Endothelial Dysfunction in Obstructive Sleep Apnea

Rohit Budhiraja, M.D.1,2,3; Sairam Parthasarathy, M.D.1,2,3; Stuart F. Quan, M.D.1,2,3

1Division of Pulmonary and Critical Care, Southern Arizona Veterans Affairs Health Care System (SAVAHCS), Tucson, AZ; 2Arizona Respiratory Center, The University of Arizona, Tucson, AZ; 3Pulmonary and Critical Care Medicine Section, Department of Medicine and Sleep Disorders Center, University of Arizona College of Medicine, Tucson, AZ

Obstructive sleep apnea (OSA) is a common disorder and is associated with adverse cardiovascular consequences, including hypertension and coronary artery disease. While the mechanisms responsible for increased risk of cardiovascular events in OSA have not yet been fully elucidated, hypoxia, inflammation, obesity, metabolic dysregulation, and sympathetic activation, may contribute to these consequences. Endothelial dysfunction may be another link between OSA and cardiovascular disease. Dysfunctional endothelium is characterized by an imbalance in production of vasoactive hormones, increased adherence of inflammatory mediators to endothelial cells and hypercoagulability, and is a known risk factor for cardiovascular events. Studies have directly measured vascular endothelial function in patients with OSA and found a muted response compared to controls. Other studies have evaluated biochemical markers of endothelial function including circulating levels of vasoactive and thrombosis mediators and provide further proof of endothelial dysfunction in this disorder. A better appreciation of the role of the dysfunctional endothelium in OSA will help shed light on the pathogenesis of cardiovascular disease in this disorder and may lead to development of novel therapies aimed at preventing untoward outcomes.

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Address correspondence to: Rohit Budhiraja, M.D., Division of Pulmonary & Critical Care, Department of Medicine, Southern Arizona Veterans Affairs Health Care System (SAVAHCS), 3601 South 6th Avenue, Tucson, AZ 85723; Tel: (520) 792-1450; Fax : 520-629-1861; E-mail: rohit.budhiraja@med.va.gov

INTRODUCTION

Obstructive sleep apnea (OSA) is a widely prevalent disorder characterized by recurrent partial or complete obstruction of upper airway during sleep. Compelling data from several large cross-sectional and longitudinal studies strongly suggest a role for OSA in the development of cardiovascular disorders, including hypertension, coronary artery disease, and stroke.1,2 However, the mechanistic paradigm whereby OSA may lead to cardiovascular pathology is yet to be fully elucidated. One mechanism may involve OSA initiating and/or propagating vascular endothelial dysfunction through diverse pathways such as hypoxemia, reactive oxygen species (ROS) production, and sympathetic activation. Endothelial dysfunction may lead to vasoconstriction, vascular smooth muscle proliferation, hypercoagulability, thrombosis, and eventually, to adverse cardiovascular events.3 The data continue to accrue suggesting an improvement in endothelial dysfunction with therapy for OSA.

THE NORMAL VASCULAR ENDOTHELIUM

Endothelium is a dynamic tissue layer which constitutes a source and/or target of multiple growth factors and vasoactive mediators involved in regulating the physical and biochemical properties of the systemic vessels, as well as vascular contractility and cell growth.4 The endothelium is a not a homogeneous tissue. Its diversity includes anatomic variability in shape, size, and thickness, and functional heterogeneity, such as magnitude of nitric oxide-dependent dilation in different vascular sites. This diversity partially accounts for site-specific manifestations of different disorders such as retinopathy in diabetes and hepatic sinusoid involvement in veno-occlusive disease.5 However, control of vascular tone, maintenance of homeostasis, and angiogenesis, apart from provision of a selectively permeable barrier between blood and tissues, are the predominant actions of the endothelial layer at most sites.6

ENDOTHELIAL DYSFUNCTION IN OSA

Several studies have suggested impaired endothelial function in patients with OSA.6,7 The sources of the endothelial injury are still not clear, but potential etiologies include hypoxemia with ROS generation and systemic inflammation. OSA is also associated with obesity, hypertension, and metabolic dysregulation, which themselves may contribute to adverse effects on endothelium. Endothelial injury results in alteration of endothelial
hormones that are responsible for maintaining vascular tone and preventing abnormal cell proliferation, increased coagulability and altered leukocyte trafficking; and exposes subendothelial structures to diverse growth factors in the blood. The resultant vasoconstriction, vascular smooth muscle proliferation, and hypopercoagulability may lead to adverse cardiovascular consequences associated with OSA, such as hypertension, coronary artery disease, and cerebrovascular disease.

