present in leukocytes and is activated during inflammatory processes. Another source of NADPH oxidase is from activated endothelial cells. However, this form produces lower amounts of superoxide for signaling purposes. Other sources of ROS include several other enzymes like xanthine oxidase, and "uncoupled" endothelial nitric oxide synthase (eNOS) (26, 30). However, oxidative stress can also result from diminished anti-oxidant capacities. The most well known antioxidants include enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxidase. Additionally, small molecules such as vitamins C and E, glutathione and uric acid possess antioxidant capacities (25).

4.3. Activation of nuclear transcription factors by ROS

While ROS molecules are essential for normal cellular function (25, 27, 28), their production is increased

in various hypoxic conditions, resulting in upregulation of various ROS sensitive transcription factors and their downstream genes. Two of the most affected and best studied nuclear transcription factors under hypoxic conditions are hypoxia inducible factor (HIF)-1 α and nuclear factor (NF) κ B. While NF κ B is best known for its involvement in inflammatory pathways, (HIF)-1 α is best known for its role in regulating genes that are important in adaptation to hypoxia. Recently HIF-1 α was also shown to participate and interact with inflammatory pathways (25, 31-33). A discussion is devoted to these transcription factors under “inflammatory pathways in OSA.” Additional information describing other ROS modulated transcription factors such as activator protein (AP)-1, Sterol regulator element binding proteins (SREBPs), NF-(erythroid-derived 2) related factor (Nrf2) antioxidant responsive element (ARE) and GATA-4 with potential significance to OSA have been described elsewhere (25, 31-34).

4.4. Evidence for oxidative stress in OSA

The last decade has witnessed an unprecedented accumulation of evidence demonstrating increased oxidative stress in OSA. In most studies circulating oxidative stress markers were determined. Yet, a direct increase in the production of ROS was described only in a small number of studies. For instance, ROS formation was shown to increase in stimulated neutrophils and monocytes which primarily function in host defense mechanisms (35-37). In a study conducted by Schulz *et al.* increased ROS production was shown in stimulated neutrophils from OSA patients. Treatment with nCPAP attenuated the levels of ROS (36). Later on Dyugovskaya *et al.* demonstrated increased ROS production in stimulated monocytes and neutrophils. Interestingly, ROS production was also significantly increased in non-stimulated monocytes of patients with OSA, indicating a higher basal state of activation than in control monocytes (35, 37).

Of the circulating oxidative stress markers investigated in OSA, the lipids are by far the most frequently studied due to their high ability to undergo oxidation which makes them a sensitive marker for atherosclerosis. Lipid peroxidation was shown to be higher in OSA patients than in controls, while effective treatment with nCPAP attenuated the oxidative stress burden (38-40). Also circulating levels of oxidized low density lipoprotein (oxLDL) were shown to increase in OSA (41-43). Additionally, increases in urinary excretion of 8-hydroxy-2'-deoxyguanosine indicative of DNA oxidation were also demonstrated in OSA (44). Protein carbonylation which is another marker of oxidative stress was also recently described in patients with OSA (45). Treatment with nCPAP or dental device attenuated some of these oxidative stress markers (38, 39, 46, 47).

Importantly, increased oxidative stress and lipid peroxidation were also associated with atherosclerotic measures such as increased carotid intima media thickness (48). Such findings were corroborated by studies on animal models mimicking OSA showing accelerated atherosclerosis in mice treated with chronic IH as compared to normoxia (49). Moreover, the increased oxidative stress

in these animal models resulted from activation of NADPH oxidase. Increased activity of NADPH oxidase was shown in a variety of tissues including the brain, myocardium, the liver, and carotid bodies (50-52). Moreover, using genomic microarray further supports these finding on increased oxidative stress in OSA (53).

Decreases in antioxidant capacities contributing to increased oxidative stress burden were described in OSA as well. For instance, the total anti-oxidant capacity of serum from OSA patients was decreased (40). Similarly, the anti-oxidant capacity of serum albumin was impaired, while treatment with nCPAP improved this capacity (54). The antioxidant vitamins A and E were shown to be lower in OSA patients (40, 55). Paraoxonase-1 (PON1) an antioxidant enzyme was also decreased in OSA (38). This enzyme protects both LDL and high density lipoprotein (HDL) from oxidation. These observations are in accord with the increased levels of oxLDL reported in OSA. Jointly, the findings from human studies, the attenuation by nCPAP treatment and studies from animal models mimicking OSA, support the role of oxidative stress in these patients.

