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Forum Review

Oxidative Stress in Obstructive Sleep Apnea: Putative Pathways to the Cardiovascular Complications

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ABSTRACT

Obstructive sleep apnea (OSA) is a major public health problem because of its high prevalence in morbidity and mortality. A growing body of evidence suggests that OSA is an important risk factor for cardiovascular diseases. Although the mechanism for the initiation and aggravation of cardiovascular disease has not been fully elucidated, one theorized mechanism is intermittent hypoxia, which is produced by each sleep-disordered breathing event. This repeated hypoxia and reoxygenation cycle is similar to hypoxia–reperfusion injury, which initiates oxidative stress. Recent studies have suggested that OSA is associated with increased levels of oxidative stress or antioxidant deficiencies or both. Oxidative stress is involved in the activation of redox-sensitive transcription factors, which regulate downstream products such as inflammatory cytokines, chemokines, and adhesion molecules. This pathway may be able to explain the pathogenesis of atherosclerosis, a common pathologic factor underlying all types of cardiovascular disease. In addition, endothelial dysfunction derived from oxidative stress can contribute to cardiovascular diseases. This review summarizes current available evidence for and against the occurrence of oxidative stress in OSA and discusses the putative pathways initiating cardiovascular consequences associated with OSA. *Antioxid. Redox Signal.* 10, 755–768.

INTRODUCTION

OBSTRUCTIVE SLEEP APNEA (OSA) syndrome is a major public health problem, the prevalence of which has been estimated at ~5% of adults in Western as well as Asian countries (43, 140). OSA is characterized by repetitive episodes of complete or partial upper-airway obstruction occurring during sleep. Sleep apnea is terminated by a brief arousal from sleep, and ventilation resumes. By definition, apnea and hypopnea last a minimum of 10 sec. In general, the severity of OSA is measured by the apnea–hypopnea index (AHI). AHI is measured by the number of apnea–hypopnea events per hour of sleep. Disrupted and fragmented sleep induces excessive daytime sleepiness, deficits in cognitive performance, and mood disorders, which can lead to traffic accidents or other tragedies (1, 6, 66, 122, 139). Moreover, a number of studies have indicated that OSA is associated with an increased risk for cardiovascular diseases, including systemic hypertension (58, 76, 87), pulmonary hypertension (99), cardiac arrhythmia (68, 94), ischemic heart diseases (84, 85, 101), and stroke (24, 133).

Nasal continuous positive-airway pressure (CPAP) therapy for OSA was first reported in 1981 (111). Since then, it has become the most effective and widely used treatment for OSA. It treats apneas–hypopneas by providing air under positive pressure through a nasal mask, thus creating a pneumatic splint in the pharynx. This pneumatic splint prevents collapse of the pharyngeal airway. To date this is the only intervention for OSA shown to have a favorable impact on both cardiovascular and neurobehavioral morbidities (3, 22, 64). However, ~25–50% of patients with OSA will either refuse the offer of CPAP therapy or will not tolerate it (144). It is still unclear how those patients who refuse CPAP or patients who do not have excessive daytime sleepiness should be treated. Further, although some studies have demonstrated the long-term effects of CPAP on

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cardiovascular diseases or healthcare costs (19, 110, 118, 130), still more studies are needed to establish the evidence for the long-term effects of this treatment.

The physiologic changes that could affect cardiac systems in OSA include the consequences of repetitive apneas [*i.e.*, intermittent hypoxia, intrathoracic pressure changes, arousal (and therefore fragmented sleep), and sympathetic nerve activation] (59). Among these, intermittent hypoxia is proposed to be a major mediator of cardiovascular alterations. Each episode of apnea or hypopnea or both is usually followed by a marked decrease in arterial oxygen saturation, which rapidly normalizes after ventilation resumes.

This hypoxia–reoxygenation might be analogous to recurrent episodes of hypoxia–reperfusion injury. Hypoxia–reperfusion injury refers to damage that occurs after the restoration of blood flow to ischemic or hypoxic tissue. This reoxygenation/reperfusion phase is thought to result in the production of reactive oxygen species (ROS). ROS are highly reactive molecules that can damage cells and promote oxidative stress. A number of studies have shown that markers of oxidative stress are associated with OSA (54, 113), thus suggesting that some features of hypoxia–reperfusion injury are present when the model is one of repetitive episodes of hypoxia–reoxygenation.

Over the past decade, a deeper understanding of the contribution of inflammation and the immune response to the pathogenesis of atherosclerosis, which is the common pathologic factor underlying cardiovascular diseases, has led to it being redefined as an inflammatory process (29, 62). Activation of the redox-sensitive transcription factor and gene expression that regulate this inflammatory process may participate in the development of atherosclerosis (54). In general, a structural change in the arterial wall for atherosclerosis is evaluated by the measurement of intima–media thickness. Functional impairment in the arterial wall, called endothelial dysfunction, as described by Ross (92), is a decrease in vasodilation and potentiated vasoconstriction, leading to compensatory reactions that alter the normal homeostatic properties of the endothelium. Further, endothelial dysfunction is known to be caused by oxidative stress and to precede or accelerate the development of atherosclerosis. Recent studies have indicated that carotid artery intima–media thickness, as well as endothelial dysfunction, is associated with OSA (2, 4, 15, 23, 26, 44, 49, 72, 75, 105, 112, 117).

In this review, we summarize currently available information on the evidence for the association between oxidative stress and OSA. Further, we discuss the putative pathways to cardiovascular complications, which involve oxidative stress, and therapies directed at opposing oxidative stress. These therapies may be a potential strategy for intervention in the large population of OSA patients who do not tolerate CPAP therapy.

EVIDENCE FOR OXIDATIVE STRESS IN OSA PATIENTS

Oxidative stress is caused by an imbalance between the production of ROS and antioxidant activity that is important for the detoxification of these molecules. Therefore, elevated production of ROS and reduced antioxidant capacity can indicate the presence of oxidative stress. Many markers indirectly indicate the presence of oxidative stress. These markers include lipid peroxidation products, oxidized protein, and oxidative DNA damage. Susceptibility to *in vitro* addition of oxidants in biologic samples has also been used to estimate the occurrence of oxidative stress (113). With methods, a number of studies have investigated the relation between OSA and oxidative stress.

