Editorial Commentary

Environmental Smoke Exposure
A Complex Cardiovascular Challenge

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Passive smoking, or environmental tobacco smoke (ETS) exposure, is a significant public health concern. It is widespread and has been implicated in excess cardiovascular mortality. In the United States, as many as 50,000 cardiovascular deaths per year may be attributable to passive smoking.

The mechanisms by which passive smoking may increase cardiovascular risk are becoming increasingly clear, with added insights offered by an intriguing study appearing in this issue of Hypertension. Using an elegant experimental design, Argacha et al assessed the vascular effects of ETS exposure in humans. They hypothesized, first, that vascular effects of ETS are in part secondary to increased plasma nicotine levels after ETS exposure and, second, that the vascular effects of passive smoking are sustained even after stopping the smoke exposure. To test these hypotheses, they placed subjects in a ventilation hood and exposed them randomly for 1 hour to sidestream tobacco smoke, sidestream nontobacco smoke (from herbal cigarettes), and normal air. Moreover, subjects received nicotine and placebo tablets in random order.

The investigators observed that sidestream tobacco smoke, but not air or nontobacco smoke, increased the augmentation index and heart rate, an effect that persisted even after the end of tobacco smoke exposure. There were no effects on central or peripheral blood pressure. The changes in the augmentation index correlated with the increase in plasma nicotine during ETS exposure, and similar increases in the augmentation index could be induced by nicotine but not placebo tablets. Moreover, sidestream tobacco smoke induced a reduction in late heat-induced microvascular hyperemia, indicating disturbed microvascular reactivity. Interestingly, levels of asymmetrical dimethylarginine, an endogenous inhibitor of NO synthase, were increased both by ETS and by nontobacco smoke.

Their robust experimental design examines several aspects of vascular modulation, i.e., nicotine-dependent changes in measures of arterial pulse wave reflection, changes in skin microvascular reactivity, and increased asymmetrical dimethylarginine levels. Nonetheless, these are indirect measures of vascular function. Sidestream tobacco smoke, as well as nontobacco smoke, altered neither peripheral nor central blood pressure. Pulse wave contour analysis provides only an indirect assessment of arterial stiffness. Increased augmentation index with passive smoking may be gender dependent and results from early reflection of the arterial pulse wave, possibly caused by large artery stiffening but also by increased resistance vessel tone.

Studies examining effects of nicotine on neural circulatory control suggest that nicotine acutely increases sympathetic nerve activity, as does sidestream tobacco smoke. These data, taken together with the present study, suggest that sidestream tobacco smoke may cause sympathetic activation via elevations in plasma nicotine. This increase in sympathetic activity heightens small artery and arteriolar tone, thereby altering pulse wave reflection and probably contributing to the elevated augmentation index observed with sidestream tobacco smoke and with nicotine.

Sympathetic activation induced by nicotine and sidestream tobacco smoke may also contribute to the disturbance of skin microvascular reactivity observed by Argacha et al. Skin microvascular dilatation in response to heat may depend largely on endothelium-derived NO. Therefore, this easily measurable variable is widely used as a surrogate for endothelial function. On the other hand, skin microvascular reactivity may not be representative of large artery endothelial function. Skin vessels are sensitive to sympathetic control, and skin sympathetic activation causes skin arteriolar vasoconstriction that may not be overridden completely by NO-dependent vasodilation. Thus, it is conceivable that nicotine-induced sympathetic excitation is responsible for the blunted skin microvascular reactivity occurring after tobacco smoke exposure but not after herbal smoke exposure.

In any event, there is a large body of evidence that sidestream tobacco smoke impairs endothelial function. Smoke, per se, causes increased formation of reactive oxygen species and thereby may impair endothelium-dependent vasodilation. Argacha et al have shown that both tobacco exposure and nontobacco sidestream smoke exposure increase plasma levels of asymmetrical dimethylarginine, a potent endogenous inhibitor of NO synthase. This factor may be an important contributor to smoke-induced endothelial dysfunction, with relevance not only to ETS, but also, as the authors note, to the even larger problem of exposure to polluted air. Finally ETS and nicotine have direct effects on the endothelium, mediated in part by platelet factors, reactive oxygen species, and endothelin release. Interestingly, nicotine may alter the endothelial cell cytoskeleton related to actin and vimentin rearrangement. This is generally associated with increased endothelial cell stiffness, which is itself associated with reduced NO bioavailability.
The acute effects of sidestream smoke on impaired microvascular reactivity in response to ETS exposure persisted for ≤20 minutes after discontinuing the exposure to smoke. Sidestream tobacco smoke may also cause chronic impairment of endothelial function, evident even in young, healthy children.\textsuperscript{10} Repeated ETS exposure may eventually lead to chronic structural and functional alterations of large arteries. Further studies investigating the acute and chronic effects of nicotine and sidestream tobacco smoke on large artery stiffness (local arterial distensibility and aortic stiffness) are warranted. Increased arterial stiffness may be an important predictor of cardiovascular morbidity and mortality and could serve as an intermediary mechanism linking ETS exposure with an increased risk for cardiovascular events.

In summary, Argacha et al\textsuperscript{3} provide important and novel insights into the mechanisms of vascular damage by ETS exposure. Passive smoking evokes complex processes involving arterial stiffening, altered arterial pulse wave reflection, disturbed microvascular reactivity, and endothelial dysfunction, probably dependent to a large extent on increases in plasma nicotine and sympathetic excitation but also in part secondary to other mechanisms, such as increases in asymmetrical dimethylarginine. The detrimental effects of ETS exposure on cardiovascular health outlined in the present study are limited to acute effects of passive smoking and speak eloquently to the need for further studies addressing the mechanisms by which passive smoking elicits chronic changes in vascular structure and function.

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**References**

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