Cardiovascular Morbidity in Obstructive Sleep Apnea

Oxidative Stress, Inflammation, and Much More

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Sleep-disordered breathing and obstructive sleep apnea (OSA) are highly prevalent disorders throughout the lifespan, which may affect up to 2–10% of the population, and have now been firmly associated with an increased risk for cardiovascular and neurobehavioral complications. Nevertheless, the overall pathophysiologic mechanisms mediating end-organ injury in OSA remain undefined, particularly due to the very frequent coexistence of other disease states, such as obesity, that clearly complicate the potential cause–effect relationships. Two major, and to some extent overlapping, mechanisms have been proposed to explain the morbid consequences of OSA, namely increased generation and propagation of reactive oxygen species and initiation and amplification of inflammatory processes. The evidence supporting the validity of these concepts as well as that detracting from such mechanisms will be critically reviewed in the context of clinical and laboratory-based approaches. In addition, some of the contradictory issues raised by such evaluation of the literature will be interpreted in the context of putative modifications of the individual responses to OSA, as determined by genetic variants among susceptibility-related genes, and also by potential environmental modulators of the phenotypic expression of any particular end-organ morbidity associated with OSA.

Keywords: inflammation; oxidative stress; reactive oxygen species; intermittent hypoxia; sleep fragmentation

The increasing prevalence of obstructive sleep apnea (OSA) across the lifespan has prompted attention to the morbid consequences of this rather frequent condition. Of particular interest, there has been quite conclusive epidemiologic data indicating that OSA is pathophysiologically linked to cardiovascular disorders, such as hypertension, ischemic heart disease, and cerebrovascular disease. Furthermore, when such conditions are preexisting, their clinical course and the progression of those conditions will be accelerated in the presence of coexisting OSA.

Despite the extensive body of literature linking OSA and cardiovascular disease, the mechanisms underlying this association remain incompletely identified. OSA-induced biological changes could involve any of the various physiologic disturbances associated with the disease, namely intermittent hypoxia, intermittent hypercapnia, sleep fragmentation, and intrathoracic pressure changes. Among these, intermittent hypoxia is most likely the preponderant factor causing the cardiovascular alterations that may manifest in patients with OSA. Indeed, patients with OSA may suffer from repeated episodes of hypoxia and normoxia, which are in many ways reminiscent of ischemia–reperfusion events, and are currently believed to promote the production of reactive oxygen species (ROS) and the promotion of oxidative stress (1–5), which in turn may adversely affect endothelial regulation through NO-mediated pathways (6). In addition, OSA has been implicated in the induction and propagation of inflammatory cascades that in turn can both promote and exacerbate atherogenesis and vascular dysfunction.

In this article, we briefly, yet critically, review the evidence supporting or refuting the existence of oxidative stress and inflammatory processes as the putative mechanisms linking the increased prevalence and severity of cardiovascular involvement to OSA. Whenever possible, we allude to studies in the pediatric population, because, in many ways, children are less likely to be "contaminated" by coexisting confounders, such as obesity, smoking, other comorbidities, and medications. We will further examine whether these assumptions can be validated by more rigorous experimental models, and ultimately propose a model that incorporates these concepts into a unifying paradigm (Figure 1).

Question 1: Is OSA Associated with Increased Systemic Oxidative Stress?

The evidence for increased oxidative stress in patients with OSA, although very attractive, is somewhat controversial. Barcelo and collaborators (7, 8) reported that thiobarbituric acid–reactive substance (TBARS) formation was higher in patients with severe OSA compared with healthy subjects, and that continuous positive airway pressure (CPAP) treatment improved the abnormal lipid peroxidation events. In another study of 114 patients, morning levels of TBARS and peroxides were also significantly higher in patients with OSA (with or without cardiovascular disease) compared with control subjects (9), and similar to Barcelo and colleagues' study (7), CPAP treatment decreased nocturnal levels of TBARS and peroxides in patients, and such beneficial effect has been more recently accomplished using mandibular prosthesis treatment of OSA (10). Of note, increased oxidized low-density lipoprotein levels were also detected in patients with OSA (11). Christou and colleagues (12) also found that the levels of diacron-reactive oxygen metabolites (i.e., the ability of transition metals to catalyze the formation of free radicals in the presence of peroxide, as monitored by oxidized alchilamine products) were elevated in the blood of 21 patients with OSA compared with control subjects. In two other recent studies, El-Sohl and coworkers showed that inhibition of xanthine oxidase by allopurinol led to improved endothelial function

