

REVIEW TOPIC OF THE WEEK

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

Mechanisms and Implications for Cardiovascular Risk



Holly R. Middlekauff, MD,* Jeanie Park, MD,† Roya S. Moheimani, BS‡

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.

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

From the *Division of Cardiology, Department of Medicine, University of California-Los Angeles, Los Angeles, California; †Renal Division, Department of Medicine, Emory University School of Medicine, and the Veterans Affairs Medical Center, Atlanta, Georgia; and the ‡David Geffen School of Medicine, University of California-Los Angeles, Los Angeles, California. This work was supported by a Tobacco-Related Disease Research Program, Exploratory/Developmental Research Award (18XT-00115 [to H.R.M.]), the U.S. Public Health Service (MO1-RR00865 [to the UCLA General Clinical Research Center] and K23-HL098744), and Satellite Healthcare, a not-for-profit renal care provider (to Dr. Park). The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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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

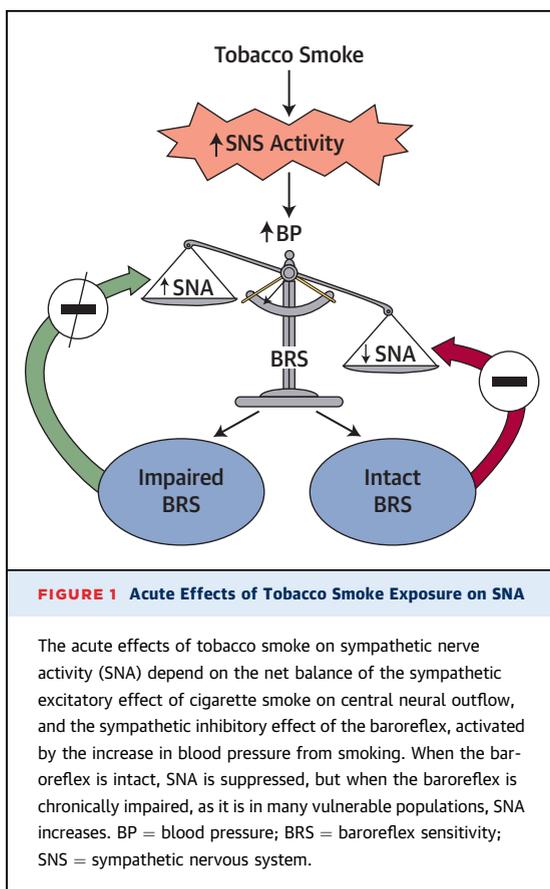
TRPA1 = transient receptor potential ankyrin 1

TRPV1 = transient receptor potential vanilloid 1

TABLE 1 Adverse Cardiovascular Sequelae of Sympathetic Predominance		
↑ Arrhythmias	↑ Heart Failure	↑ Myocardial Infarction
↓ Refractory period	↓ ECC	↑ Vasoconstriction
↑ Triggered activity	↑ Apoptosis	↑ Vasospasm
↑ Automaticity	↑ Oxidative stress	↑ Shear stress
↓ VF threshold	↑ Afterload	↑ Platelet aggregation
↑ Ischemia		↑ MVO ₂ (↑ HR ↑ BP ↑ Contractility)

BP = blood pressure; ECC = excitation-contraction coupling; HR = heart rate; MVO₂ = myocardial oxygen consumption; VF = ventricular fibrillation.

increase in muscle SNA due to a lack of baroreflex restraint. In contrast, in younger, healthy smokers whose negative baroreflex feedback loop is intact, acute smoking leads to a decrease in muscle SNA due to the activation of intact baroreflexes by the pressor effect of catecholamines released from nerve terminals by cigarette smoke. A significant correlation between baroreflex sensitivity and changes in muscle SNA during acute smoke exposure has been reported (19,20). Interestingly, in middle-age



habitual smokers, acute smoking increases blood pressure to a greater extent in women compared with men (21). One would then expect this augmented blood pressure response to reflexively suppress SNA to a greater degree in women, but SNA responses to acute smoking are similar in both sexes, consistent with an augmented sympathetic response to tobacco smoke exposure in women (21). It is tempting to speculate that habitual smoking leads to greater baroreflex impairment in women than in men. Indeed, smoking has been reported to confer a greater cardiovascular risk in female smokers than in male smokers (22). In addition to older patients, patients with hypertension, heart failure, or diabetes also have impaired baroreflex function, perhaps illuminating one potential mechanism whereby smoking may increase cardiac risk in these vulnerable groups.