5. INFLAMMATORY PATHWAYS IN OSA

Inflammation is perceived as the body's response to combat insults such as invading bacteria, viruses, and other microorganisms. However, inflammatory cascades are also activated in response to physical or chemical irritation. As such, endothelial injury as well elicits inflammation. Inflammatory cascades are complex in nature and involve induction of nuclear transcription factors of which nuclear factor κ B (NF κ B) is the primary target.

5.1. Nuclear factor κ B (NF κ B)

The nuclear transcription factor NF κ B orchestrates many vital cellular functions including cell proliferation, death, and immune responses by regulating a great number of downstream genes. Many of these activated genes, like adhesion molecules and inflammatory cytokines, participate in inflammation and promote atherosclerotic sequences (56). Besides hypoxia or ROS, many factors activate NF κ B, including adhesion molecules and inflammatory cytokines (57).

Several lines of evidence implicate NF κ B upregulation in patients with OSA. Increased NF κ B activity was demonstrated in neutrophils and monocytes and in venous endothelial cells of patients with OSA (58-61). Moreover, nuclear NF κ B activity was also increased in neutrophils of healthy subjects that were exposed to IH *in vitro* (62). Accordingly, some of its gene products such as adhesion molecules and inflammatory cytokines were also increased (35, 63), and jointly attest to increased NF κ B activation in OSA (35, 37, 64, 65).

5.2. Hypoxia inducible factor (HIF)-1 α

The HIF-1 α transcription factor is activated as an adaptive response to hypoxic conditions. Upregulation of this master regulator is essential to further upregulate a great number of downstream genes in order to counteract

the reduced oxygen availability. It does so by activating sets of genes encoding for glucose and energy metabolism, angiogenesis, vascular reactivity and remodeling. Thus far, up-regulation of HIF-1 α was not demonstrated directly in patients with OSA. Still, some of its gene products such as erythropoietin, endothelin and vascular endothelial growth factor (VEGF), were mainly shown to increase (26, 66-68). Moreover, by using various cells in culture and rodent models of IH, HIF-1 α activation was increased (reviewed in (69, 70)). These findings however were inconsistent (71-74). These inconsistencies likely resulted from the various cell types used and the different patterns and intervals of IH applied (71). Also, activation of HIF-1 α was implicated in hypertension (75) and in components of the metabolic syndrome in rodents treated with chronic IH (76). In accord with this line, a recent study on an animal model mimicking OSA demonstrated activation of HIF-1 α in myocardial tissue as well as increased expression of its downstream gene endothelin. Endothelin is a potent vasoconstrictor, and was implicated in the cardiovascular consequences of IH (77).

In several studies NF κ B and HIF-1 α were also shown to crosstalk in hypoxic conditions. For instance, under hypoxic conditions the transcription of HIF-1 α was shown to be activated by a NF κ B dependent mechanism. However, also the NF κ B pathway was affected by the HIF-1 α pathway (78, 79). These findings further imply that HIF-1 α participates in inflammatory pathways, in hypoxic conditions, and thus adding complexity to the functions of these transcription factors under IH (34). Additional information regarding the complex interactions between these transcription factors has been described elsewhere (80).

5.3. Activation of inflammatory and endothelial cells in OSA

The increased expression of ROS and augmented oxidative stress which activate a plethora of inflammatory pathways, facilitate the recruitment and accumulation of blood cells on the endothelium lining the vasculature. The activation of NF κ B via its gene products also promotes endothelial cells/blood cells interactions leading to endothelial cell injury and dysfunction (26). Circulating leukocytes and platelets are the primary source of adhesion molecules and inflammatory cytokines and may injure the vasculature when activated. In the normal state circulating blood cells flow freely in the circulation, while expressing low levels of adhesion molecules and intracellular inflammatory cytokines. However, when activated by various stimuli including hypoxia/reoxygenation, or OSA, increased expression of adhesion molecules and cytokines is noted. Similar activation of inflammatory pathways occurs in endothelial cells.

5.3.1. Adhesion molecules

Adhesion molecules are expressed in a highly regulated and sequential manner which is manifested in leukocytes, platelets and endothelial cells. These molecules facilitate interactions between activated blood cells and endothelial cells, and promote adhesion to the vascular

endothelium. Two major groups participate; the selectins and the integrins. The selectins facilitate weak interactions between the leukocytes endothelial cells and platelets - termed rolling. Three major groups participate; the L-selectins (on leukocytes), the E-selectins (in endothelial cells) and the P-selectins (in platelets and endothelial cells). The integrins allow for a firm binding to endothelial cells but also facilitate transmigration into the interstitial layer through the endothelial cell layer (81, 82).