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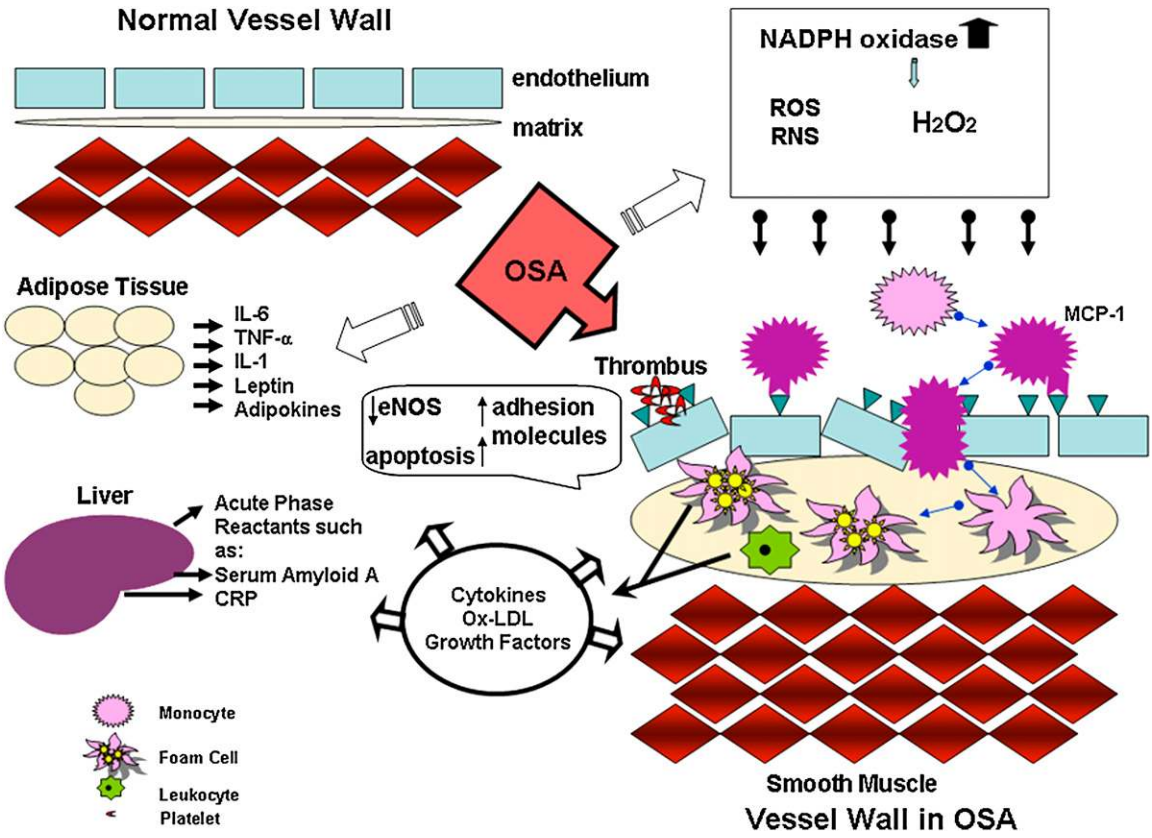

