Endothelial Function in Obstructive Sleep Apnea

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Untreated obstructive sleep apnea (OSA) is an independent risk factor for hypertension, myocardial infarction, and stroke. The repetitive hypoxia/reoxygenation and sleep fragmentation associated with OSA impair endothelial function. Endothelial dysfunction, in turn, may mediate increased risk for cardiovascular diseases. Specifically, in OSA, endothelial nitric oxide availability and repair capacity are reduced, whereas oxidative stress and inflammation are enhanced. Treatment of OSA improves endothelial vasomotor tone and reduces inflammation. We review the evidence and possible mechanisms of endothelial dysfunction as well as the effect of treatment on endothelial function in OSA.
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Obstructive sleep apnea (OSA), a condition that affects 9% to 25% of the American adult population, is characterized by repetitive apneas, causing hypoxemia and arousals from sleep.[1,2] Untreated OSA is an independent risk factor for hypertension, myocardial ischemia, and stroke[3-5]; however, the mechanisms underlying the association between OSA and cardiovascular diseases are not well understood. More recent research suggests that OSA directly affects the endothelium, providing a possible link between OSA and the development of cardiovascular disease.

Endothelial dysfunction is an early marker of vascular abnormality preceding clinically overt cardiovascular disease. The intact endothelium regulates vascular tone and repair capacity, maintaining proinflammatory, anti-inflammatory, and coagulation homeostasis.[6] Alteration of these homeostatic pathways results in endothelial dysfunction before structural changes in the vasculature.[7]

Abnormal endothelial function may play an important role in increased cardiovascular risk associated with OSA. For example, OSA patients who are otherwise free of cardiovascular comorbidities have increased endothelial oxidative stress, inflammation, and reduced endothelial repair capacity, strongly suggesting that OSA independently impairs endothelial function.[8-13] Endothelium-dependent vasodilation is impaired in otherwise healthy patients with OSA, suggesting reduced nitric oxide (NO) bioavailability.[14,15] Furthermore, treatment of OSA improves endothelial function and appears to reduce the risk of fatal and nonfatal cardiovascular events.[16,17] Reversal of endothelial dysfunction may play an important role in treatment-mediated reduction of cardiovascular risk in these patients.

The present review will first focus on evidence of endothelial dysfunction in patients with untreated OSA. Possible mechanisms of endothelial dysfunction in OSA will then be considered. Lastly, the effect of OSA treatment on endothelial function will be discussed.

Evidence of Endothelial Dysfunction in Untreated OSA

The evaluation of endothelial function in patients with OSA includes assessment of vasomotor tone,

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endothelial proinflammatory/anti-inflammatory activity, coagulation homeostasis, and endothelial repair capacity.

Regulation of Vasomotor Tone

The healthy endothelium maintains balance between vasodilation and vasoconstriction in response to physical and biochemical stimuli.[6] Endothelial dysfunction is characterized by impaired endothelium-dependent vascular relaxation in response to mediators such as acetylcholine or to increased blood flow.[7] This can be clinically measured by ultrasound studies of forearm blood flow responses to various endothelial stimuli. Flow-mediated dilation, which measures the change of the brachial artery diameter after a brief period of forearm ischemia, is a noninvasive method commonly used to assess endothelium-dependent vasodilation.[18] The transient brachial artery dilation that follows ischemia appears to be primarily regulated by NO bioavailability, although endothelium-derived prostanoids may play an adjunctive role.[19-21]

The cardiology and diabetes literature has shown that impaired endothelial-dependent vasodilation in response to acetylcholine or reactive hyperemia has prognostic value based on correlations with increased risk of subsequent cardiovascular events (such as myocardial infarction and stroke). Researchers in the sleep apnea field have shown that OSA, like coronary artery disease and diabetes, can independently contribute to impaired endothelial function as well. For example, endothelium-dependent vasodilation measured by forearm blood flow after intraarterial infusion of acetylcholine, an endothelium-dependent vasodilator, is reduced in otherwise healthy patients with severe OSA compared with age- and body mass index (BMI)–matched controls.[14,15] Similarly, flow-mediated dilation is reduced in otherwise healthy patients with untreated OSA, indicating reduced NO bioavailability.[16] Among 1,037 elderly patients with OSA who participated in the Sleep Heart Health/Cardiovascular Health Study, flow-mediated dilation remained impaired even after adjustment for BMI and cardiovascular comorbidities.[22] Brachial artery reactivity correlated with the degree of hypoxemia rather than apnea-hypopnea index (AHI), suggesting that hypoxemia/reoxygenation plays a crucial role in reducing NO bioavailability and promoting endothelial dysfunction in OSA.[22] However, we are also aware of studies showing no major association between OSA and endothelial dysfunction that have not been published, presumably as a result of publication biases. Thus, further work is required.

Although impaired flow-mediated dilation suggests that there is a decrease in NO bioavailability, further studies have shown that, in the plasma and in endothelial cells, there is indeed less NO in OSA patients compared with controls. Initial studies show that circulating NO levels are decreased in untreated OSA.[23,24] Furthermore, plasma levels of asymmetric NG,NG-dimethylarginine, an endogenous inhibitor of endothelial NO synthase (eNOS), are increased and correlate inversely with flow-mediated dilation in patients with untreated OSA.[25] In freshly harvested venous endothelial cells, there are decreased eNOS activity and increased nitrotyrosine production, a byproduct of NO degradation.[13] In aggregate, these studies provide direct evidence that NO bioavailability is reduced in OSA patients without overt cardiovascular disease.

On the other hand, the evidence for increased production of vasoconstricting substances such as endothelin-1 and angiotensin II in patients with OSA is inconsistent. Plasma levels of aldosterone and angiotensin II in patients with OSA have been reported to be elevated or similar to controls.[26,27] Endothelin-1 levels, however, have been variable; and the effect of OSA itself on endothelin-1 appears complicated. For instance, nocturnal plasma levels of endothelin-1 are increased in patients with untreated OSA and unspecified comorbidities compared with their bedtime values, indicating an acute adverse effect of OSA on nocturnal regulation of vasomotor tone.[28] Similarly, both nocturnal and diurnal endothelin-1 levels are higher in patients with OSA compared with slightly younger and less obese healthy controls.[28] However, coexistent cardiovascular diseases may influence endothelin-1 levels independently from OSA; and studying patients with comorbidities who may not be well matched by age and BMI can be problematic. In patients with OSA and coexistent cardiovascular diseases, plasma levels of the endothelin-1 precursor big endothelin-1 were elevated, whereas levels of endothelin-1 were similar,

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