Vascular Dysfunction in Sleep Apnea
Not Just a Peripheral Concern

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Cardiovascular disease remains one of the leading causes of morbidity and mortality. Obstructive sleep apnea (OSA) has been increasingly implicated in a breadth of cardiovascular diseases, including systemic hypertension, heart failure, stroke, arrhythmias, myocardial ischemia, and pulmonary arterial hypertension.1 The importance of this association, especially in the context of OSA as an etiologic factor, is compellingly relevant to disease management strategies, given the high prevalence of OSA and its likely rising trajectory secondary to the ongoing obesity epidemic.2 OSA may be present in approximately 20% of American adults, only a minority of whom have ever been diagnosed; this is true even for patients with established cardiovascular disease3 and despite the widespread availability of several effective treatment modalities (including continuous positive airway pressure [CPAP]).

It is only over the past 2 decades that serious investigative interest has been paid to the interactions between OSA and cardiac and vascular disease and dysfunction. Deciphering the mechanisms, causal relationships, and potential therapeutic targets in the links between OSA and cardiovascular morbidity has not been an easy task, in part because of the constellation of comorbidities that characterize a large proportion of sleep apnea patients. OSA leads to multiple sources of cardiovascular stress, including nocturnal hypoxemia and hypercapnia, precipitous intrathoracic pressure changes, repetitive arousals, and poor sleep quality with consequent sleep deprivation. These, in turn, have been linked to endothelial dysfunction,4 systemic inflammation, sympathetic activation,5 metabolic dysregulation, hypercoagulability, and atrial enlargement, the combination of which may contribute to the initiation and progression of a range of cardiovascular diseases. Of these, endothelial dysfunction has been a particularly attractive candidate mechanism because of the importance of the endothelial cell to blood flow, vessel tone, and prevention of intravascular thrombosis. OSA may impair endothelial function,4 and CPAP treatment is reported to improve endothelial function in OSA patients.6

Butt et al,7 in this issue of Hypertension, revisit the characteristics and implications of endothelial dysfunction in OSA, using a carefully designed, well-conducted, multifaceted evaluation of macrovascular and microcirculatory function in 3 groups of 36 patients each: in those with OSA, in those with hypertension, and in healthy controls. In addition, they report the results of this same comprehensive multivessel evaluation of endothelial physiology in the OSA patients after treatment with CPAP for an average of 26 weeks. Evaluation procedures used in this study included transthoracic myocardial contrast echocardiography with a dipyridamole challenge, flow-mediated and nitroglycerin-mediated dilatation of the conduit brachial artery measured by ultrasound, cutaneous perfusion responses of skin microvasculature to acetylcholine and sodium nitroprusside as measured by laser Doppler, pulse wave velocity analysis, and the analysis of circulating endothelial cells.

A key finding of their study is that, according to the contrast echocardiography measurements, patients with untreated OSA had significantly lower indices of myocardial perfusion, both myocardial blood flow volume and flow velocity, compared with healthy controls, at rest and even after the dipyridamole vasodilatory challenge. The degree of impairment in myocardial perfusion seen in the OSA patients was similar to that of the hypertensive group in this study, and these perfusion indices improved strikingly after the OSA patients were treated with CPAP.

At present, ultrasound contrast agents are being increasingly used both in clinical practice and in research protocols. These agents consist of microbubbles with relatively permeable phospholipid shells filled with a high molecular weight gas (sulfur hexafluoride in the case of the SonoVue contrast agent used in their study), which are administered by a continuous infusion until a steady state is reached. Then, a pulse of high mechanical index energy is administered, leading to disruption of the microbubbles in the imaging frame. Bubbles from adjacent tissues subsequently rush in to take the place of their destroyed compatriots, and the rate at which they do so is proportional to the total flow of blood in the myocardial tissue.8 Although this technique can be used in identification of perfusion defects, Butt et al7 use it to estimate the velocity and relative volume of blood in the myocardium, both before and after administration of the dipyridamole vasodilatory stress.