A few studies have failed to show increased oxidative stress in OSA patients. *In vivo* studies by Wali *et al*. (129) did not show differences in the susceptibility of LDL to oxidative stress or in antioxidants such as glutathione peroxidase and catalase activities in red blood cells between OSA patients and controls. Ozturk *et al*. (81), by evaluation of glutathione, lipid peroxidation concentration, and osmotic fragility of red blood cells, also recently failed to support the notion of increased oxidative stress in OSA patients. Both of these studies had a small number of OSA patients, using only 15 and six each. More recently, Svatikova *et al*. (114) measured the plasma indices of lipid peroxidation, although the sample size was not large. These indices of lipid peroxidation were evaluated with oxidized LDL and thiobarbituric acid–reactive substance (TBARS), and isoprostanes, produced by free radical–induced peroxidation of arachidonic acid. This failed to detect any difference between 41 moderate to severe OSA male patients without other diseases and 35 matched controls.

Comparatively, many studies have produced supportive evidence for the presence of oxidative stress in OSA patients. Christou *et al*. (20) measured diacron-reactive oxygen metabolites (D-ROM). D-ROM indicates the ability of transition metals to catalyze the formation of free radicals in the presence of peroxide, which are trapped by an alchialamine. The data showed that the level of D-ROM was higher in OSA patients ($n = 21$) compared with controls ($n = 5$). Moreover, D-ROM value was linearly correlated with AHI.

Barcelo *et al*. (9) reported that the plasma levels of oxidized LDL, which was evaluated by TBARS and LDL susceptibility to oxidation, were increased in 14 male OSA patients compared with 13 healthy controls. Further, Barcelo *et al*. showed that >1 year of CPAP use reduced the susceptibility of LDL to oxidation in OSA patients.

Lavie *et al*. (57) demonstrated that morning plasma levels of TBARS and peroxides were significantly increased in the 114 OSA patients with or without cardiovascular diseases, compared with 30 nonapneic controls. Lavie *et al*. went on to show that CPAP treatment for 9 months significantly decreased TBARS and peroxides in five patients.

Carpagnano *et al*. (16) measured 8-isoprostanes in exhaled breath condensate and venous blood in 18 OSA patients and 12 healthy age- and weight-matched controls. Concentrations were significantly higher in the OSA group than in controls, and 8-isoprostanes in exhaled breath condensate were reduced by 2 days of CPAP treatment.

A recent study from our group also demonstrated that urinary excretion of 8-hydroxy-2′-deoxyguanosine (8-OHdG), which is a DNA base modified by oxidants, was significantly higher in patients with severe OSA (AHI $\geq$ 30) compared with nonsevere OSA. Notably, the best predictor for 8-OHdG was the oxygen desaturation index rather than AHI, arousal index, or the duration of oxygen saturation below 90%. Although AHI and the respiratory disturbance index (RDI) are common parameters used to assess

the severity of sleep-disordered breathing (SDB), these indices reflect various components of SDB. This is the case, as the definition of hypopnea includes desaturation or *arousal*. In the situation of desaturation, this study suggests that intermittent hypoxia can play a key role in oxidative stress (134).

By comparison, few studies indicate reduced antioxidant activity in OSA. One is a study by Christou *et al*. (21), which showed lower values for antioxidant capacity in the venous blood samples of patients with severe OSA. The level of antioxidant capacity was evaluated with the Trolox Equivalent Antioxidant Capacity (TEAC) assay.

More recently, Barcelo *et al*. (7) indicated decreased plasma levels of total antioxidant status (TAS), antioxidant vitamins A and E, and increased values of γ-glutamyltransferase (GGT) in 47 patients with OSAS compared with 37 healthy subjects. This was theorized to lead to impairment of protective systems for oxidative stress. CPAP treatment for 12 months normalized some of those values.

A limited number of studies in OSA have indicated the presence of oxidative stress directly with ROS production in inflammatory leukocytes. Schulz *et al*. (103) demonstrated increased superoxide production by neutrophils obtained from OSA patients after stimulation with the bacterial tripeptide formylmethionylleucylphenylalanine (fMLP) and the calcium ionophore A23. Effective CPAP therapy led to a rapid and long-lasting decrease of superoxide release by these neutrophils.

Dyugovskaya *et al*. (25) demonstrated increased phorbol myristate acetate (PMA)-dependent ROS production by CD64+ or CD11c+ monocytes and granulocytes from OSA patients. Furthermore, CPAP treatment was associated with decreased basal ROS production in CD11c+ monocytes.

Although some studies questioned the presence of oxidative stress in OSA, most studies supported it. As summarized in Table 1, these controversial results may be caused by the difference in the adoption of SDB parameters. Most of the studies referenced in Table 1 used AHI (or RDI) as a SDB param-

Table 1. Sleep Parameters from References Demonstrating the Association between OSA and Oxidative Stress

Authors (reference no.)	*Sample size*	*Sleep disordered parameters*	*Definition for hypopnea*
Wali et al.* (129)	15 OSA 6 controls	AHI, % time with SpO2 $<$ 85%	Not mentioned
Ozturk et al.* (81)	6 OSA 10 controls	AHI, % time with SpO2 $<$ 90% lowest SpO2	Airflow reduction + arousal and/or 4% desaturation
Svatikova et al.* (114)	41 OSA 35 controls	AHI, arousal index	Not mentioned
Christou et al. (20)	21 OSA 5 controls	AHI, % time with SpO2 $<$ 90%, mean SpO2, lowest SpO2	Reduction f RIP amplitude $\geq$50%
Barcelo et al. (9)	14 OSA 13 controls	AHI, mean SpO2, mean nadir SpO2	Not mentioned
Lavie et al. (57)	114 OSA 30 controls	RDI, % time with SpO2 $<$ 90%, minimum SpO2	Not mentioned
Carpagnano et al. (16)	18 OSA 12 controls	AHI, ODI, % time with SpO2 $<$ 90%,	Reduction of airflow and/or respiratory movements + arousal and/or 3% desaturation
Yamauchi et al. (134)	70 severe OSA 56 non-severe OSA	AHI, apnea index, arousal index, ODI, % time with SpO2 $<$ 90%, mean nadir SpO2	Reduction of RIP amplitude $\geq$50%
Christou et al. (21)	17 OSA 8 controls	AHI, % time with SpO2 $<$ 90%, mean SpO2, lowest SpO2	Reduction of respiratory amplitude + arousal and/or 3% desaturation
Barcelo et al. (7)	47 OSA 37 controls	AHI, mean SpO2	Airflow reduction + arousal and/or 4% desaturation
Schulz et al. (103)	18 OSA 10 controls	AHI, % time with SpO2 $<$ 90%, mean SpO2, lowest SpO2	Reduction of RIP amplitude $\geq$50%
Dyugovskaya et al. (25)	18 OSA 31 controls	RDI	Not mentioned

*Negative study, RIP: respiratory inductance plethysmograph.

eter. As mentioned previously in this section, AHI may represent the severity of SDB, but AHI may also represent several other physiologic changes associated with OSA (Fig. 1). Investigators have hypothesized that the intermittent hypoxia associated with OSA is a crucial factor in oxidative stress; however, AHI does not necessarily reflect intermittent hypoxia alone. The oxygen desaturation index rather than AHI might be adequate as an indicator for the severity of intermittent hypoxia. As shown in Fig. 1, intermittent hypoxia may or may not be a component of OSA as defined under the rubric of the AHI and RDI.