Figure 1. Schematic diagram illustrating putative alterations in the normal vessel wall with obstructive sleep apnea (OSA). OSA will induce activation of NADPH oxidase and increased formation of hydrogen peroxide (H_2O_2) as well as reactive oxygen (ROS) and nitrogen (RNS) species. OSA will also influence adipose tissue biological processes, and enhance the formation and release of cytokines such as interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis alpha (TNF-α), as well as promote the release of leptin and adipokines. In the liver, acute phase reactants such as serum amyloid A and C reactive protein (CRP) will be increasingly formed and released into the circulation. Circulating monocytes will be activated, express monocyte chemotactic protein 1 (MCP-1), and induce expression of adhesion molecules on the endothelial cell surface, while reducing the expression and activity of endothelial nitric oxide synthase (eNOS) and promoting endothelial cell apoptosis. Activated monocytes will migrate through disrupted endothelial cell tight junctional spaces into the vessel wall, where they will transform into activated macrophages, which in turn will internalize and accumulate fat, thereby becoming foam cells, the prototypic cell type of the initial atheromatous lesion. Furthermore, endothelial cells will also interact with platelets, and activate the initiation and propagation of thrombus formation, while signaling from all of these multiple cell populations will lead to increased proliferation of smooth muscle in the vessel wall.

in patients with OSA (13), whereas Grebe and colleagues improved endothelial function using supplemental vitamin C (14). Interestingly, the increased presence of glycation products, the end result of increased oxidative stress, was found in patients with OSA who had normal glucose homeostasis (15). Finally, the presence of oxidative DNA damage was suggested by Yamauchi and colleagues (16), who demonstrated that urinary 8-hydroxy-2′-deoxyguanosine excretion was significantly higher in patients with severe OSA versus control subjects (16).

The cellular antioxidant systems commonly used as defense mechanisms against free radicals can be altered in response to increased oxidative stress, and may therefore provide indirect cues as to the presence of the latter. Christou and collaborators (17) reported that the antioxidant capacity in the blood of 14 patients with moderate OSA was reduced compared with control subjects, when using the Trolox Equivalent Antioxidant Capacity assay. More recently, Barcelo and collaborators have reported their findings on the plasma levels of total antioxidant status; glutathione peroxidase; γ-glutamyltransferase; vitamins A, E, B12, and folate; and homocysteine in 47 patients with OSA and 37 healthy subjects. Although decreased total antioxidant status, vitamins A and E, and increased γ-glutamyltransferase levels were found in OSA, and improved after CPAP therapy, the other markers remained unchanged (8). In another recent study, Tan and colleagues showed that not only isoprostane serum levels were elevated in patients with OSA but that, despite similar lipid levels, high-density lipoprotein was dysfunctional (assessed by incubating plasma high-density lipoprotein with native low-density lipoprotein in the presence of dichlorofluorescein, which fluoresces on interaction with lipid oxidation products), particularly considering that 30% of these findings were accounted for by the severity of OSA (11). Taken together, results from all of the studies described previously indicate the occurrence of oxidative stress in systemic circulation of patients with OSA, which appears to impose an additional burden on the antioxidant systems.

However, it must be emphasized that not all of the studies have yielded such conclusive findings, particularly when patients with OSA have been carefully selected for the presence of other comorbidities that may lead to the existence of an underlying oxidative stress superimposed on OSA. Indeed, no significant differences in lipid peroxidation emerged among patients with OSA (18). In a study from our laboratory, we examined the levels of isoprostanes in the urine of a group of 47 young, otherwise healthy children, with and without sleep apnea, and found no evidence for a correlation between increased oxidative stress and

the severity of any of the OSA-related polysomnographic measures in these children (19). One of the potential explanations for the discrepant findings may reside in the patient selection methodology (inclusion or exclusion of patients with concomitant morbidities, such as obesity or diabetes, which are traditionally associated with oxidative pathophysiologic mechanisms), as well as in the overall severity and duration of the disease before testing. Indeed, when obese or overweight children with OSA were studied using serum uric acid as the biomarker for oxidative stress, significant correlations between disease severity and uric acid emerged (20). Furthermore, as shown by Jordan and colleagues, assessments of oxidative markers in serum may be methodologically insensitive or exhibit a great degree of circadian variability, and therefore multiple markers may need to be determined simultaneously to improve the robustness of the findings (21). Taken together, the data would support the assumption that OSA is indeed associated with increased oxidant stress and other associated responses that modulate inflammation and proliferation (22). Notwithstanding such considerations, the implications of such findings need to be integrated with the now considerable evidence supporting a major role for oxidative stress in the initiation and propagation of events that ultimately promote atherosclerosis and vascular dysfunction (23). Finally, a recent study by El Sohl and colleagues suggested that OSA is associated with increased endothelial cell apoptosis, and that the latter, which could be mediated by oxidative stress, correlates with the degree of vascular dysfunction (24). Although concerns were raised regarding the methodologies used in this latter study in subsequent letters to the editor, this article nevertheless provides the initial step toward exploration of endothelial cell loss as being involved in the vascular deficits seen in patients with OSA.

