Neurogenic Retrograde Arterial Flow During Obstructive Sleep Apnea: A Novel Mechanism for Endothelial Dysfunction?

To the Editor:

Patients with obstructive sleep apnea (OSA) exhibit impaired brachial artery flow-mediated dilation during wakefulness, a phenomenon that has been attributed to a carryover into the awake state of the consequences of recurrent cycles of hypoxia and reperfusion during sleep, resulting in decreased NO bioavailability and vascular inflammation. However, recent prospective studies have failed to identify clearly an independent predictive relationship between markers of oxidative stress and endothelial function. Our unanticipated detection of retrograde arterial flow during spontaneous obstructive apnea in an experimental subject who fell asleep when studied during the daytime leads us to propose a novel, additional mechanism for the development of this marker of endothelial dysfunction.

A 67-year-old man (blood pressure: 142/84 mm Hg; heart rate: 49 bpm) with known severe untreated OSA (apnea-hypopnea index: 63 events per hour) and treated hypertension (40 mg of losinopril), whose apneas precipitated marked arterial oxygen desaturation (down to 60%), was participating in a study of muscle sympathetic nerve activity in hypertension. The experimental protocol entailed simultaneous measurements of breathing, continuous digital blood pressure (Portapres, Finapres Medical Systems BV, Amsterdam, the Netherlands), heart rate, muscle sympathetic nerve activity (microneurography), and assessment of brachial artery diameter and blood velocity (Vivid 7, GE Medical Systems, Milwaukee, WI) to determine the flow-mediated vasodilator response. All of the study protocols were approved by the University Health Network Research Ethics Board, and informed written consent was obtained.

During the acquisition of baseline measurements, the subject drifted off to sleep and was observed to spontaneously develop cycles of obstructive apnea. As anticipated, these were accompanied by marked increases in efferent muscle sympathetic nerve activity (Figure A). Not expected was the conversion of unidirectional brachial artery flow during normal breathing to an oscillation between antegrade and retrograde flow during apneas (Figure A and B). To our knowledge, this is the first reported description of this vascular phenomenon with spontaneous apneas. Anecdotal evidence suggests that this observation may also be present with voluntary apneas in healthy younger men.

In experimental models, retrograde and oscillatory shear stress profiles can promote atherogenic and thrombogenic vascular states. In humans, acute rises in sympathetic vasoconstrictor nerve traffic to skeletal muscle, as elicited reflexively by graded lower body negative pressure, increase conduit artery retrograde and oscillatory shear rates. Stepwise increases in brachial artery retrograde flow, induced by distal cuff inflation, influence only slightly antegrade flow, but augment markedly retrograde peak velocity and attenuate flow-mediated dilation. Thus, our interpretation of the observation illustrated is that, in this individual, spontaneous OSA triggered hypoxia-induced sympathetic activation causing arteriolar vasoconstriction. This increase in downstream resistance, in turn, generated within each cardiac cycle a retrograde component to brachial blood flow.

In this patient, a midday flow-mediated dilation response of 4.5% was observed. Acute induction of endothelial dysfunction by this additional mechanism would be expected to result in greater impairment of flow-mediated dilation immediately after awakening from undetected or untreated OSA than in the evening, that is, after hours of normal breathing. Indeed, such diurnal variation in ischemic reactive hyperemia has been reported recently by Jurado-Gámez et al. This and other markers of endothelial dysfunction abate rapidly with treatment of OSA by continuous positive airway pressure, as does elevated muscle sympathetic nerve activity. In summary, the potential relationship among OSA, conduit artery blood flow pattern, endothelial function, and circadian variation in cardiac event rates in this population warrants future investigation.

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Letter to the Editor

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Figure. A. Cardiopulmonary and brachial artery blood velocity recordings in a hypertensive man who fell asleep and developed spontaneously obstructive apneas. On transition from regular breathing to obstructive apnea, brachial artery blood flow becomes bidirectional, with progressively increasing retrograde flow velocity. MSNA indicates muscle sympathetic nerve activity. B. Enlarged brachial artery blood velocity profiles during normal breathing and spontaneous obstructive apneas. Red circle highlights, in 1 cardiac cycle, an example of increased retrograde flow during spontaneous apnea. BA indicates brachial artery. Values presented are means of the 3 cardiac cycles depicted.
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