EVIDENCE FOR OXIDATIVE STRESS FROM ANIMAL MODELS OF INTERMITTENT HYPOXIA

As mentioned previously, the physiologic changes that affect the cardiac systems in OSA patients include intermittent hypoxia, intrathoracic pressure changes, fragmented sleep, and sympathetic nerve activation. However, it is not easy to examine the influence of these changes individually in human studies. In contrast, animal models or *in vitro* studies of intermittent hypoxia can focus on the cardiovascular changes present in OSA due to only intermittent hypoxia. It is helpful to examine the pathophysiology associated with intermittent hypoxia and its impact on the cardiovascular system without the other factors additionally present in OSA.

A limited number of studies showed the presence of intermittent hypoxia-induced oxidative stress on the cardiovascular system. Campen *et al*. (13) and Joyeux-Faure *et al*. (46) indicated that chronic intermittent hypoxia in mice resulted in mild to moderate systemic and pulmonary hypertension, in addition to increased myocardial damage; although they did not assess the level of oxidative stress.

Chen *et al*. (17) demonstrated that chronic intermittent hypoxia–exposed rats exhibited increased levels of myocardial lipid peroxides, decreased superoxide dismutase in left ventricles, and myocardial dysfunction.

In addition, neurologic behavior disorders may result from hypoxia–reoxygenation. Row *et al*. (93) demonstrated impairment of spatial learning associated with higher levels of lipid peroxidation and isoprostane concentrations in the brain tissue of rats that were exposed to intermittent hypoxia. Furthermore, pretreatment with the antioxidant PNU-101033E reduced the intermittent hypoxia-induced oxidative stress as well as impairment of spatial learning.

Xu *et al*. (132) demonstrated a significant increase in ROS production in the mouse brain cortex and cortical neuronal cells. This was detected by fluorescent oxidation assays on exposure of the mice to chronic intermittent hypoxia, followed by increased expression of the oxidative stress response markers, c-Fos, c-Jun, and NF-κB, in the mouse brain cortex. Furthermore, transgenic mice over expressing Cu, Zn-superoxide dismutase exposed to chronic intermittent hypoxia conditions had a lower level of steady-state ROS production and reduced neuronal apoptosis in the brain cortex compared with that of normal control mice.

Zhan *et al*. (142) showed that long-term intermittent hypoxia increased the expression of the NADPH oxidase gene and protein responses in wake-active mouse brain regions. Both transgenic absence and pharmacologic inhibition of NADPH oxidase activity conferred resistance to not only long-term hypoxia/reoxygenation hypersomnolence, but also to carbonylation, lipid peroxidation injury, and the proinflammatory response, including inducible nitric oxide synthase activity (iNOS).

Veasey *et al*. (124) indicated that long-term intermittent hypoxia increased total sleep time and reduced sleep latency in mice. This was apparently caused by increased oxidative injury detected by elevated isoprostane, protein carbonylation, nitration, and induction of antioxidant enzymes glutathione reductase and methionine sulfoxide reductase in wake-promoting regions of the basal forebrain and brainstem.

In summary, these studies present evidence that oxidative stress caused by intermittent hypoxia affects both the cardiovascular system and neurologic behavior. However, several key questions remained unanswered. For instance, the severity and length of intermittent hypoxia varies between studies. This produces a confound, in that it remains unknown what effect differing protocols are likely have on these matters. Figure 2 shows the intermittent-hypoxia paradigm in these studies and presumable ODI (or AHI). Further, it is still unclear which kind of intermittent hypoxia is most important to which organ damage. What is needed in this area is a set of studies or a single study linking specific lengths and severities of intermittent hypoxia to specific disease.

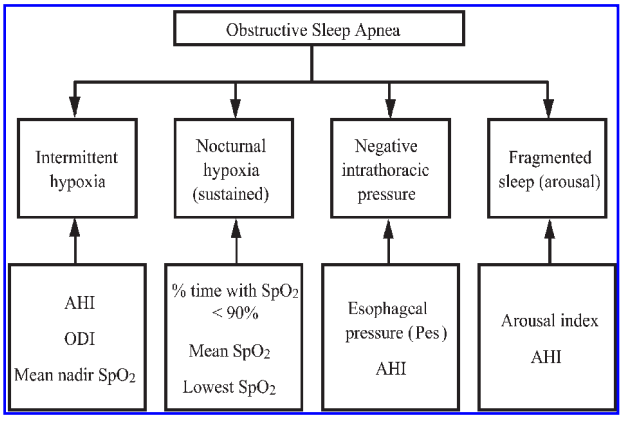

FIG. 1. OSA-related physiologic changes and associated sleep-disordered breathing parameters. AHI, apnea–hypopnea index; ODI, oxygen desaturation index.

Activation of redox-sensitive transcription factor

The production of ROS is associated with a differential expression of specific genes. These genes are regulated by the activation of redox-sensitive transcription factors such as nuclear factor kappa B (NF-κB) and hypoxia-inducible factor-1 (HIF-1). Recently, some studies have focused on the association between the activation of these transcription factors and OSA or intermittent hypoxia.

