

Mechanisms of endothelial dysfunction in obstructive sleep apnea

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Abstract: Endothelial activation and inflammation are important mediators of accelerated atherogenesis and consequent increased cardiovascular morbidity in obstructive sleep apnea (OSA). Repetitive episodes of hypoxia/reoxygenation associated with transient cessation of breathing during sleep in OSA resemble ischemia/reperfusion injury and may be the main culprit underlying endothelial dysfunction in OSA. Additional factors such as repetitive arousals resulting in sleep fragmentation and deprivation and individual genetic susceptibility to vascular manifestations of OSA contribute to impaired endothelial function in OSA. The present review focuses on possible mechanisms that underlie endothelial activation and inflammation in OSA.

Keywords: endothelial, obstructive sleep apnea, inflammation, dysfunction

Introduction

Obstructive sleep apnea (OSA), a condition that affects up to a quarter of the American adult population, remains largely unrecognized, and less than 5% of all OSA patients receive treatment (Young et al 1993, 1997). Raising awareness among medical practitioners, and cardiologists in particular, about the high prevalence of unrecognized OSA is of great importance considering that OSA is an independent and potentially reversible risk factor for hypertension, myocardial ischemia and stroke (Peker et al 1999; Peppard et al 2000; Yaggi et al 2005; Yumino et al 2007). Increased cardiovascular morbidity in patients with untreated OSA is attributed to accelerated atherosclerosis (Kato et al 2000; Ip et al 2004; Drager et al 2005, 2007; Minoguchi et al 2005; Saletu et al 2006; Savransky et al 2007). The initial stimulus that triggers accelerated atherogenesis has not been definitively established.

Impaired endothelial function plays an important role in the development of cardiovascular manifestations of OSA. Normal endothelium regulates vasomotor tone and preserves inflammatory and coagulation homeostasis (Aird 2007). These functions are altered in patients with OSA compared with healthy subjects (Carlson et al 1996; Ohga et al 1999; Kato et al 2000; Dyugovskaya et al 2002, 2005; Ip et al 2004; Nieto et al 2004; Jelic et al 2008). Reduced numbers of endothelial progenitor cells and increased endothelial cell apoptosis in untreated OSA indicate impaired endothelial repair capacity (El Solh et al 2007, 2008; Jelic et al 2008; Martin et al 2008). In addition, increased sympathetic nervous activity may also contribute to cardiovascular morbidity in OSA (Narkiewicz and Somers 2003; Maser et al 2008). However, the reversibility of autonomic alterations with OSA-specific therapy remains controversial (Narkiewicz et al 1999; Esler and Eikelis 2006; Mills et al 2006).

Repetitive hypoxia/reoxygenation associated with transient cessation of breathing during apneas and hypopneas is considered the main culprit for the impairment of endothelial function in OSA. Repetitive arousals resulting in sleep fragmentation and chronic sleep deprivation may also contribute to vascular dysfunction in OSA.

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Lastly, individual genetic susceptibility may play a role in development of cardiovascular manifestations of untreated OSA. The present review will focus on possible mechanisms of endothelial dysfunction in OSA.

Repetitive hypoxia/reoxygenation

Repetitive hypoxia/reoxygenation during transient cessation of breathing as occurs in OSA resembles ischemia/reperfusion injury. Although perfusion remains intact during obstructive events in OSA, alterations involving generation of reactive oxygen species, inflammation and reduced nitric oxide (NO) availability are similar to those observed in models of ischemia-reperfusion (Liao et al 1995; Wang et al 1996; Kato et al 2000; Laursen et al 2001; Dyugovskaya et al 2002; Takemoto et al 2002; Kuzkaya et al 2003; Ip et al 2004; Minoguchi et al 2005; Antoniadis et al 2006).

