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REVIEW TOPIC OF THE WEEK

Adverse Effects of Cigarette and Noncigarette Smoke Exposure on the Autonomic Nervous System

Mechanisms and Implications for Cardiovascular Risk

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ABSTRACT

This review summarizes the detrimental effects of cigarette and noncigarette emission exposure on autonomic function, with particular emphasis on the mechanisms of acute and chronic modulation of the sympathetic nervous system. We propose that the nicotine and fine particulate matter in tobacco smoke lead to increased sympathetic nerve activity, which becomes persistent via a positive feedback loop between sympathetic nerve activity and reactive oxidative species. Furthermore, we propose that baroreflex suppression of sympathetic activation is attenuated in habitual smokers; that is, the baroreflex plays a permissive role, allowing sympathoexcitation to occur without restraint in the setting of increased pressor response. This model is also applicable to other nontobacco cigarette emission exposures (e.g., marijuana, waterpipes [hookahs], electronic cigarettes, and even air pollution). Fortunately, emerging data suggest that baroreflex sensitivity and autonomic function may be restored after smoking cessation, providing further evidence in support of the health benefits of smoking cessation. (J Am Coll Cardiol 2014;64:1740–50) © 2014 by the American College of Cardiology Foundation. Open access under CC BY-NC-ND license.

Exposure to cigarette smoke is the number one preventable cause of cardiovascular disease in the United States (1). Although smoking rates in the United States have declined over the past 5 decades, 43.8 million Americans (19% of the adult population) continue to smoke, and smoking accounts for 440,000 deaths in the United States per year (2). This persistence of cigarette smoking, coupled with the recent diversification of available inhaled substances and delivery systems, including marijuana, electronic cigarettes (*e*-cigarettes), and waterpipes (hookahs), and the recent recognition that exposure to air pollution also increases cardiac risk, mandate review and synthesis of accumulating data to identify shared mechanisms of cardiac risk.

Although many of the potential mechanisms by which smoking dramatically increases cardiac risk and mortality, including adverse effects on platelets and endothelium, and increased inflammation and oxidative stress were recently comprehensively reviewed (3), the effects of tobacco exposure on the autonomic nervous system were not. The autonomic nervous system is composed of afferent nerve fibers located throughout the body, including the lungs, heart, and vasculature. These afferent nerve fibers are sensitive to both mechanical and metabolic

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(chemical) stimuli, with the general purpose of defending homeostasis. When stimulated, these afferent fibers relay impulses back to the central nervous system, where they may have either excitatory or inhibitory influences. For example, to prevent wide fluctuations in blood pressure, arterial baroreceptors, afferent nerves located in the aortic arch and carotid sinus, are sensitive to mechanical stimuli; when an increase in blood pressure results in stretch and distortion, they send inhibitory signals back to the brain that decrease central sympathetic efferent nerve outflow and increase vagal outflow. Strong evidence supports the concept that smoking alters the balance of the autonomic nervous system, and specifically, that tobacco smoke exposure leads to a predominance of sympathetic nerve activity (SNA). Cigarette smoking increases the risk for atrial and ventricular arrhythmias (4,5), sudden death (1), and acute myocardial infarction and causes hemodynamic changes that exacerbate heart failure (6), and increased SNA contributes to all of these complications (**Table 1**).

We will review the evidence that: 1) nicotine, with a contribution from fine particulate matter ($PM_{2.5}$; defined as <2.5 μm in hydrodynamic diameter), underlies the *acute* sympathoexcitatory effects of tobacco smoke, which are opposed by intact arterial baroreflexes; 2) $PM_{2.5}$ in tobacco smoke generates reactive oxygen species and inflammation, which play a crucial role in sustained sympathetic activation; baroreflexes are blunted in habitual smokers, and, therefore, play a permissive role; and 3) this proposed model, integrating a positive feedback loop between SNA and reactive oxygen species/inflammation, and a blunted negative feedback loop between SNA and the baroreflex, is potentially shared by other toxic emission sources, including marijuana, *e*-cigarettes, waterpipes, and air pollution. Details of the PubMed search and additional references and discussion are available in the Online Appendix.

EVIDENCE THAT ACUTE AND LONG-TERM TOBACCO SMOKE EXPOSURE INCREASES SNA

ACUTE EXPOSURE. Tobacco smoke is composed of gases and $PM_{2.5}$, consisting of over 4,000 identified potential toxicants, including nicotine. Because nicotinic acetylcholine receptors are present in the central nervous system, autonomic ganglia, and at the neuromuscular junction, early investigations of the neurovascular effects of tobacco focused on the acute effects of nicotine, which play an important role in its interactions with the autonomic nervous system. Acutely, nicotine causes the local release of catecholamines from adrenergic nerve terminals (7,8). In humans, nicotine exposure through smoking or intravenous nicotine administration leads to an acute increase in blood pressure and heart rate, peaking within 5 to 10 min of exposure (9,10). Although plasma nicotine levels continue to rise with increased exposure, nicotine tolerance develops rapidly, and the hemodynamic effects stabilize or decline (9,11). Direct microneurographic recordings of postganglionic muscle SNA in humans during nicotine administration have shown that, in addition to releasing catecholamines at the adrenergic nerve terminal, nicotine increases SNA (12).

Heart rate variability (HRV), used as a measure of the relative, typically reciprocal, influence of sympathetic and vagal input to the heart, can be quantified using either time domain or frequency domain analyses, which provide comparable results. Depressed HRV first emerged as a powerful independent predictor of increased mortality following myocardial infarction (13) and signifies a shift in the sympathovagal balance toward sympathetic predominance, accompanied by decreased vagal activity. Acute oral nicotine exposure in never-smokers acutely decreases HRV, consistent with a shift in the cardiac sympathovagal balance toward increased SNA (14). The observations that during cigarette smoking (but not during sham smoking), plasma catecholamines, blood pressure, and heart rate increase acutely, and that acute hemodynamic effects are prevented by pharmacological adrenergic blockade support the notion that the acute cardiovascular effects of cigarette smoke are also mediated by the effects of nicotine on the autonomic nervous system (7).

The net effect of acute smoking and nicotine exposure on SNA depends on the relative balance between the direct sympathetic excitatory effects of tobacco smoke and the opposing sympathoinhibitory effects mediated by the baroreflex (**Figure 1**). Paradoxically, early studies reported a sympathoinhibitory effect of acute tobacco smoke exposure in humans (15–18). Follow-up studies revealed that this apparent decrease in muscle SNA was mediated by the engagement of the baroreflex in response to the acute increase in blood pressure; if the increase in blood pressure was prevented pharmacologically, acute tobacco exposure increased muscle SNA (17,18). In older long-term smokers with relatively impaired baroreflex function, acute smoking produces an

ABBREVIATIONS AND ACRONYMS

CB = cannabinoid

***e*-cigarette** = electronic cigarette

HRV = heart rate variability

$PM_{2.5}$ = fine particulate matter <2.5 μm in hydrodynamic diameter

SNA = sympathetic nerve activity

TRPA1 = transient receptor potential ankyrin 1

TRPV1 = transient receptor potential vanilloid 1