Hypertension, Sleep Apnea, and Atherosclerosis

John S. Floras

Having obstructive sleep apnea (OSA) increases the relative odds of also having coronary artery disease by 27% and of having suffered a stroke by 58%. Approximately 50% of individuals with OSA are also hypertensive, and those who are not initially so have an ~3-fold increase in their likelihood of developing hypertension after 4 years if their apnea-hypopnea index (AHI) is ≥15 events per hour.2–4

Some of this propensity to cardiovascular events may accrue from site-specific consequences of OSA. For example, if transmission of the acoustic energy generated by snoring stimulated the development of carotid atherosclerosis,5 conceivably this action could increase the odds for stroke but not for myocardial infarction. Conversely, during each futile effort to breathe against the occluded pharynx, mechanical strain elicited by the abrupt generation of negative intrathoracic (and, hence, augmented epicardial artery transmural) pressure could rupture coronary plaques.6 A parallel increase in left ventricular wall stress, accompanied by oxygen desaturation during apnea, might induce myocardial ischemia, or ischemic (and, hence, augmented epicardial artery transmural) pressure could rupture coronary plaques. A parallel increase in left ventricular wall stress, accompanied by oxygen desaturation during apnea, might induce myocardial ischemia, or non-ST segment elevation infarction.7 These cardiac effects of OSA could increase coronary risk but should not affect the likelihood of cerebrovascular events, whereas simultaneous increases in left atrial transmural pressure and concurrent fluctuations in autonomic tone might well raise the odds of developing embolic stroke by triggering atrial fibrillation.8

Over the long term, more important than these local actions may be the immediate and sustained systemic consequences of OSA. These include recurrent cycles of apnea and hypopnea, sympathetic excitation and withdrawal, hypoxia reoxygenation and oxidative stress, impaired tonic and reflex vagal heart rate modulation, platelet aggregation, activation of inflammatory pathways, oxidation of lipoproteins, expression of adhesion molecules, hyperaldosteronism, impaired endothelial responsiveness and vascular smooth muscle proliferation.3,4 By modifying vascular function or structure, or by initiating or promoting atherosclerosis, these stimuli, acting individually or in concert, could increase the likelihood of developing hypertension, coronary disease, or cerebrovascular disease. Indeed, in a previous study involving middle-aged, untreated OSA patients without conventional risk factors for cardiovascular disease, Drager et al9 found significant increases in carotid intima-media thickness (IMT), carotid diameter, and pulse wave velocity in patients with severe OSA compared with healthy control subjects. In a randomized, controlled trial involving 24 such patients, ablation of OSA by 4 months of treatment with continuous positive airway pressure led to significant reductions in pulse wave velocity and carotid IMT but not carotid diameter.10 Thus, OSA would appear to increase independently the risk of atherosclerosis and effective treatment to promote its resolution.

If approximately 30% of adults with hypertension also have OSA1 and if most of the systemic mechanisms listed above are also active in experimental and human hypertension, 2 important clinical questions, with respect to both pathophysiology and treatment, become: (1) which of these 2 independent stimuli elicit the greater proatherosclerotic response and (2) if both are present in the same individual, do their vascular effects overlap because of redundancy of mechanisms or do they add?

In the present issue of Hypertension, Drager et al11 test the hypothesis that OSA and hypertension exert independent proatherosclerotic carotid effects that summate when these 2 conditions coexist in the same person. These investigators quantified carotid IMT, diameter, and distensibility in 94 middle-aged, nonsmoking individuals without diabetes mellitus who were not taking medication for any condition other than hypertension. Subjects were selected from patients referred to their sleep laboratory for diagnostic purposes, from established hypertensive subjects evaluated in their unit, and from a pool of healthy individuals. The latter 2 cohorts underwent formal polysomnography. Subjects were first dichotomized on the basis of no sleep apnea (AHI <5 events per hour) and moderate-to-severe sleep apnea (AHI >15 events per hour) and were then subdivided into 4 study groups: 22 healthy controls, 25 individuals with untreated OSA alone, 20 with treated hypertension alone, and 27 with both untreated OSA and treated hypertension.

Subjects within each of these 4 groups were remarkably well matched for age (46 years), sex (predominantly male), body mass index (30 kg/m²), and lipid levels. OSA was severe but equally so in both apneic groups (mean AHI: 50 events per hour). Systolic blood pressure was identical in both hypertensive groups (143 mm Hg) and averaged 117 mm Hg in the 2 normotensive groups.