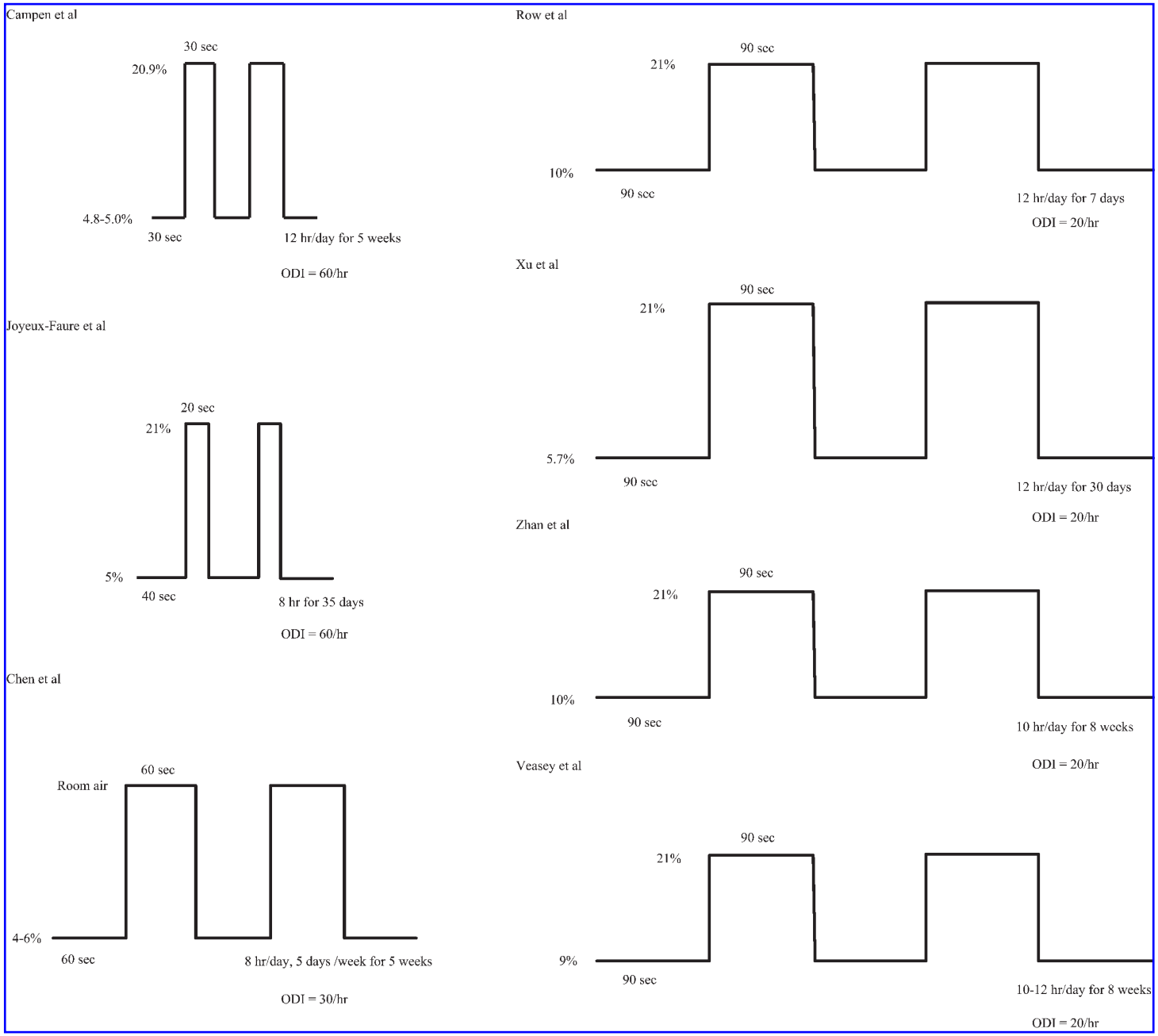

FIG. 2. Paradigm for intermittent hypoxia in each study.

NF-κB. NF-κB is activated by many stimuli, including cytokines, activators of protein kinase C, viruses, and oxidants. This transcription factor acts on many genes for proinflammatory cytokines, chemokines (chemotactic cytokines that attract inflammatory cells to sites of inflammation), enzymes that generate mediators of inflammation, immune receptors, and adhesion molecules. The proinflammatory cytokines include tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, IL-2, IL-6, and macrophage colony-stimulating factor (M-CSF). Chemokines include IL-8 and monocyte chemoattractant protein-1 (MCP-1). Inflammatory enzymes include iNOS and inducible cyclooxygenase-2. Immune receptors include IL-2 receptor (α chain) and T-cell receptor (β chain). Adhesion molecules include intercellular adhesion molecule 1 (ICAM-1), vascular-cell adhesion molecule 1 (VCAM-1), and E-selectin. These products play a key part in the initial recruitment of leukocytes to sites of inflammation. Furthermore, some of these products, like TNF-α and IL-1β, also cause the activation of NF-κB. This type of positive regulatory loop may amplify and perpetuate local inflammatory responses (10).

In an *in vitro* model of intermittent hypoxia, Ryan *et al*. (97) used HeLa cells (an epithelial cell line) exposed to intermittent hypoxia to show that they exhibit activation of NF-κB. The *in vivo* effect of prolonged intermittent hypoxia exposure on the activation of NF-κB and related clinical studies had not been recorded in the literature until 2005.

In a recent study from our group, we measured the activation of NF-κB, which is evaluated by levels of nuclear p65 concentration in peripheral blood monocytes, extracted from OSA patients. Activation of NF-κB was significantly higher in OSA patients compared with healthy controls. Moreover, short-term CPAP treatment has been shown to reduce NF-κB activation (135).

In the same year, Htoo *et al*. (39) showed increased activation of NF-κB in neutrophils extracted form peripheral blood in OSA patients. In addition, Greenberg *et al*. (31) demonstrated that chronic intermittent hypoxia activated NF-κB in cardiovascular tissues including the aorta, heart, and lungs of mice. Further, activation of NF-κB was accompanied by increased cardiovascular expression of iNOS protein. In the same study, Greenberg *et al*. also showed higher levels of NF-κB activation in the monocytes of OSA patients, and 1-month CPAP treatment reduced NF-κB activation (31).

HIF-1. The transcriptional factor HIF-1 is a master regulator in oxygen homeostasis, controlling multiple physiologic processes and regulating the expression of hundreds of genes. HIF-1 regulates vascular endothelial growth factor (VEGF) and its receptor FLT-1, iNOS, α1B-adrenergic receptor, endothelin-1, heme oxygenase, and erythropoietin (38, 63, 106). Most of those products play an important role in endothelial function and the tissue-repair process during inflammation. Evidence exists for associations among OSA and HIF-1–mediated products such as VEGF (41, 56, 102, 116) and endothelin-1 (28, 88, 98). However, the association between HIF-1 activation and intermittent hypoxia has not been confirmed by *in vitro* studies.