Endothelial nitric oxide availability

Indirect evidence such as impaired flow-mediated brachial arterial dilation and decreased circulating NO levels measured by serum nitrite/nitrate suggest reduced NO availability in OSA patients (Kato et al 2000; Ip et al 2000, 2004; Noda et al 2007). Plasma levels of an endogenous inhibitor of endothelial nitric oxide synthase (eNOS) are increased and correlate inversely with flow-mediated dilation in patients with untreated OSA (Ohike et al 2005). Plasma levels of L-arginine, the substrate for NO production, increase after a single night of CPAP therapy in patients with OSA (Lavie et al 2003). Decreased eNOS activity and increased nitrotyrosine production, a byproduct of nitric oxide degradation, in freshly harvested venous endothelial cells provide direct evidence that nitric oxide bioavailability is reduced in OSA patients without overt cardiovascular disease (Jelic et al 2008).

Expression and activity of eNOS, a main source of basal endothelial NO, have been reported to be upregulated (Arnet et al 1996; Le Cras et al 1998; Coulet et al 2003; Shirai et al 2003), downregulated (McQuillan et al 1994; Liao et al 1995; Phelan and Faller 1996; Laufs et al 1997; Toporsian et al 2000; Takemoto et al 2002), or unchanged (Murata et al 2001; Tahawi et al 2007) in various experimental models of hypoxia and repetitive hypoxia/reoxygenation. Contradictory reports of eNOS expression and activity appear to be due to temporal variations in experimental hypoxemic conditions, and differences in the species and vascular bed from which endothelial cells were derived. Long-term intermittent hypoxia that mimicked OSA, administered in 30-second cycles for 6–8 hours daily for 35 days, resulted in elevated

diurnal resting mean arterial blood pressure in rats (Fletcher et al 1992; Tahawi et al 2007). Attenuated vasodilation in response to acetylcholine, a vasodilator that stimulates endothelial release of NO, and greater vasoconstriction with the NOS inhibitor N^G-nitro-L-arginine methyl ester in rats exposed to long-term hypoxia/reoxygenation compared with controls, suggest decreased NO availability (Tahawi et al 2007). After prolonged hypoxia, eNOS activity is reduced (Kiss et al 1998; Takemoto et al 2002), resulting in impaired vascular reactivity (Danton et al 2002).

Several mechanisms of hypoxia-induced eNOS down-regulation have been proposed (Coulet et al 2003; Tai et al 2004). On a transcriptional level, hypoxia-induced activation of hypoxia inducible factor-2 initially upregulates eNOS mRNA followed by a prolonged decrease in eNOS mRNA level (Coulet et al 2003). On a post-transcriptional level, hypoxia destabilizes eNOS mRNA, in part via the Rho kinase pathway in human venous and pulmonary artery endothelial cells (Takemoto et al 2002). Hypoxia increases arginase II activity in endothelial cells, which degrades L-arginine, an essential substrate for NO production by eNOS (Clarkson et al 2005). Oxidation of the eNOS cofactor tetrahydrobiopterin (BH₄) by reactive oxygen species such as peroxynitrite appears to be an important mechanism linking oxidative stress to endothelial dysfunction (Kuzkaya et al 2003; Antoniadis et al 2006). Decreased BH₄ availability promotes superoxide production by eNOS, an altered enzyme state labeled “uncoupling” (Vasquez-Vivar et al 1998; Xia et al 1998). Exposure to hypoxia for 24 hours leads to a time-dependent decrease in eNOS activator heat shock protein 90 that correlates with a decrease in eNOS activity in pulmonary artery endothelial cells (Garcia-Cardena et al 1998; Su and Block 2000). In contrast to short-term exposure to oxidative stress, prolonged oxidative stress as observed in untreated OSA reduces eNOS activity by suppressing its phosphorylation (Thomas et al 2002; Tanaka et al 2005). Reduced NO availability results in endothelial dysfunction and thereby increases the risk for vascular diseases in patients with OSA.

Endothelial and systemic inflammation

Elevated levels of plasma C-reactive protein (Shamsuzzaman et al 2002), leukocyte superoxide (Schulz et al 2000; Dyugovskaya et al 2002) and soluble adhesion molecules (Ohga et al 1999) suggest the presence of chronic systemic inflammation in OSA patients. Upregulation of cyclooxygenase-2 (COX-2) and inducible NOS in venous endothelial cells harvested from patients with untreated

OSA provides direct evidence of vascular inflammation in OSA (Jelic et al 2008).