Compared with control subjects, carotid IMT, which related directly in multivariable analyses to both systolic blood pressure and the AHI, was 19% thicker in the OSA-alone and the hypertension-alone groups and 40% thicker in those with both conditions. Thus, OSA and hypertension associate independently with the presence of carotid atherosclerosis; when these conditions coexist, they act by additive summation to increase further IMT. Compared with control subjects, carotid diameter, which related directly only to the AHI, was

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From the University Health Network and Mount Sinai Hospital Division of Cardiology, University of Toronto, Toronto, Ontario, Canada.

Correspondence to John S. Floras, Suite 1614, 600 University Ave, Toronto, Ontario, M5G 1X5 Canada. E-mail john.floras@utoronto.ca

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8% wider in those with OSA, 9% wider in those with hypertension, and 20% wider in subjects with both OSA and hypertension \((P<0.001)\). Thus, when these conditions coexist, their net effect on carotid diameter is the sum of their independent actions. Compared with control subjects, carotid distensibility, which related inversely in multivariable analyses to both age and systolic blood pressure, but not to the AHI, was attenuated, not significantly, by 14% in the OSA group, significantly, by 21% in the hypertensive group, and by 37% when both OSA and hypertension were present. After adjustment for systolic blood pressure, distensibility was attenuated by 22.5% in those with both OSA and hypertension \((P=0.03)\). Drager et al\(^{11}\) concluded, on the basis of these findings, that the association of OSA and hypertension has additive effects on markers of early atherosclerosis.

The present investigation is remarkable for the selection of 4 cohorts so well matched otherwise for conventional risk factors for atherosclerosis and in whom otherwise potent stimuli, such as smoking and diabetes mellitus, were absent; for the detailed characterization of carotid IMT, diameter, and distensibility; and for its compelling findings. With the high prevalence of hypertension in OSA patients, it is commendable that they were able to assemble such a large group of nonobese normotensive subjects with such severe OSA, and, given the common finding of masked hypertension in such individuals, that they were able to affirm that 24-hour ambulatory blood pressure was similar to that of normotensive subjects without OSA. However, unknown is whether the present vascular observations, derived from a selected cohort whose mean AHI was \(\approx 50\) events per hour, are also exhibited by the much larger adult population with mild or moderate OSA. Nonetheless, the authors develop a compelling argument for adding OSA to the list of risk factors in humans for atherosclerosis.

These investigators acquired ambulatory blood pressure data only in the normotensive and the OSA-alone subjects and assume that their hypertensive and their OSA + hypertensive subjects had similar average 24-hour blood pressure values. However, it is conceivable that nocturnal and early morning blood pressures, in particular, were higher in the OSA + hypertension group than in the hypertension group alone, contributing to their greater burden of atherosclerotic disease. Unfortunately, without such ambulatory blood pressure data, the investigators’ key finding cannot be considered definitive.

The principal conclusion advanced by Drager et al\(^{11}\) is that these independent and additive effects of OSA and hypertension on early signs of atherosclerosis increase the risk of patients with these conditions for myocardial infarction and stroke. In a similarly designed cross-sectional study involving 38 of the present participants, these investigators had found previously that hypertension and OSA exert independent and additive effects on arterial pulse wave velocity and left ventricular hypertrophy. In the Perspectives section, they advocate now identifying and treating OSA. However, this proposal is not based on the results of large randomized trials with cardiovascular end points but follows from observational data and imaging data such as carotid IMT. Although carotid IMT was found in a recent meta-analysis to be a strong predictor of future vascular stroke and myocardial infarction, currently its merit as a surrogate for cardiovascular outcomes is a controversial subject.

The present findings, coupled with these investigators’ previous reports, raise a series of questions with broader implications for clinical investigation in hypertension. If there is a high prevalence of OSA in a hypertensive population and if the impact of OSA and hypertension on carotid IMT, diameter, pulse wave velocity, and left ventricular hypertrophy is additive, is the magnitude of atherosclerotic cardiovascular risk that we presently attribute on the basis of current epidemiological knowledge to hypertension alone overestimated by the confutation of OSA and high blood pressure in so many people? If an additional effect of OSA was not considered and controlled for, have previous investigations of vascular and cardiac adaptations to hypertension overestimated the impact of high blood pressure, per se, on arterial or ventricular structure and function? Could the neutral or modest effects of trials of blood pressure lowering on atherosclerotic burden reflect failure to identify and treat a variable, ie, OSA, that would continue to promote atherosclerotic progression if unaddressed? By contrast, the treatment of OSA with continuous positive airway pressure has been shown in a randomized, controlled trial to regress carotid IMT. If the answers to these questions are affirmative, to advance our present understanding, future epidemiological and phenotypic research should include, as a precondition, characterization of hypertensive patients based on the presence or absence of OSA. When designing atherosclerotic regression trials, a strong argument can now be made for stratification of patients by OSA and OSA treatment status.

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References


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