Ryan *et al*. (97) failed to detect the activation of HIF-1 by using intermittent hypoxia–exposed Hela cells. Contrary to this, Yuan *et al*. (141) demonstrated the activation of HIF-1 by intermittent hypoxia with PC12 cells. An *in vivo* study performed by Peng *et al*. (86) demonstrated elevated levels of HIF-1α expression in the cerebral cortex of mice exposed to intermittent hypoxia. However, no study directly demonstrated the upregulation of HIF-1 in OSA patients. This may be due to the difficulty in measuring the levels of HIF-1. Additionally, it may be that HIF-1 is more sensitive to activation by sustained hypoxia than intermittent hypoxia.

Taken together, these findings suggest that oxidative stress caused by OSA-induced intermittent hypoxia activates NF-κB. Although better evidence for HIF-1 activation in OSA must be collected, it is speculated that HIF-1 is activated in OSA, as its downstream proteins are confirmed to be elevated. These activated transcription factors induce inflammatory responses in the arterial wall and impair endothelial function, leading to cardiovascular consequences in OSA.

ATHEROSCLEROSIS AS AN INFLAMMATORY DISEASE AND OSA

Atherosclerotic lesions are asymmetric focal thickening of arterial intima. These lesions consist of cells, connective tissue elements, lipids, and debris. Blood-borne inflammatory and immune cells constitute an important part of an atheroma, the remainder being vascular endothelial and smooth muscle cells. The atheroma is preceded by a fatty streak, an accumulation of lipid-laden cells beneath the endothelium. Most of the cells in this fatty streak are macrophages, together with some T cells (35). Recently, many studies demonstrated an independent relation between OSA and the carotid artery intima–media thickness (2, 4, 23, 72, 105, 112, 117).

Inflammation plays an important role in all stages of atherosclerosis, a common pathologic factor underlying many types of cardiovascular disease. A brief summary of the review by Libby *et al*. (62) follows (a full description of the putative process underlying atherosclerosis is beyond the scope of this work).

Blood leukocytes bond poorly to the endothelium. This changes when the endothelial monolayer becomes inflamed. Once inflamed, activated endothelial cells express several types of leukocyte adhesion molecules.

Examples of leukocyte adhesion molecules included in this process are VCAM-1 and selectin, which cause blood cells rolling along the vascular surface to adhere to the site of activation. Once stuck to the endothelium, the leukocytes penetrate into the intima. Chemoattractant molecules are responsible for this transmigration. For instance, MCP-1 appears responsible for the direct migration of monocytes into the intima at lesion-site formation. Once within the arterial wall, the blood-derived inflammatory cells take part in and maintain a local inflammatory response. The macrophages express scavenger receptors targeted at lipoproteins. The resultant ingestion of lipid causes the macrophages to become foam cells.

As this self-perpetuating inflammatory process continues, the activated leukocytes and arterial cells can secrete cytokines such as interferon-γ, IL-1, TNF-α, and growth factors. These cytokines, in turn, can promote migration and proliferation of arterial smooth muscle cells. Medial arterial smooth muscle cells express enzymes, which are specialized in that they can degrade

the elastin and collagen in response to inflammatory stimulus. This breakdown of the arterial extracellular matrix permits the penetration of the arterial smooth muscle cells through the elastic laminae and collagenous matrix of the growing plaque. During this process, many kinds of mediators are involved, many of which are regulated by NF-κB. These mediators, again as described in Libby *et al*. (62) have been measured in a great number of studies involving patients with OSA.

Although it remains unclear whether the circulating levels of adhesion molecules accurately reflect the adhesion molecules attached to the endothelium, circulating levels of ICAM-1, VCAM-1, L-selectin, and E-selectin tend to be elevated in patients with OSA. CPAP treatment has been shown to decrease the level of ICAM-1 and E-selectin (18, 78, 79). One study investigating the expression of adhesion molecules in monocytes of OSA patients was published in 2002 (25). In this study, increased expression of CD15 (the counterreceptor for selectins on endothelial cells) and CD11c (counterreceptor for ICAM-1 on endothelial cells) was detected, and those expressions were significantly decreased with CPAP treatment.

Among many inflammatory cytokines, TNF-α, IL-6, and C-reactive protein (CRP) have been examined in OSA. CRP has emerged as one of the important serum markers of systemic inflammation. CRP is synthesized by the liver and regulated by cytokines, particularly IL-6, and identified as one of the risk factors of future cardiovascular disease (11, 12, 89–91, 107). In addition, recent studies suggested that CRP itself may contribute to the development of atherosclerosis through leukocyte activation and endothelial dysfunction (82, 83, 125, 137, 145).

Ryan *et al*. (95) recently measured serum CRP level in 110 subjects after polysomnography. CRP level was associated with obesity, but not the severity of OSA. Further, 6 weeks of CPAP treatment did not reduce the CRP level. In addition, three studies, one by Kobayashi *et al*. (51) with 35 severe OSA patients and 16 control subjects; another, by Guilleminault *et al*. (32) with 239 subjects (156 OSA patients, 39 UARS patients, and 54 controls); and another by Kaditis *et al*. (47) with 141 children failed to find any relation between OSA and serum CRP levels.

Contrary to these results, a number of studies (ranging in sample size from 22 to 316 subjects) successfully indicated significant association between OSA and circulating CRP levels in adults as well as children and adolescents, and decreased CRP levels with CPAP treatment (14, 36, 53, 71, 72, 108, 119, 136, 138, 143).

Although these studies were well performed, they have led to largely contradictory results, most likely due to the entanglement of obesity, CRP, and OSA. What is needed to resolve and fully understand the relation between obesity, CRP, and OSA is a large study capable of measuring all three variables at once. Through this study, which would best be performed under case–control methods and with a large sample size, we could quantify the relation between the variables, thus showing how they interact.

Plasma or serum levels of TNF-α and IL-6 are increased in patients with OSA (51, 72, 96, 126, 138). Minoguchi *et al*. (70) investigated serum levels of TNF-α, as well as spontaneous production of TNF-α by monocytes, and found that both were significantly higher in patients with moderate-to-severe OSA than in healthy obese controls and patients with mild OSA. Further, in patients with moderate-to-severe OSA, treatment with CPAP for 1 month significantly improved sleep quality and decreased spontaneous production of TNF-α by monocytes and serum levels of TNF-α.

Recently, we investigated the activation of NF-κB and TNF-α production in peripheral blood monocytes of OSA patients. NF-κB activation and TNF-α production were significantly higher in nine OSA patients than in seven control subjects, and those values were decreased by 1 night of CPAP therapy. Our findings suggest that the inflammatory cascade involving NF-κB and its downstream production of pro-inflammatory cytokines is one possible pathway for pathogenesis of arthrosclerosis (135).