Question 2: Does OSA Affect NO-dependent Endothelial Function via an Oxidative Stress Mechanism?

One of the major consequences of OSA is the emergence of endothelial dysfunction, as evidenced by the presence of altered NO-dependent vasodilation responses in patients with OSA, and its reversal after effective implementation of treatment for OSA (6, 25–28). The reduced NO release from the endothelium appears to involve the down-regulation and uncoupling of endothelial NO synthase as well as the parallel increase in circulating levels of endogenous inhibitors of NO synthase, such as asymmetric NG-dimethylarginine (ADMA) (29–31). One of the potential mechanisms underlying the down-regulation of endothelial NO synthase expression and function involves oxidative stress, whereby the latter will readily modify the activity of endothelial NO synthase (32–35), and conversely, enhanced NO availability will attenuate oxidative stress and protect the endothelium as well as endothelial repair mechanisms, such as recruitment and proliferation of endothelial progenitor cells (36–39). Furthermore, the interaction between NO and free radicals, such as the superoxide anion, will lead to increased formation of peroxynitrite, and promote a variety of biological cascades that promote atherogenesis (40). Taken together, the cumulative evidence would point toward a reduction in NO availability in the context of OSA, and the latter has indeed been recently verified when measuring the exhaled alveolar NO fraction (41, 42)

Question 3: Is There Evidence for Increased Systemic Inflammation in OSA?

Increases in systemic oxidative stress are traditionally implicated in the activation of immune cells, which, in turn, are primary generators of ROS and inflammation. Following this assumption, Schultz and colleagues examined systemic inflammatory responses in 18 patients with OSA, and found markedly enhanced release of superoxide from stimulated polymorphonuclear neutrophils (measured by superoxide dismutase–inhibitable reduction of cytochrome *c*) compared with control subjects, and further showed that CPAP therapy resulted in decreased superoxide release (43). Studies from Dyugovskaya and colleagues have further elucidated potential immune mechanisms that appear to be activated by OSA. These investigators have based their approach on the premise that T cells play a significant role in atherogenesis, both through cytokine production and/or by directly contributing to vascular injury. They reported that CD4 and CD8 T cells of patients with OSA undergo phenotypic and functional changes, and acquire cytotoxic activity, with a shift in CD4 and CD8 T cells toward type 2 cytokine dominance and increased IL-4 expression. Conversely, IL-10 expression in T cells was negatively correlated with the severity of OSA, whereas tumor necrosis factor (TNF)-α was positively correlated with the apnea–hypopnea index. Furthermore, CD8 T cells of patients with OSA exhibited marked increases in TNF-α and CD40 ligand, and were particularly cytotoxic against endothelial cells. All these findings were markedly improved or reversed by treatment with CPAP (44–46). Elevated systemic TNF-α levels were found in OSA, and improved after treatment (47), whereas in contrast with such findings, no evidence of increased TNF-α levels was found in a large group of patients with OSA and control subjects (n = 155) (48), suggesting that the increased expression and activity of this cytokine may be restricted to localized effects within the endothelial surface. Notwithstanding these findings, a recent publication in the *Journal* (49) suggests that not only TNF-α levels are increased but they correlate with the degree of sleepiness and the severity of hypoxia (49). We have recently reported very similar findings in children with OSA (50), whereby TNF-α serum levels were not only elevated in a significant proportion of children with polysomnographic evidence of OSA but that the magnitude of TNF-α levels was primarily correlated with the degree of respiratory event–induced sleep fragmentation (50).