Treatment of obstructive sleep apnea with continuous positive airway pressure (CPAP) therapy has been suggested to improve endothelial function in the systemic circulation.

Measurement of Endothelial Dysfunction in OSA

The assessment of endothelial function in OSA has included functional evaluation of vascular responses by assessing changes in blood flow in response to endothelium-dependent vasodilators or hypoxemia, quantification of levels of circulating apoptotic endothelial cells, and plasma indices of diverse endothelial biomarkers including myriad vasoactive, inflammatory, and homeostatic mediators.

Some studies have utilized intra-arterial infusion of endothelium-dependent vasodilators such as acetylcholine and sodium nitroprusside to assess microvascular arterial endothelial function at baseline in OSA patients, as well as in response to CPAP therapy. Acetylcholine induces endothelium-dependent dilation via endothelial muscarinic membrane receptor-mediated stimulation of nitric oxide synthase. In the presence of endothelial damage, however, acetylcholine may promote smooth muscle-mediated vasoconstriction. Measurement of brachial artery pressure, flow, and resistance responses to intra-arterial infusions can thus provide a measure of endothelial integrity. Plethysmography was used to measure forearm blood flow in these studies.

Other studies aimed at detecting endothelial dysfunction have utilized high-resolution ultrasonographic measurements of flow-mediated dilation of the brachial artery. Flow-mediated dilation refers to nitric oxide-mediated vasodilatation resulting from shear-mediated activation of endothelial nitric oxide synthase in response to hypoxia in patients with OSA compared to controls, and normalization of the response with 4-6 weeks of CPAP therapy.
Determination of levels of circulating endothelial cells (CECs) is a relatively novel technique which provides a direct marker of endothelial damage. Circulating endothelial cells are increased in myocardial injury and atherosclerotic peripheral vascular disease. An in-vitro study suggested that in acute coronary syndromes, the extent of endothelial apoptosis correlates with the extent of coronary disease. Based on the above data, a recent study investigated the levels of circulating apoptotic endothelial cells in subjects with OSA and found that the levels were increased compared to non-OSA subjects, correlated with abnormal vasorelaxation, and attenuated with CPAP therapy.

Finally, a multitude of studies have evaluated the levels of inflammatory mediators, markers of oxidative stress, vasoactive mediators, and markers of coagulability as the cause or consequence of endothelial dysfunction. These are described in detail below.

Oxidative Stress and Endothelium

OSA is a condition of increased oxidative stress. Free radical production from neutrophils and monocytes is augmented in OSA patients and attenuates with CPAP therapy. Enhanced free radical production may also result from hypoxia-reoxygenation or from sympathetic activation. Furthermore, lipid peroxidation is greater in patients with OSA resulting in production of reactive oxygen species (ROS). Oxidant stress can, in turn, lead to endothelial injury, and consequently, atherosclerosis. Additionally, reactive oxygen species can upregulate the production of adhesion molecules in the endothelium, diminish nitric oxide synthase activity, and promote nitric oxide breakdown.

Endothelium and Inflammation

OSA is associated with increased levels of inflammatory mediators as well as upregulation of the expression of adhesion molecules in the vascular endothelium. The circulating levels of intracellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and E-selectin are elevated in patients with OSA. A central role for cell adhesion molecules has been suggested in the development of disorders such as atherosclerosis. Adhesion of circulating leukocytes to the endothelial cells is an important step in this process. Monocytes derived from OSA patients demonstrate increased adherence to vascular endothelial cells in vitro in comparison to those derived from control subjects. Migration of leukocytes beneath the endothelium following adherence can lead to formation of early atherosclerotic lesions. CPAP therapy for OSA attenuates expression of adhesion molecules on monocytes and ROS production by CD11+ monocytes and decreases monocyte adherence to human endothelial cells.

Another inflammatory cytokine, interleukin 6 (IL-6), is known to play a pivotal role in atherogenesis. A recent study revealed increase in the levels of soluble IL-6 receptors in persons with sleep apnea. The IL-6 and its receptor can induce chemokine and leukocyte recruitment and contribute to atherogenesis.

C-reactive protein (CRP), a marker and a contributor to the vascular inflammatory process, is also increased in patients with OSA, and the levels decrease with CPAP therapy. Studies suggest an inverse association between CRP levels and endothelial function. While the sentinel event that triggers the inflammatory cascade is not clear, hypoxia may provide the initial insult, mediated by the production of ROS derived from hypoxia-reoxygenation. Moreover, local inflammation resulting from the recurrent collapse of upper airway can lead to systemic inflammation. This is suggested by a recent study that showed overexpression of IL-8 in human bronchial epithelial cells in response to a vibratory stimulus.