Accumulation and adhesion of circulating leukocytes to the vascular endothelium lead to vessel inflammation and progression of atherosclerosis (Price and Loscalzo 1999; Aird 2007). Monocyte expression of the adhesion molecules CD15 and CD11c is increased in patients with OSA compared with controls matched for age and cardiovascular comorbidities, although not BMI (Dyugovskaya et al 2002). Enhanced oxidative stress and adhesion to cultured endothelial cells in monocytes collected in the morning from OSA patients suggest an adverse effect of OSA on diurnal vascular proinflammatory/antiinflammatory homeostasis (Dyugovskaya et al 2002). Lymphocytic production of interleukin-4 (IL-4), a proinflammatory cytokine, is greater, while production of IL-10, a potent antiinflammatory cytokine, is decreased in otherwise healthy patients with moderate to severe OSA, compared with subjects with an AHI <10/h (Dyugovskaya et al 2005).

Hypoxia/reoxygenation increases COX-2 gene and protein expression in endothelial cells in vivo and in vitro (Domoki et al 1999; Li et al 2003; Wu et al 2003). Although COX-2 is widely accepted as a proinflammatory agonist, its upregulation can be cardioprotective in ischemia-reperfusion injury (Bolli et al 2002). In addition, the use of COX-2 inhibitors may result in an increased incidence of cardiovascular events (Antman et al 2005). COX-2 appears to have a dual role in inflammation: initially inducing the inflammatory process and later aiding its resolution (Gilroy et al 1999). Upregulation of COX-2 in OSA may result in increased oxidative stress caused by superoxide production and increased vasoconstrictor and/or inflammatory prostanoid production leading to increased platelet activation and endothelial dysfunction (Antman et al 2005). Alternatively, induction of endothelial COX-2 in OSA patients may be a defense mechanism against repetitive hypoxia/reoxygenation.

Experimental models of repetitive hypoxia/reoxygenation that mimic OSA suggest that the proinflammatory transcription factor NF- κ B is activated selectively over the hypoxia-inducible factor-1 (HIF-1) adaptive pathway in cultured endothelial cells, suggesting a maladaptive response to hypoxic stimulus in OSA (Ryan et al 2005; Greenberg et al 2006). NF- κ B upregulates several proinflammatory genes, including tumor necrosis factor- α (TNF- α) and IL-6 (Williams and Scharf 2007). Circulating levels of IL-6 and TNF- α are consistently elevated in patients with OSA, independently from central obesity (Alam et al 2007). The

initial sensing and signaling event for NF- κ B activation remains unknown since it does not appear to be influenced by oxidative stress (Hayakawa et al 2003). In contrast, other investigators reported elevated levels of vascular endothelial growth factor (VEGF) and nocturnal erythropoietin, both mediated by the HIF-1 pathway, suggesting HIF-1 activation in patients with OSA (Lavie et al 2002; Winnicki et al 2004). Since hypertension is associated with elevated VEGF concentrations, these discrepancies regarding activation of the adaptive HIF-1 pathway in OSA may be due to the coexistence of hypertension in some OSA patients (Valipour et al 2004). Alternatively, similar to COX-2 upregulation, VEGF upregulation may be an adaptive response to repetitive hypoxia/reoxygenation in OSA (Shweiki et al 1992; Forsythe et al 1996; Marti et al 1998; Dor et al 2001).

In summary, endothelial proinflammatory/antiinflammatory homeostasis is shifted toward vascular inflammation in patients with untreated OSA.