An important circulating marker of inflammation, C-reactive protein (CRP), which is produced in the liver through IL-6 activity, is one of the best predictors for future cardiovascular morbidity (28, 29), and directly participates in atheromatous lesion formation (51). Increased circulating levels of CRP have been rather consistently reported in both adults (52–65), as well as in children with OSA (66, 67), and are reduced on effective treatment (54, 68). However, similar to previous studies examining oxidative stress, some investigators have failed to identify CRP increases in OSA (69–74), suggesting that the determinants of CRP elevation in the presence of OSA cannot be exclusively accounted for the severity of the condition but are also dictated by multiple other circumstances. Among the latter, the presence of concurrent risk factors (e.g., obesity, medications, diabetes, cigarette smoking) may be indeed a major determinant of the variance in CRP responses. In fact, the interactions between the severity of OSA, lifestyle and environmental conditions, and genetically derived individual susceptibility have now been proposed as the major potential players involved in the magnitude of the oxidative stress and inflammatory responses associated with OSA (75, 76). Of interest, a recent study has identified the TNF-α −308 polymorphism as being associated with OSA, thereby linking inflammatory responses to the sleep-associated respiratory disturbance (77). Similarly, a recent study in the *Journal* indicates that decreases in CRP will occur with effective CPAP treatment of adult patients with OSA

in conjunction with an amelioration of the carotid intima-media thickness (78).

Expression of adhesion molecules on circulating monocytes may serve as yet another indication of the activation of systemic inflammation in OSA. Using 18 patients with moderate to severe OSA and 26 healthy control subjects, Dyugovskaya and colleagues found that OSA was associated with increased expression of adhesion molecules CD15 and CD11c, and increased adherence of monocytes in culture to human endothelial cells (44–46, 79). Similar findings regarding circulating levels of adhesion molecules and their down-regulation upon treatment have been reported by several groups of investigators in both adult and pediatric cohorts (80–83). Overall, these findings suggest that OSA elicits activation of cell–cell interactions involving the endothelial cellular substrate that, in turn, may promote atherogenesis, and that treatment of OSA is effective in reducing the systemic inflammatory responses, including those associated with generation of free radicals.

Question 4: Do Experimental Models Confirm the Presence of Increased Oxidative Stress and Inflammatory Responses?

Recent development of animal and cell-based models mimicking components of OSA has allowed for more systematic exploration of some of the mechanisms associated with end-organ dysfunction in patients with OSA (84–87). Although we are still far from gaining comprehensive insights into the most likely complex multiplicity of interactions occurring between the various cellular elements involved in the process of OSA-induced vascular disease, conclusive evidence now supports the observation that repetitive hypoxic events during sleep are associated with increased sympathetic activity and hypertension (88). Furthermore, episodic hypoxia appears to induce abnormal arteriolar function, possibly via altered NO release (89).

Recently, in a series of elegant *in vitro* experiments, Lattimore and colleagues showed that application of episodic hypoxia (IH) elicited increased cholesterol uptake by macrophages, one of the cardinal events associated with atherogenesis (90). Furthermore, IH during sleep induced marked alterations in lipid regulation in both obese and nonobese mice, a finding that is compatible with the notion of acceleration of atherogenesis (91, 92).

Similarly, when HeLa cells were exposed to IH, luciferase reporter assays uncovered a maladaptive process to the repeated hypoxic events, whereby hypoxia-inducible factor (HIF)-1α was not up-regulated (in contrast with sustained hypoxia); instead, there was a marked up-regulation of the transcriptional activity of nuclear factor (NF)-κB, a critical proinflammatory regulator (93). These findings were further reproduced *in vivo*, whereby mice exposed to IH demonstrated increased NF-κB activity and inducible NO synthase (a downstream gene) in monocytes and cardiovascular tissues (94). Of note, remarkably similar findings occur in the central nervous system, and indeed inducible NO synthase plays a mechanistic role in cognitive and neural deficits (95, 96). Thus, induction of cellular processes culminating in the activation and propagation of the inflammatory response appears to occur in response to IH. However, for the sake of completeness, some contradictory evidence has also emerged in regard to the absence of IH-induced changes on HIF-1α expression and activity. Indeed, IH appears to modify HIF-1α expression in the pheochromocytoma (PC)-12 cell line when exposed to IH, possibly through a calcium calmodulin kinase–dependent mechanism (97). Such changes in HIF-1α may be of importance for *in vivo* regulation of circulating triglycerides and in the modulation of inflammatory responses to IH, because transgenic mice with partial deficiency of HIF-1α developed no increases in IL-6 plasma levels when exposed to IH (98). Thus, considering the role of oxidative stress in the modulation of the proinflammatory activity of NF-κB and the antiinflammatory actions of HIF-1α (99), the stage is clearly ready for future studies aiming to assess the impact of such transcription factors on the cardiovascular system in the context of OSA.