Endothelial Dysfunction and Vasoactive Mediators

The endothelium is a source of several vasoactive mediators. A balance between these mediators, including vasoconstrictive factors such as the renin-angiotensin-aldosterone system, endothelin-1, and thromboxane; and vasorelaxant factors such as nitric oxide and prostacyclin; is thought to mediate normal vascular tone, homeostasis, and vascular injury repair and growth. An alteration in this balance can change vascular milieu and the architectural and tensile properties of the vasculature, promoting vasoconstriction and impeding endothelium-dependent vasorelaxation.

Nitric Oxide. Flow-mediated dilation of peripheral arteries depends on nitric oxide release from endothelial cells and is a widely accepted marker of vascular endothelial function, including that in coronary arteries. Data from a large population-based epidemiologic study, the Sleep Heart Health Study, have demonstrated impaired brachial artery flow-mediated dilation in persons with OSA. There was a stronger association between brachial reactivity and hypoxemia rather than AHI, suggesting that hypoxemic stress may be a pivotal factor contributing to endothelial dysfunction. Further evidence for this hypothesis is provided by a recent study that demonstrated an improvement in flow mediated dilation in patients with OSA after intravenous injection of Vitamin C, an antioxidant and free radical scavenger. Notably, endothelium dependent vasodilatation is impaired in these patients, even in the absence of hypertension or other illnesses including overt cardiovascular disease, suggesting that OSA is an independent risk factor for endothelial dysfunction. Furthermore, the levels of circulating nitric oxide, determined by measuring serum nitrates and nitrates, derivatives of nitric oxide, are decreased in OSA subjects compared with controls, and revert promptly to normal levels with CPAP therapy. Conversely, plasma concentrations of asymmetric NG, NG-dimethylarginine, an inhibitor of endothelial nitric oxide synthase, are increased in OSA and decrease with CPAP therapy.

Endothelin-1. Endothelin-1 (ET-1) is a potent vasoconstrictor peptide that is ubiquitous in human vascular endothelial cells and has mitogenic properties. One study found an increase in both plasma ET-1 and blood pressure in rats exposed to intermittent hypoxia/hypercapnia, as might be seen with sleep apnea. The human studies assessing ET-1 levels in OSA have yielded conflicting results. Several studies report that patients with OSA have higher systemic levels of the ET-1 than their healthy counterparts and the levels decrease with CPAP therapy. Such an increase in levels of this peptide may play a role in the genesis of hypertension in OSA. However, some other studies have failed to find an association between OSA and ET-1 elevation. Notably, a majority of patients and controls in one of these studies had history of hypertension and cardiovascular disorders, suggesting the possibility of endothelial dysfunction in both groups, and hence, no significant difference in the ET-1 levels between the 2 groups. Yet another study found elevations of plasma big ET-1 (a precursor of ET-1) levels in untreated OSA patients, which at-
P-selectin is also increased in patients with OSA and decrease with CPAP therapy. In contrast, plasma ET-1 concentrations were within the physiological range in these patients. Finally, a recent study found elevated endothelin-1 levels in moderate or severe OSA, but not in mild OSA.

Renin-Angiotensin System. The renin-angiotensin system causes vasoconstriction, endothelial damage, and cell growth, especially via the angiotensin I (AT1) receptor. Endothelium-derived nitric oxide regulates renin release in vivo. The endothelium also mediates vascular angiotensin formation by taking up renin. Angiotensin II induces expression of ET-1 in endothelial cells. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II antagonists improve endothelial function in patients with hypertension. Activation of renin-angiotensin by recurrent hypoxia may contribute to elevation in blood pressure in OSA patients. Indeed, Fletcher et al demonstrated an increase in mean arterial pressure in rats exposed to intermittent hypoxia akin to that seen in OSA and attenuation of this response by using an AT1 receptor inhibitor. Higher plasma levels of aldosterone and angiotensin II have been reported in patients with OSA.

Leptin. While obesity is an important risk factor for OSA, OSA itself may be associated with an increased propensity to gain weight. Altered circulating leptin levels or leptin insensitivity have been proposed to underlie this phenomenon. Indeed, leptin levels are higher in patients with OSA and decrease with CPAP therapy. Leptin, in turn, is associated with endothelial dysfunction and cardiovascular disorders. In support of the link between leptin and atherogenesis is the finding that the ob/ob homozygote mouse, which lacks the functioning leptin ob gene, is resistant to atherosclerosis despite being grossly obese. Furthermore, higher leptin levels have been demonstrated to be associated with impaired arterial distensibility in humans. Leptin receptors are present on endothelial cells, suggesting that the endothelium may be a target for leptin. These receptors may play a role in leptin actions such as angiogenesis and vascular smooth muscle proliferation. Leptin also induces ROS production in human endothelial cells, which again can be important in atherogenesis.