All leukocytes subpopulations studied thus far in OSA; monocytes, polymorphonuclear cells (PMNs) and various T cells subpopulations, have expressed higher levels of adhesion molecules in comparison with controls, but monocytes and lymphocytes also express increased avidity to endothelial cells (35, 37, 64, 65, 83, 84). Specifically, in PMNs various measures of activation were determined. While selectins were increased, integrins remained unchanged (37). Notably, activated PMNs from OSA had also prolonged life span. Thus, increased expression of adhesion molecules, ROS and prolonged life span can induce endothelial cell injury. Similar findings were described in lethal myocardial reperfusion (85) and in acute coronary syndromes (86, 87).

The role of monocytes in initiation and propagation of atherosclerotic sequences is well established (81, 88). Monocytes of patients with OSA also express increased activation and elevated levels of adhesion molecules of the selectins and the integrins (35). Thus, increase in adhesion molecules jointly with increases in ROS levels, inflammatory cytokines and increased avidity to endothelial cells *in vitro* implicate monocytes in injuring the endothelium of patients with OSA (35, 65, 89).

T lymphocytes like monocytes are prevalent in atherosclerotic lesions and modulate atherosclerotic responses primarily by secretion of cytokines and antibodies (90, 91). In patients with OSA all T cells investigated thus far (Natural killer (NK) lymphocytes, CD8 $^{+}$, CD4 $^{+}$, and gamma-delta T cells) expressed an activated and a cytotoxic phenotypes towards endothelial cells *in vitro*, but also inflammatory cytokines were increased in these cells (64, 83, 84). Though, some subpopulations were more cytotoxic to endothelial cells than others (92).

Activation, increased expression of adhesion molecules, and higher aggregability *in-vitro* were also reported in platelets of patients with OSA. Increased expression was mainly notable in platelet P-selectin, while treatment with nCPAP attenuated this expression (93-96). Additional atherosclerotic measures such as hematocrit counts, and blood viscosity were also increased, possibly contributing to the increased incidence of cardiovascular morbidity in OSA (97-99).

Increased expression of adhesion molecules derived from endothelial cells was mainly determined in the circulation. OSA patients expressed higher E- and P-selectins (100, 101), intracellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-