Endothelial oxidative stress

Recent studies have demonstrated increased lipid peroxidation and generation of reactive oxygen species (ROS) by blood cells in OSA (Barcelo et al 2000; Christou et al 2003a, 2003b; Lavie et al 2004; Jung et al 2005; Yamauchi et al 2005; Tan et al 2006). Vasoreactivity in OSA can be improved by antioxidants such as ascorbate and allopurinol, suggesting that oxidative stress contributes to endothelial dysfunction (El Solh et al 2006; Grebe et al 2006). The reoxygenation/reperfusion phase of the hypoxia/reoxygenation cycle appears to promote production of ROS leading to oxidative stress in OSA (Dean and Wilcox 1993; Prabhakar 2002; Lavie 2003). Short-term intermittent hypoxia enhances cardiac susceptibility to ischemia/reperfusion injury in mice whereas longer exposure does not, suggesting temporal variation in response to oxidative stress (Park and Suzuki 2007). Repetitive episodes of hypoxia/reoxygenation increase production of reactive oxygen species in experimental models (McQuillan et al 1994; Liao et al 1995). Exposure of lean rodents to repetitive hypoxia/reoxygenation increases lipid peroxidation and decreases tissue-scavenging mechanisms in both heart and brain tissues (Xu et al 2004; Chen et al 2005). Superoxide rapidly scavenges NO, generating peroxynitrate, a toxic metabolite that nitrosylates tyrosine residues, forming nitrotyrosine, a marker of oxidative stress (Knepler et al 2001). Levels of circulating free nitrotyrosine are similar in patients with OSA and healthy subjects (Svatikova et al 2004). In contrast, expression of nitrotyrosine in endothelial cells harvested from otherwise healthy patients with OSA is greater

than controls, suggesting enhanced endothelial oxidative stress (Jelic et al 2008). Endothelial expression of nitrotyrosine more closely reflects endothelial oxidative stress in OSA than levels of circulating free nitrotyrosine since the *in vivo* half-life of nitrotyrosine is short, and its volume of distribution is 20-fold greater than the plasma volume indicating its extensive distribution in the extravascular compartment (Tabrizi-Fard et al 1999). As endothelial oxidative stress increases and fewer cofactors are available for nitric oxide synthesis, eNOS preferentially promotes superoxide production, thereby perpetuating a vicious cycle of endothelial injury (Vasquez-Vivar et al 1998; Xia et al 1998; Laursen et al 2001).

Repetitive hypoxia/reoxygenation promotes endothelial apoptosis by activating cell death receptors and mitochondria-dependent apoptotic pathways (Dhar-Mascareno et al 2005; Zhang et al 2005). Exposure of rat aortic rings to increasing concentrations of isolated endothelial apoptotic microparticles derived from cultured endothelial cells or patients with myocardial ischemia alters endothelium-dependent vasodilation and nitric oxide production while simultaneously increasing superoxide production (Boulanger et al 2001; Brodsky et al 2004). Furthermore, increased

concentrations of endothelial apoptotic microparticles impair angiogenesis *in vitro* (Brodsky et al 2004).

Thus, repetitive hypoxia/reoxygenation as observed in OSA adversely impacts endothelial function by promoting oxidative stress and inflammation, and reducing nitric oxide availability.

Sleep fragmentation and deprivation

Chronic sleep deprivation is associated with a 50% decline in endothelium-dependent vasodilation in healthy subjects suggesting reduced NO availability (Takase et al 2004). Levels of pro-inflammatory markers such as C-reactive protein (CRP), IL-6, and TNF- α are elevated after partial and sustained sleep deprivation in healthy subjects (Meier-Ewert et al 2004; Vgontzas et al 2004; Irwin et al 2006; Haack et al 2007). Levels of soluble TNF- α receptor 1 and IL-6 are elevated in healthy men after 4 days of sustained sleep deprivation, suggesting a role for sleep deprivation as a pro-inflammatory stimulus (Shearer et al 2001).

Sleep deprivation may alter coagulation homeostasis. Elevated levels of plasma D-dimer are associated with