Xanthine Oxidoreductase. Xanthine oxidoreductase (XOR) is a complex molybdoflavoenzyme that catalyzes the hydroxylation of hypoxanthine to xanthine and of xanthine to uric acid. Reduction of molecular oxygen by XOR yields superoxide and hydrogen peroxide, which can contribute to endothelial injury. Circulating plasma xanthine oxidase causes vascular dysfunction and has been implicated in ischemia-reperfusion injury. Furthermore, increased serum levels of uric acid constitute a risk factor for cardiovascular disease. Hypoxia, a common feature of OSA, increases XOR levels in endothelial cells. While XOR levels have not been studied in patients with OSA, the levels of uric acid, final product of the purine metabolism, are increased in OSA and decrease with CPAP.

Endothelial Dysfunction and Hypercoagulability

The diverse factors secreted by the normal endothelium—including nitric oxide and prostacyclin which decrease platelet aggregation, thrombomodulin which promotes activated protein C generation, and heparin sulfates which serve as cofactors of antithrombin III—help maintain normal fluidity of the blood. Endothelial dysfunction may lead to homeostasis alterations resulting in a procoagulant and atherogenic state. The loss of the endothelial “barrier” function exposes the subendothelial structure of the vessel wall to circulating growth factors and mediators of cell proliferation. The vascular collagen can bind to von Willebrand factor, leading to platelet activation and aggregation, and thence, thrombus formation. Indeed, patients with OSA have been reported to have increased platelet aggregation. The blood levels of procoagulant tissue factor, constitutively released by adventitial layer of blood vessels, increase with endothelial damage, and further propagate plasma coagulation.

Other studies confirm the presence of a hypercoagulable state in OSA. Levels of coagulation factors XIIa, VIIa, and thrombin-antithrombin complex are elevated in OSA. Plasma fibrinogen levels and type I plasminogen activator inhibitor (PAI-1) activity are also increased. CPAP treatment is associated with a decrease in fibrinogen levels and PAI-1 activity.

P-selectin is stored in platelets and the Weibel-Palade bodies of endothelial cells and mediates the interaction of endothelium with leukocytes and platelets. P-selectin glycoprotein ligand-1 expressed on leukocytes and platelets binds to P-selectin present on endothelial cells and promotes attachment and rolling, a primary step in initiation of atherosclerosis. Elevated levels of soluble P-selectin are associated with increased risk of future cardiovascular events. A recent study found P-selectin upregulation in a rat model of OSA. P-selectin is also increased in patients with OSA, and the levels correlate with severity of OSA.

Genetics

A genetic predisposition may confer an increased risk for development of endothelial dysfunction, or the consequences thereof, in some patients with OSA. The TNF-α (–308A) allele, a polymorphism in TNF-α gene responsible for overproduction of TNF-α, is more prevalent in subjects with OSA than normal controls. Overproduction of TNF-α can result in endothelial dysfunction. An insertion/deletion (I/D, intron 16) polymorphism of the angiotensin-converting enzyme (ACE) gene modulates the circulating ACE levels, D allele being associated with higher plasma ACE activity. One study suggested that ACE-D may interact with OSA and increase the risk of hypertension in patients with mild to moderate sleep apnea. ACE is a primary enzyme responsible for conversion of angiotensin I to angiotensin II. Angiotensin II is increased in OSA, and can jeopardize endothelial function, as described earlier. Angiotensin II may also lead to overexpression of VEGF mRNA through AT-1 receptors, resulting in overproduction of vascular endothelial growth factor. Vascular endothelial growth factor is a potent angiogenic cytokine that can contribute to progression of atherosclerosis.

CONCLUSION

Recent research provides strong evidence for endothelial dysfunction in obstructive sleep apnea. The resultant vasoconstriction, abnormal cell proliferation and hypercoagulability may contribute to the genesis or progression of atherosclerotic cardiovascular and cerebrovascular disorders, which are frequently encountered in OSA patients. While the currently available therapies for OSA, such as CPAP therapy, ameliorate endothelial dysfunction, they are cumbersome and have suboptimal patient acceptance or adherence. An improved understanding of the role of dysfunctional endothelium in promoting the adverse consequences of OSA has the potential to stimulate develop-
ment of adjunct therapies, medical or genetic, that specifically improve endothelial function, in an effort to alleviate the associated cardiovascular morbidity.

REFERENCES