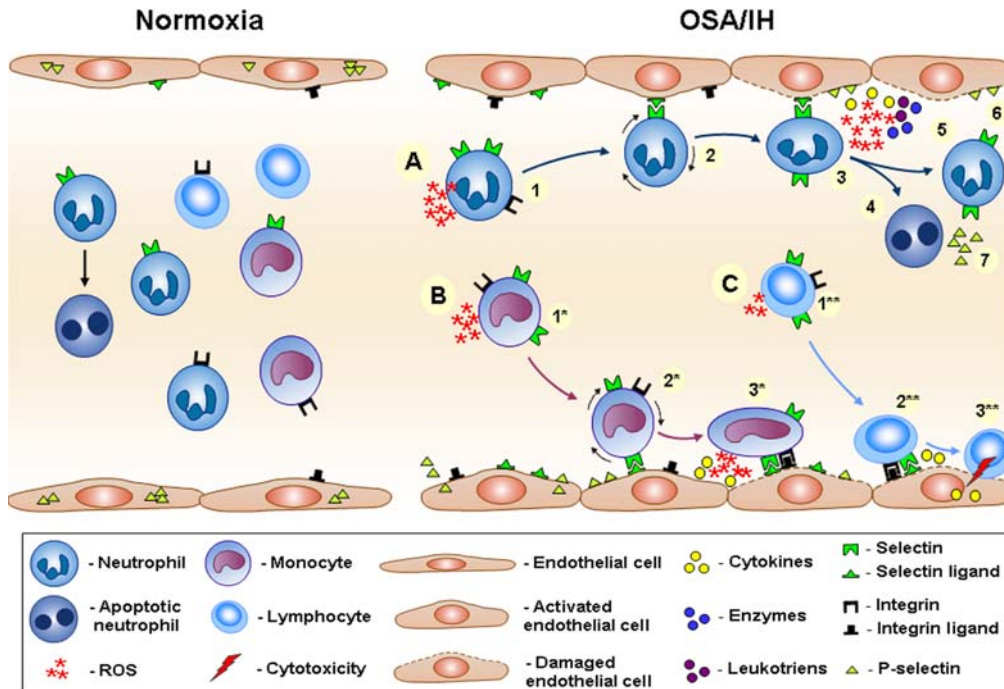


Figure 2. A - In activated PMNs, ROS production is increased and so is the expression of selectins (1). The increased expression of selectins on PMNs and endothelial cells promotes rolling and capture of the PMNs (2). After attachment, PMNs release inflammatory cytokines, proteolytic enzymes, leukotriens and additional ROS molecules in the vicinity of the endothelial cells inducing endothelial cell injury (3). Delayed PMN apoptosis may further exacerbate this injury. The captured PMNs may then either undergo apoptosis (4) or if apoptosis is delayed, PMNs could possibly detach from the endothelium and return to the circulation (5). This may facilitate their recapture to continue endothelial cell injury. The intracellular P-selectin which is rapidly translocated from activated endothelial cells (or platelets) to the cell surface (6), could also be shed to the circulation (7), and may possibly contribute to delay PMN apoptosis. B. Similarly, activated monocytes (1*) release ROS molecules and express increased amounts of selectins and integrins in response to intermittent hypoxia while rolling onto the endothelium via selectins (2*) and firmly adhering to the endothelial cells via integrins (3*), further releasing ROS molecules and inflammatory cytokines, that can damage the endothelium (described in 35). C. Activated lymphocytes (1**) release low amounts of ROS and express adhesion molecules which facilitate rolling and firm adhesion to endothelial cells (2**), promoting endothelial cell damage by utilizing various mechanisms of cytotoxicity (3**). This figure was reproduced with permission from (37)

1) (100, 102-104). These are well established markers of active atherosclerotic processes as well as predictors of future cardiovascular events (105). Also, endothelial cells derived from the vasculature of OSA patients expressed an activated phenotype, increased oxidative stress, lower NO bioavailability and compromised capacity for repair (106). However, in studies addressing the presence of endothelial progenitor cells (EPCs) in the circulation and their repair capacity in OSA, the findings are inconsistent (107-109). Yet, in a recent study conducted on children with OSA, the authors identified two patients' sub-groups which differed in their endothelial functioning and the number of circulating EPCs. The sub-group with endothelial dysfunction had lower numbers of circulating EPCs while the sub-group with normal endothelial function had higher numbers of circulating EPCs. Interestingly, the endothelial function of each patient was significantly correlated with EPCs numbers but not with the severity of OSA (110). These findings may explain the inconsistencies observed in earlier studies investigating EPCs, and indicate the importance of EPCs recruitment and function for maintaining normal endothelial function.

Jointly, increased activation of leukocytes and platelets and expression of adhesion molecules facilitate and promote interactions with endothelial cells. Additional contributors; ROS molecules and cytotoxicity against endothelial cells further augment endothelial cell injury. Figure 2 represents a schematic illustration of these interactions between leukocytes and endothelial cells leading to endothelial cell injury in OSA (37).

5.3.2. Inflammatory cytokines

The cytokines are multipurpose molecules participating in immune functions associated with inflammation but are also essential to growth, differentiation and tissue repair. They are synthesized and released by various cells and participate in the regulation of the innate and adaptive immune system through intricate interactions with other cytokines and transcription factors. Many of their functions are involved in the progression of atherosclerosis. They control macrophage activation, scavenger receptor expression, smooth muscle cell proliferation, NO production and apoptosis, and induce endothelial cell activation (111). The major pro-

inflammatory cytokines include tumor necrosis factor (TNF)-alpha, interleukin (IL)-6 and IL-8. These were shown to be regulated by oxygen tension and free radicals via activation NFkappaB and AP-1 (112). In turn, these cytokines can further activate inflammatory transcription factors and augment inflammatory responses through activation of various blood cells and endothelial cells (Figure 1).

In patients with OSA, circulating TNF-alpha levels were primarily shown to increase in plasma or serum (63, 113, 114). But, also in monocytes and in various cytotoxic T lymphocytes (83, 84, 89). TNF-alpha in particular is involved with the initiation and progression of cardiovascular pathology by inducing endothelial dysfunction (111, 115). Also, the inflammatory IL-6 and IL-8 were increased in OSA (57, 114, 116-118) while the levels of the anti-inflammatory cytokine IL-10 were decreased in plasma and in T lymphocytes (84, 92). Thus, this attenuation results in an imbalance between the levels of the pro-inflammatory TNF-alpha and the anti-inflammatory cytokine IL-10 (64, 84). Altered balance between the levels of TNF-alpha and IL-10 was suggested to promote pathologic conditions such as stroke and during cardiac surgery (119). Collectively, these findings further support increased inflammatory-atherogenic processes in patients with OSA.