The causal link between IH and oxidative stress is also gradually emerging from these *in vitro* and *in vivo* models (100). Indeed, increased production of ROS as elicited by IH may play a role in the sympathetic dysregulation traditionally seen in patients with OSA, possibly through increased efflux of catecholamines from the adrenal medulla (101). Furthermore, chronic exposures to IH in rats will increase cardiac muscle lipid peroxidation and left ventricular dysfunction (102). In both rats and mice, as well as in cell culture systems, IH is associated with evidence of oxidative stress and up-regulation of one of the key elements underlying the production of ROS, namely the expression and activity of NADPH oxidase (103–107). Indeed, virtually all types of vascular cells can produce $O_2^{\cdot}$ and H_2O_2, two of the most significant ROS in the vessel wall (108). Production of $O_2^{\cdot}$ occurs via the one-electron reduction of molecular oxygen, a reaction that is mediated by several enzymatic systems and the mitochondria. Among the enzymes capable of $O_2^{\cdot}$ production are xanthine oxidase and the NADPH oxidases, with the latter enzymes playing a critical role in ROS production within the vasculature (109, 110). $O_2^{\cdot}$ itself may directly impinge on vascular signaling cascades, but more importantly, can produce other reactive species. For example, the reaction of $O_2^{\cdot}$ with $NO^{\cdot}$ inactivates $NO^{\cdot}$, a primary regulator of vascular relaxation and vasodilation, causing the generation of peroxynitrite, which itself has deleterious consequences. Alternatively, dismutation of $O_2^{\cdot}$ by superoxide dismutase produces H_2O_2, a more stable ROS. H_2O_2 is implicated in the regulation of signaling pathways leading to vascular smooth muscle growth, contraction, migration, and inflammation (111, 112). Considering the rather extensive and intricate roles played by the NADPH oxidase family of enzymes in both inflammatory cell and vascular cell physiologic and pathologic states (113–116), we propose that the increased expression and activity of this enzyme in various end organs after IH is likely to play a major role in the cardiovascular morbidity associated with OSA.

Conclusions

In summary, the last decade has clearly allowed for rather extensive evidence to accumulate, and to justify our belief on the existence of a causative link between OSA and cardiovascular disease. However, the exact mechanisms for such association remain thus far elusive. Carefully conducted studies in the future, including well-randomized interventional trials, are likely to unravel the central role played by oxidative stress and inflammatory cascades in the end-organ injury associated with OSA. Although it is highly likely that no single gene will account for all the proposed processes involved in vascular dysfunction, we propose that the nature and magnitude of interactions between several cellular populations, namely the endothelium, platelets, T cells, and macrophages, will be key determinants in the extent and progression rate of the cardiovascular morbidity that can be ascribed to OSA. At the molecular level, altered NADPH oxidase expression and activity as induced by OSA will emerge as a key player in the deleterious cardiovascular consequences of OSA, and potentially provide therapeutic targets aiming to minimize the rather detrimental consequences of OSA. However, we should not forget the large array of proinflammatory genes, which are either activated or modulated in the various

cellular subsets by the increased transcriptional activity of NF-κB, AP1, HIF-1α, and possibly other transcriptional factors, and their interactions to potentially affect many other genes, including anti- and prooxidant systems; cellular survival, proliferation, and differentiation; and lipid metabolism and raft signaling. Furthermore, the potential interactions between gene polymorphisms (conferring individual susceptibility determinants), lifestyle components modulating overall end-organ vulnerability, and the phenotypic expression of OSA and its consequences will have to be identified and incorporated into future prediction schemes of morbidity risks associated with OSA.

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