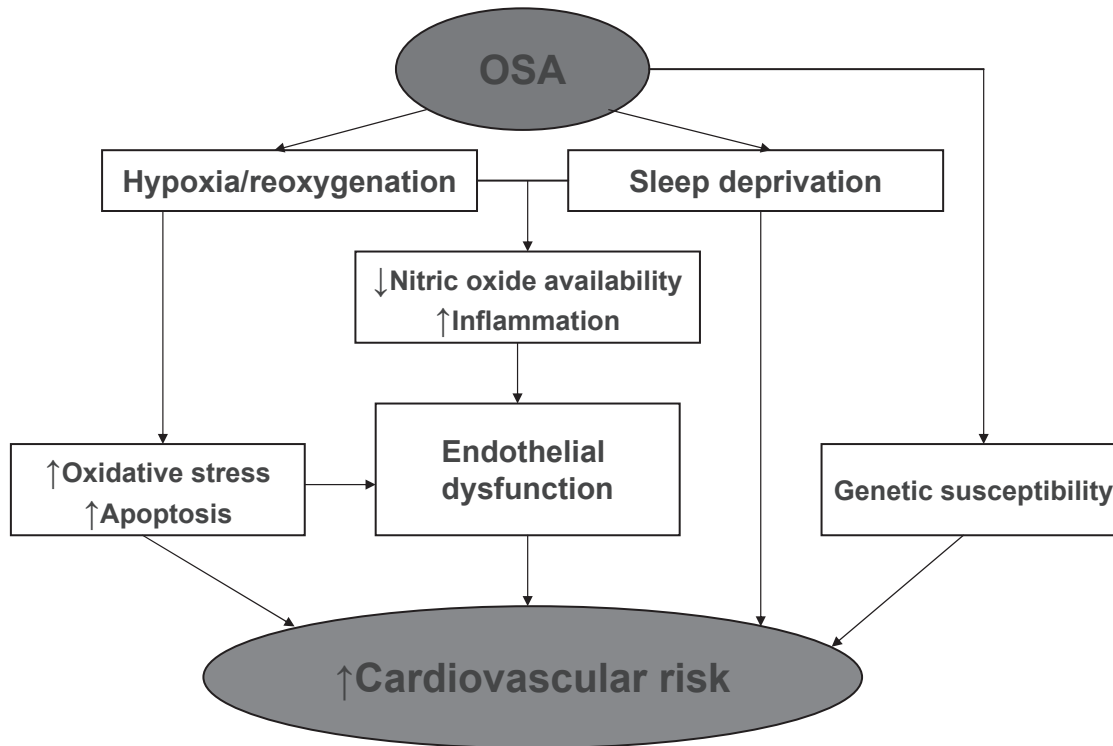


Figure 1 Intermediary mechanisms that mediate increased cardiovascular risk in obstructive sleep apnea (OSA). Repetitive hypoxia/reoxygenation associated with transient cessation of breathing while asleep promotes endothelial dysfunction in patients with OSA by increasing vascular inflammation, oxidative stress and apoptosis while reducing nitric oxide availability. Sleep fragmentation and deprivation resulting from repetitive arousals during sleep compound the effects of hypoxia/reoxygenation injury by independently promoting vascular inflammation. Genetic susceptibility may contribute to cardiovascular risk associated with OSA.

increased awake time after sleep onset in elderly subjects (Mausbach et al 2006; von Kanel et al 2006). Arousal index is correlated with plasma levels of von Willebrand's factor, a mediator of platelet adhesion (von Kanel et al 2007). Wake after sleep onset time is correlated with levels of soluble tissue factor, an initiator of the coagulation cascade, after adjustment for AHI (von Kanel et al 2007).

Based on available evidence, sleep deprivation alone does not appear to promote oxidative stress. Sleep deprivation does not affect oxidant production, antioxidant enzyme activity, lipid peroxidation or protein oxidation in brain, liver, and skeletal muscle in a rat model (Gopalakrishnan et al 2004).

Chronic sleep deprivation is associated with greater prevalence of obesity that might itself increase cardiovascular risk in OSA. Sleep fragmentation, assessed with actigraphy, is associated with higher BMI and risk of obesity in community-dwelling elderly (van de Berg et al 2008). Acute partial sleep deprivation reduces levels of leptin, a hormone regulating satiety and energy homeostasis, elevates levels of ghrelin, a hormone associated with appetite, and increases subjective sensation of hunger, creating a weight-gaining phenotype in healthy subjects (Spiegel et al 2004). Compared with longer sleep duration, self-reported sleep duration of ≤ 5 hours was associated with incident diabetes in 8992 subjects followed over 8–10 years (odds ratio = 1.5) (Gangwisch et al 2007). Self-reported reduced sleep duration in 70,000 participants in the Nurses Health Study was associated with increased cardiovascular risk over a 10-year period after adjustment for age, snoring and BMI (Ayas et al 2003). Acute sleep deprivation of healthy young men and women is associated with increased p-wave dispersion on electrocardiography, an electrophysiologic marker for the prediction of paroxysmal atrial fibrillation (Dilaveris et al 1998; Sari et al 2008). In addition, OSA itself has been associated with increased p-wave dispersion and incidence of atrial fibrillation (Gami et al 2004; Can et al 2008). Sustained sleep deprivation for 36 h increased sympathetic and decreased parasympathetic activity as measured by heart rate and blood pressure variability (Zhong et al 2005). Sleep deprivation-induced elevated sympathetic activity may contribute to adverse cardiovascular outcomes in OSA.