6. ENDOTHELIAL DYSFUNCTION AND ATHEROSCLEROSIS IN OSA

Endothelial dysfunction precedes atherosclerosis and in fact it represents a subclinical condition of atherosclerosis. Basically, it refers to a state at which endothelial dependent vasorelaxation is impaired concomitantly with the decreased bioavailability in NO, and results in vascular constriction. Apart from its strong vasodilatory properties, NO is also a mediator of various functions which protect the endothelium from injury. For instance, NO limits recruitment of blood leukocytes and the expression of adhesion molecules on leukocytes. By that, NO protects the endothelium from interacting with the injurious potential of leukocytes. It also inhibits vascular smooth muscle cell proliferation and platelet aggregation and adhesion. Moreover, NO also limits atherosclerotic consequences such as plaque disruption and intravascular thrombosis (81, 120). Jointly all of NO's functions help to maintain a healthy and functional endothelium by preventing endothelial dysfunction and its cardiovascular consequences.

Impaired endothelial function can result from diverse stimuli apart from oxidative stress, inflammatory cytokines and OSA. Morbidities such as hypercholesterolemia, hypertension or diabetes were shown to impair endothelial function (34). Moreover, endothelial dysfunction correlates with various inflammatory markers of vascular disease. Thus, circulating levels of adhesion molecules as ICAM-1, C-reactive protein (CRP), and TNF-alpha which may predict future cardiovascular events, were shown to increase in patients with OSA (121).

In OSA, several studies reported on a decrease in circulating NO levels and their increase after nCPAP treatment (122-124). Based on these studies it was suggested that the bioavailability of NO is compromised in OSA, most likely through deactivation of NO by oxidative stress (26, 105). Also, in a more recent study investigating venous endothelial cells derived from patients with OSA, the activity of endothelial nitric oxide synthase (eNOS) was decreased and the oxidative stress marker nitrotyrosine which is indicative of NO inactivation by oxidative stress was increased (106). Subsequently, endothelial dysfunction as well as markers of atherosclerosis, were reported in patients with OSA (125-128). It was shown that in patients with OSA, free of co-morbidities or cardiovascular diseases, intima-media thickness was increased, and so were arterial plaque formation and calcified artery atheromas (117, 129-131). Additionally, treatments with nCPAP or a dental device improved some of these sub-clinical signs (47, 132, 133). Also, by using antioxidant treatments, endothelial function was improved in OSA (134, 135). Such findings with regard to endothelial dysfunction and atherosclerosis further support increased prevalence in cardiovascular morbidity in the setting of OSA.

7. CONCLUSION AND PROSPECTIVE

In recent years much has been learnt about the contribution of OSA to the development of cardiovascular morbidities. Yet the mechanisms underlying these associations are not entirely understood. It is well accepted by now that the cyclic nature of the multiple intermittent hypoxia episodes in OSA which resemble hypoxia/reoxygenation injury are responsible for inducing ROS production and oxidative stress, thus, damaging macromolecules and altering signaling pathways and normal cellular functions.

Specifically in OSA, ROS molecules affect inflammatory pathways by promoting leukocyte and endothelial cell activation. Such sequences were suggested to induce endothelial dysfunction and thereby enhance cardiovascular morbidities. However, not all patients with OSA develop cardiovascular complications. It is likely that some individuals differ in their response to a given hypoxia stimulus thereby variations in the responses of HIF-1alpha and NFkappaB pathways may occur. Thus, downstream gene patterns may differ between individuals. Altered balance in favor of adaptive pathways is likely to promote the development of some form of cardio-protective mechanisms such as ischemic preconditioning (in which, sequential sub-lethal doses of a given stimulus like IH - confer protection against a more lethal stimulus). This may induce coronary collateralization in some of the patients. Accordingly, in a recent study Steiner *et al.* showed that coronary collateralization was more developed in patients who had coronary artery disease and were also diagnosed with OSA, than in those patients with coronary artery disease but without OSA (136). Such collaterals may protect the myocardium from infarction and ischemia by providing alternative routes of blood supply to regions of the heart supplied by occluded coronary arteries. These

findings indicate on the presence of an adaptive mechanism in OSA patients (137) and may also explain some of the clinical observations regarding the age decline trends in mortality observed in OSA (17, 138). Undoubtedly, the potentially protective qualities of IH in OSA should be further explored since these may have important clinical implications for new treatment strategies. Thus, a better understanding of the mechanisms that induce cardiovascular morbidities in OSA may lead to new and more effective treatment modalities in order to prevent the cardiovascular risks associated with this prevalent morbidity.

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