In addition, circulating levels of chemokines, IL-8, and MCP-1 have been reported as increased in OSA patients (36, 79, 96). OSA also is reported to be associated with elevated levels of matrix metalloproteinase-9 (MMP-9), which is thought to be activated by oxidative stress, and induces the degradation of the fibrous cap, plaque instability, and plaque rupture (120).

In summary, many kinds of mediators are regulated by NF-κB. These mediators are involved in the pathogenesis for the cardiovascular consequences of OSA. This inflammatory process seems to be quite important, as it appears to be one of the major pathways for atherosclerosis and, in turn, a variety of cardiovascular diseases (Fig. 3).

ENDOTHELIAL DYSFUNCTION IN OSA

Endothelial dysfunction that is caused by physical and biochemical stimuli precedes or accelerates the development of atherosclerosis (92) and also is considered to be a predictor for future cardiovascular diseases (127). Endothelial dysfunction is characterized by decreased vasodilation and potentiated vasoconstriction, and used to refer to an impairment of endothelium-

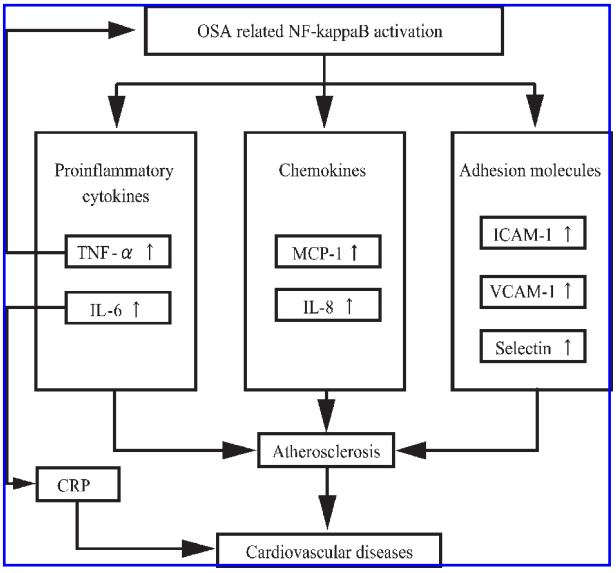

FIG. 3. Putative pathways to cardiovascular diseases associated with NF-κB activation in OSA.

dependent vasorelaxation caused by a loss of nitric oxide (NO) bioactivity in the vessel wall. One of the mechanisms for reduced availability of NO is that the production of ROS rapidly reacts with NO and contributes to NO deficiency. Therefore, oxidative stress derived from intermittent hypoxia may affect endothelial dysfunction.

Impairment of endothelium-dependent vasodilation has been reported in OSA. Carlson *et al*. (15) showed that endothelial function in forearm resistance vessels was impaired in OSA patients when compared with healthy subjects. Kato *et al*. (49) reported that patients with sleep apnea had a blunted vasodilation response to acetylcholine (acetylcholine is a vasodilator that stimulates endothelial release of nitric oxide) in the forearm, in comparison with carefully matched obese non-OSA subjects. Recently, these findings were confirmed in a large community-based sample of generally healthy older individuals (75).

With ultrasound Doppler methods, impairment of flow-mediated vasodilation (FMD) in the brachial artery was also reported to correlate with sleep-disorder parameters. Further, CPAP treatment or xanthine oxidase inhibition with allopurinol improved FMD (26, 44).

Several studies on circulating levels of NO measured as serum nitrites and nitrates demonstrated that circulating NO is lower in OSA patients and that this can be improved by use of CPAP (42, 55, 104, 121). Taken together, ROS-induced reduction of NO might be one of the pathways to cardiovascular complications in OSA patients.

HIF-1–mediated products such as VEGF and endothelin-1 also contribute to endothelial dysfunction. VEGF regulates multiple endothelial cell functions including mitogenesis, vascular permeability, and vascular tone. Serum and plasma levels of VEGF were elevated in OSA patients, and CPAP treatment reduced VEGF levels (41, 56, 102, 116).

Endothelin-1 is composed of vasoactive peptides, which include potent vasoconstrictors and are produced by endothelial cells. Recently, Gjorup *et al*. (28) reported that the night-time serial determinations of plasma endothelin-1 and blood pressure were significantly higher in OSA patients ($n = 32$) than in healthy controls ($n = 19$). Prior studies also supported these results (88, 98).

METABOLIC DYSREGULATION IN OSA

Many studies demonstrated the independent association with metabolic dysregulation including insulin resistance, diabetes mellitus, and hyperlipidemia in OSA. These studies are well summarized in the recently published review (67). Metabolic dysregulation in OSA is associated with cardiovascular disease, and oxidative stress should be involved in this relation.

Hyperlipidemia has been reported as being related to oxidative stress when evaluating the endothelial superoxide anion production, serum levels of oxidative stress marker (8-OHdG) (65, 77, 100). Moreover, recent animal studies have shown that intermittent hypoxia induced hyperlipidemia and lipid peroxidation in the lean C57BL/6J mouse (60, 61).

Hyperglycemia increases the production of ROS inside many cells including the vascular endothelial cell. This oxidative stress is implicated in the progression of long-term diabetes complications, including microvascular and macrovascular dysfunction. Furthermore, oxidative stress has been proposed as the root cause underlying the development of insulin resistance, pancreatic beta-cell dysfunction, and impaired glucose tolerance (33, 48, 69, 131). A recent animal study shows that intermittent hypoxia caused insulin resistance in lean C57BL/6J mice and that this occurred independent of activation of the autonomic nervous system (40).

Therefore, intermittent hypoxia–induced oxidative stress in OSA might contribute the initiation and/or aggravation of diabetes mellitus or hyperlipidemia as well as the metabolic dysregulaton–derived vascular complications.

HOMOCYSTEINE LEVELS IN OSA

Homocysteine is an intermediate product in the metabolism of one of the essential amino acids, methionine. Hyperhomocysteinemia causes endothelial dysfunction through various mechanisms, such as increased production of ROS, decreased release of NO, and alterations in the expression of several genes in endothelial cells. Many clinical and epidemiologic studies confirm the observation that mild elevation in total plasma homocysteine confers an increased risk for peripheral arterial occlusive disease, coronary artery disease, and cerebrovascular disease. This risk is similar to other conventional risk factors such as hyperlipidemia or smoking (54).