In summary, chronic sleep deprivation associated with OSA may potentiate the adverse effects of hypoxia/reoxygenation on cardiovascular function.

Genetic contributions

Genetic susceptibility for cardiovascular manifestations of OSA may be mediated by gene polymorphisms associated with regulation of body weight, lipid metabolism, inflammatory

response and autonomic vascular function (Keavney et al 2000; Kadotani et al 2001; Palmer et al 2003; Gottlieb et al 2004; Riha et al 2005; Borgel et al 2006; Popko et al 2007). OSA patients with and without coexistent coronary artery disease are more likely to have a family history of premature cardiovascular death than those without OSA, after adjustment for BMI (Gami et al 2007). In a murine model of OSA, genetic background determines both the pattern and magnitude of the chronotropic response to apnea (Iiyori et al 2005). Apolipoprotein E epsilon4 (ApoE epsilon4) is a well-known risk factor for cardiovascular disease (Song et al 2004; Bennett et al 2007). The APOE epsilon4 allele is associated with increased risk of OSA, particularly in individuals under age 65 (Kadotani et al 2001; Gottlieb et al 2004).

Along with male gender, obesity is the strongest risk factor for the development of OSA (Patel 2005). Obesity explains nearly 40% of the genetic heritability of OSA in a large cohort of 310 families with OSA (Patel et al 2008). Levels of ghrelin, a hormone associated with appetite, decline to near normal levels following short-term CPAP therapy in obese OSA patients without concomitant change in body weight, suggesting that OSA itself promotes ghrelin production (Harsch et al 2003).

The G-allele of a single nucleotide polymorphism in the pro-inflammatory IL-6 gene is associated with 6-fold increased odds of having OSA after adjustment for obesity (Larkin et al 2008). Increased prevalence of the TNF- α (-308A) polymorphism, a genotype associated with increased production of the pro-inflammatory cytokine TNF- α , in OSA patients compared with population controls may reflect a propensity for enhanced inflammatory response to repetitive hypoxia/reoxygenation and sleep deprivation associated with OSA (Wilson et al 1997; Riha et al 2005).

Reports of an association between angiotensin-converting enzyme (ACE) polymorphisms and OSA have been inconsistent. Treatment with an angiotensin II receptor blocker prevents elevation of blood pressure due to repetitive hypoxia/reoxygenation in an animal model of OSA (Fletcher et al 1999). The D allele and in particular the DD genotype of the ACE gene is associated with the development of hypertension and may confer an increased risk of cardiovascular disease (O'Donnell et al 1998; Bengtsson et al 1999; Keavney et al 2000). OSA increases the risk of hypertension, particularly in male carriers of the ACE gene D allele (Lin et al 2004; Boström et al 2007). However, other investigators reported no significant correlation between AHI and ACE activity in OSA patients (Xiao et al 1999; Barcelo et al 2001).

Summary

Endothelial dysfunction and inflammation mediate the cardiovascular manifestations of OSA. Repetitive hypoxia/reoxygenation, as observed in OSA, adversely impacts endothelial function by promoting oxidative stress and inflammation, and reducing NO availability. Sleep fragmentation and deprivation may potentiate hypoxia/reoxygenation injury by independently promoting vascular inflammation and pro-coagulability. Genetic susceptibility for cardiovascular manifestations of OSA may be mediated by gene polymorphisms associated with regulation of body weight, lipid metabolism, inflammatory response and autonomic vascular function.

Disclosure

The authors report no conflicts of interest in this work.

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