The findings of impaired perfusion of myocardial tissue in OSA patients are in agreement with corroborating evidence from previous smaller studies, which used different imaging modalities. Nguyen et al8 reported impaired myocardial perfusion reserve in 25 consecutive OSA patients as detected
by cardiovascular MRI, and Orea-Tejeda et al.\textsuperscript{10} reported perfusion defects on nocturnal single photon emission computer tomography imaging in 14 patients with severe obesity and OSA. Impaired myocardial perfusion or perfusion demand mismatch in OSA provides additional insight into why these patients may be at increased risk of myocardial ischemia and sudden cardiac death, particularly at night, when the hypoxic and other stressors are most evident.\textsuperscript{11}

The strengths of the study by Butt et al.\textsuperscript{7} include an extensive evaluation of the vascular system with multiple modalities, complete follow-up of patients placed on CPAP treatment, and an innovative design that includes the addition of effectively 2 control groups, healthy subjects without OSA and patients without OSA but with hypertension. It is impressive that sleep studies were used to exclude occult OSA in the hypertensive and control subjects, and all 3 of the groups were free of other comorbidities. Comparison of the OSA patients with non-OSA hypertensive controls enables some perspective on the biological significance of the endothelial dysfunction noted, using the well-documented hypertension-induced vascular dysfunction as a frame of reference. There are also several limitations. As is often the case in studies of OSA, the attempt to separate major comorbidities that could function as confounders (obesity and hypertension) is not completely successful, and some overlap between the study groups occurs, as acknowledged by the authors. In particular, one must note the presence of a significantly elevated systolic blood pressure in the OSA group (supposed to not have any hypertension) and the significant difference in waist circumference between the study groups (although the body mass index was not statistically different). This latter reservation is of particular concern, because central obesity (significantly more marked in the OSA patients) is far superior to body mass index in predicting cardiovascular risk, especially in more marked in the OSA patients) is far superior to body mass index in predicting cardiovascular risk.

In mitigation, CPAP improved endothelial function, but we do not know if there was any attenuation in central obesity, as would be expected based on work from Chin et al.,\textsuperscript{13} who showed that CPAP treatment reduced central obesity, even in the absence of significant change in body mass index. Furthermore, the findings regarding CPAP therapy would be more compelling had they been obtained as part of a randomized, controlled study in the OSA patients.

These reservations notwithstanding, Butt et al.\textsuperscript{7} help further our understanding of impaired vascular function in OSA patients. Of special interest is their finding of a seemingly diffuse multivessel endothelial dysfunction, affecting both conduit vessels and microvasculature, and involving blood vessels in the limb, skin, and heart. These observations speak to the larger concept of OSA-induced endothelial dysfunction as a systemic disease, with improvement of endothelial function in all of these territories after CPAP treatment. However, whether such improvement translates into a meaningful reduction of adverse clinical outcomes in OSA patients treated with CPAP can ultimately only be established in large randomized clinical trials.

Sources of Funding

This publication was supported by NIH/NCCR CTSA Grant Number UL1 RR024150, NIH Grant Number HL 65176, and Grants from the Ministry of Education and Health of the Czech Republic (NT 11401 5/2011, CZ.1.05/1.1.00/02.0123). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the NIH.

Disclosures

V.K.S. received a gift to Mayo Foundation from Phillips Respironics Foundation, is a consultant for Merck, Johnson and Johnson, Resplicardia, ResMed, Sova Pharmaceuticals, and Apexn Medical, and is working with Mayo Health Solutions and their industry partners on intellectual property related to sleep and cardiovascular disease. T.K. has no disclosures.

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Hypertension. 2011;58:352-353; originally published online July 11, 2011;
doi: 10.1161/HYPERTENSIONAHA.111.175976
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0194-911X. Online ISSN: 1524-4563

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World Wide Web at:
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