In patients with OSA, it is not clear whether homocysteine levels are associated with sleep-disordered breathing. Svatikova *et al*. (115) measured plasma homocysteine concentrations in 32 OSA patients without any coexisting disease and 44 closely matched controls. Their results showed that homocysteine levels were not elevated in OSA subjects. Moreover, the diurnal variation of homocysteine levels was preserved in OSA patients and not influenced by CPAP treatment. Therefore, they concluded that homocysteine *per se* is unlikely to contribute to cardiac and vascular morbidity in otherwise healthy OSA patients. Although Lavie *et al*. (54) found increased levels of homocysteine in OSA patients with concurrent ischemic heart disease, they also demonstrated that the plasma levels of homocysteine in OSA patients without comorbidities were similar to those of normal controls.

In contrast to these results, Jordan *et al*. (45) showed reduced homocysteine levels with CPAP treatment. Further, Kokturk *et al*. (52) showed that OSA patients with cardiovascular diseases (hypertension or ischemic heart disease or both) had significantly higher levels of homocysteine when compared with OSA patients without cardiovascular diseases and with non-OSA patients with cardiovascular diseases. Moreover, the levels of homocysteine in OSA patients without cardiovascular diseases were higher than those in non-OSA patients with cardiovascular diseases, and serum homocysteine levels were independently associated with the severity of OSA. More recently, similar results were reported by Can *et al*. (14). These three studies successfully indicated elevated homocysteine associated with OSA. However, the mechanisms for homocysteine regulation in OSA have not been fully expounded.

Thus far, although homocysteine and OSA share many common pathophysiologic pathways inflicting damage to the car-

diovascular system, larger-sample-size studies involving OSA patients without any coexisting diseases and carefully matched healthy controls will be needed to elucidate the relation between homocysteine and OSA.

ANGIOTENSIN II IN OSA

Angiotensin II, the principal product of the renin–angiotensin system and a potent vasoconstrictor, induces superoxide anion production by NADPH oxidases of the vasculature.

Moller *et al*. (74) showed elevated plasma levels of angiotensin II in 24 OSA patients compared with 18 controls, and 14 months of CPAP treatment decreased angiotensin II levels as well as blood pressure. Takahashi *et al*. (116) showed increased serum levels of angiotensin II and VEGF in OSA patients compared with controls. They also demonstrated that an angiotensin II receptor type 1 blocker inhibited angiotensin II–induced enhancement of VEGF *in vitro*. Angiotensin-converting enzyme (ACE) is a zinc metallopeptidase, and its main functions are to convert angiotensin I into angiotensin II and to inactive bradykinin. Barcelo *et al*. (8) demonstrated that ACE activity was higher in OSA than in healthy controls; this suggests higher levels of angiotensin II in OSA.

Although it is not clear how OSA induces elevated levels of angiotensin II or ACE activity, angiotensin II seems to be related to OSA and involved in the mechanisms for OSA-induced cardiovascular consequences. Furthermore, blocking the angiotensin II action with an ACE inhibitor or angiotensin II–receptor antagonist might be an effective treatment for the future cardiovascular diseases associated with OSA.

THE EFFECTS OF ANTIOXIDANT THERAPY

Antioxidant intake can be effective in treating oxidative stress–induced organ damage. Oxidative stress emerges when free radical production overwhelms the antioxidant systems. Higher levels of antioxidants have been shown to lead to lower stroke incidence (128) and reduced incidence of coronary heart disease (50).

Folic acid is required for the synthesis of methionine from homocysteine. Reduced folic acid, in turn, contributes to reductions in methionine synthesis, which results in the accumulation of homocysteine (5). As mentioned previously, elevated levels of homocysteine is a predictor of cardiovascular disease. Thus, folic acid should have protective effects countering cardiovascular disease. A review article by Moat *et al*. (73) discusses the association between folic acid intake and cardiovascular disease. They mention that folic acid intake reduced homocysteine levels. Further, folic acid can reverse endothelial dysfunction. In their view, this effect was not due to reducing homocysteine levels, suggesting that folic acid has pleiotropic effects on the vasculature other than homocysteine reduction. Moat *et al*. stated that the main circulating metabolite of folic acid can increase nitric oxide production and can directly scavenge superoxide radicals (73). A double-blind randomized control study investigating 3,680 adults with nondisabling cerebral infarction showed that high doses of combined folic acid, vitamin B_6, and B_{12} intake had no effect on recurrent cerebral infarction and coronary heart disease events and death compared with low-dose intake. However, this study also showed that a mean reduction of total homocysteine was significantly greater in the high-dose group than in the low-dose group (123).

Contrary to this, He *et al*. (37) examined intake of folate, vitamin B_6, and vitamin B_{12} in relation to the risk of ischemic stroke in a 14-year follow-up study with 43,732 men (40–75 years old) who were free of cardiovascular diseases and diabetes at baseline. The data showed that intake of folate and vitamin B_{12} was associated with a significantly lower risk of ischemic stroke.

Taken together, folic acid, vitamin B_6, and vitamin B_{12} supplementation may be a possible treatment for protection against future cardiovascular diseases. However, in addition to contradictory study findings, no study is investigating these effects in OSA.

Vitamin C, a known dietary antioxidant, can scavenge reactive oxygen and nitrogen species, effectively protecting other substrates from oxidative damage (34). Some studies indicate that higher plasma levels of vitamin C are associated with lower cardiovascular disease risk (27, 109). Osganian *et al*. (80) examined the relation between dietary, supplemental, and total intake of vitamin C and risk of cardiovascular diseases with 85,180 female nurses. This 16-year follow-up study showed that vitamin C supplement use was associated with a significantly reduced risk of CHD. However, dietary vitamin C was not associated with the risk of CHD after adjustment for age, smoking, and a variety of other coronary risk factors. One study is looking at the effect of vitamin C on the endothelial dysfunction in OSA. In this study, endothelial dysfunction evaluated by FMD of the brachial artery by ultrasound was improved by intravenous injection of vitamin C (30). Overall, the results of these studies suggest that vitamin C supplements could be involved in a strategy to avoid future cardiovascular disease occurrence in OSA.

In summary, antioxidant intake seems to be somewhat effective in treating or preventing cardiovascular diseases; however, little is known about whether antioxidant intake can protect the cardiovascular consequences of OSA. We must clarify this issue, as this strategy might be quite important for patients who cannot tolerate CPAP therapy.

SUMMARY AND FUTURE DIRECTIONS

In the past decade, the oxidative stress associated with OSA has been highlighted. Most of the human studies have indicated, directly or indirectly, the presence of OSA-induced oxidative stress. Although a few studies have failed to indicate the presence of OSA-induced oxidative stress, this factor has been shown to contribute to the development of cardiovascular disease. With the animal model or *in vitro* study of intermittent hypoxia, intermittent hypoxia has been shown to have a crucial role in the production of oxidative stress and seems to be a key factor for cardiovascular complications in OSA. Although the putative pathways to cardiovascular disease, as summarized in this review, are assuredly complicated, the evidence for association between the OSA involvement in each pathway has been accumulating (Fig. 4).

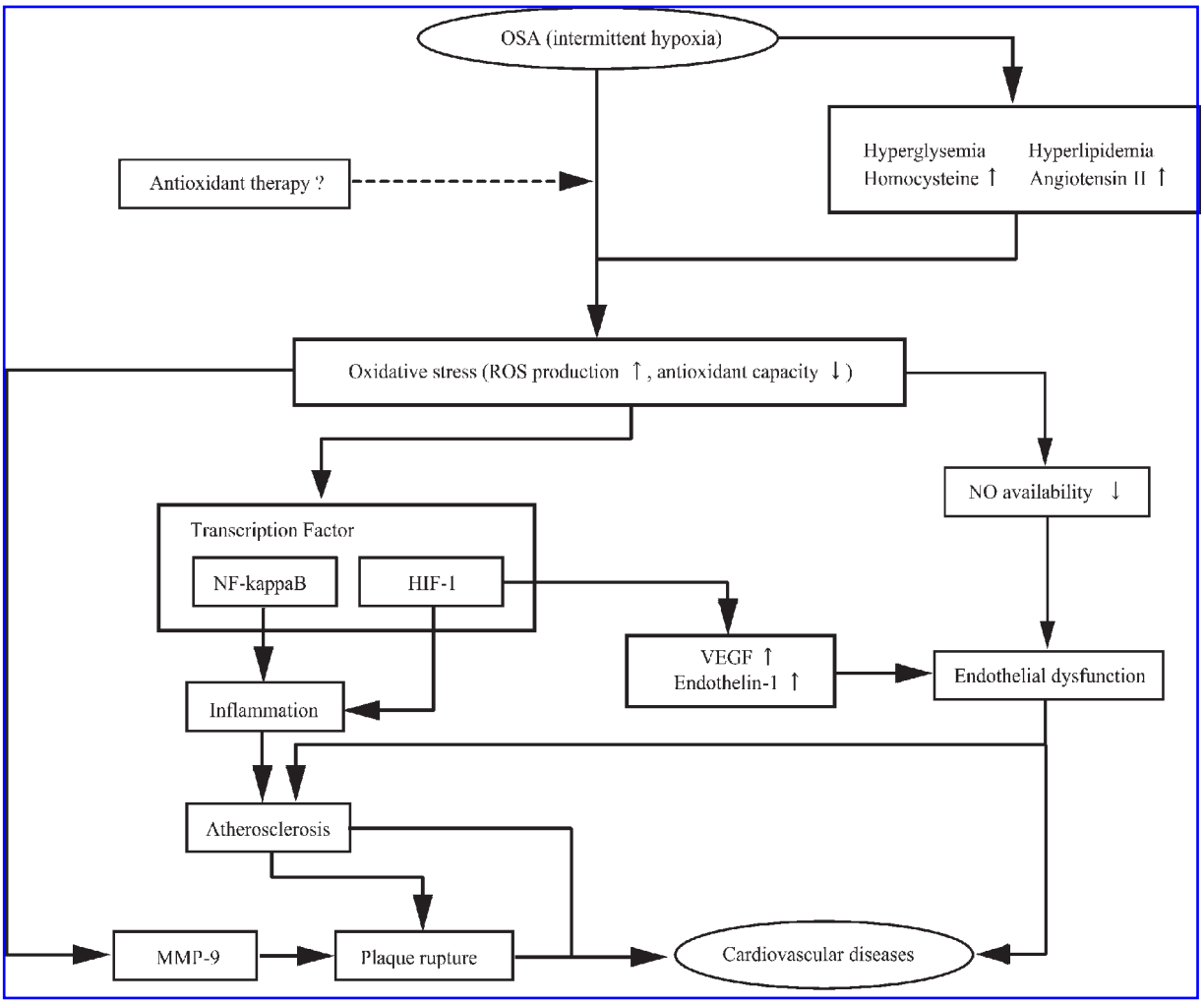

FIG. 4. Possible mechanisms for cardiovascular consequences of OSA *via* oxidative stress.

Inflammatory response and endothelial dysfunction, as found in the pathogenesis of atherosclerosis, are regulated by transcription factors such as NF-κB and HIF-1. NF-κB and HIF-1 are likely activated by OSA-related oxidative stress and may be the most important pathway in the cardiovascular consequences of OSA.

Treatment strategies for OSA patients who do not tolerate CPAP therapy may include ACE inhibitors or angiotensin II receptor antagonists in addition to antioxidant supplements. However, more studies must focus on the effects of these treatments, particularly with regard to the cardiovascular consequences of OSA. As a future therapy, the blockade of an inflammatory cascade or an agent that can improve endothelial dysfunction might additionally be useful.

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ABBREVIATIONS

8-OHdG, 8-hydroxy-2′-deoxyguanosine; ACE, angiotensin-converting enzyme; AHI, apnea–hypopnea index; CPAP, continuous positive airway pressure; CRP, C-reactive protein; D-ROM, diacron-reactive oxygen metabolites; FMD, flow-mediated vasodilation; fMLP, formylmethionylleucylphenylalanine; GGT, ã-glutamyltransferase; HIF-1, hypoxia-inducible factor-1; ICAM-1, intercellular adhesion molecule 1; IL, interleukin ; iNOS, inducible nitric oxide synthase activity; MCP-1, monocyte chemoattractant protein-1; M-CSF, macrophage colony-stimulating factor; MMP-9, matrix metalloproteinase-9; NF-κB, nuclear factor kappa B; NO, nitric oxide; OSA, obstructive sleep apnea; PMA, phorbol myristate acetate; RDI, respiratory disturbance index; ROS, reactive oxygen species; SDB, sleep disordered breathing; TAS, total antioxidant status; TBARS, thiobarbituric acid–reactive substance; TEAC, Trolox equivalent antioxidant capacity; TNF-α, tumor necrosis factor-α; VCAM-1, vascular cell-adhesion molecule 1; VEGF, vascular endothelial growth factor.

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