Similar to direct tobacco smoke exposure, second-hand smoke exposure also leads to sympathoexcitation. Secondhand smoke is composed of ~15% exhaled mainstream smoke and ~85% side-stream unfiltered smoke emerging from the tip of a burning cigarette, which contains even greater amounts of toxic compounds than does mainstream smoke (23). The acute effects of secondhand smoke on the autonomic nervous system in never-smokers have been evaluated using microneurography and HRV, and both techniques confirmed increased SNA during secondhand smoke exposure (24,25).

Nicotine is not the only component of cigarette smoke that mediates an increase in SNA; in short-term studies, PM_{2.5} also increased sympathetic tone (26). Studies of the effects of air pollution on autonomic function helped to elucidate the role of PM_{2.5} versus nicotine on SNA. Air pollution generated by the combustion of organic materials (specifically fossil fuels) is comparable in particle size and constituents to tobacco smoke, which is similarly generated by the combustion of organic materials (tobacco leaves), but with two major differences (27,28). First, the daily dose (in mg) of inhaled particulates from air pollution is generally several orders of magnitude less than is that of smoking a pack of cigarettes a day and is on par with that of a nonsmoker exposed to secondhand smoke when living with a smoker (27). It is important to remember that cardiovascular risk stemming from exposure to PM_{2.5} has a steep dose-response curve, so that even low levels of PM_{2.5} exposure are potentially dangerous (27). Second, air pollution does not contain nicotine. This latter difference permits inferences regarding the effects of PM_{2.5} on the autonomic nervous system, independent of those of nicotine. As will be detailed later, acute

exposure to air pollution increases SNA in both animal models and in humans and is associated with increased cardiovascular risk (28,29), suggesting an important role for PM_{2.5}.

In summary, acute cigarette smoke exposure in humans is associated with acute increases in blood pressure and heart rate, which have potentially detrimental effects in patients with heart failure, coronary artery disease, and arrhythmias (4,6). These acute hemodynamic effects are mediated by both increased catecholamine release and increased efferent SNA. Because nicotine administration mimics the hemodynamic and neurovascular changes induced by acute cigarette smoke exposure, a major role for nicotine in mediating these acute sympathoexcitatory effects is assumed and likely. Extrapolating from the effects of gases and PM_{2.5} in air pollution, which consists of similar toxicants to tobacco smoke, but without the nicotine, the gases and PM_{2.5} present in tobacco smoke also contribute to the acute shift in the autonomic balance toward sympathetic predominance.

LONG-TERM EXPOSURE. Although nicotine may be an important mediator of acute responses during tobacco smoke exposure, tachyphylaxis to nicotine and its neural effects is rapidly acquired (8). However, the neurovascular effects of PM_{2.5} in tobacco smoke may become sustained and chronic (30). Numerous reports have used HRV to assess chronic cardiac sympathovagal balance, and most have confirmed decreased HRV; that is, a shift toward increased sympathetic dominance in habitual smokers compared with nonsmokers and former smokers (24). Interestingly, smoking cessation as brief as 7 days has been associated with increased HRV, consistent with a shift toward the restoration of normal sympathovagal balance (24,25). Nonsmokers exposed long-term to secondhand smoke also have decreased HRV compared with that in nonsmokers without concurrent secondhand exposure (24,25). Smokers continued to smoke during data acquisition in all of these studies of the long-term effects of tobacco smoke exposure on SNA described in the preceding text; thus, it is not possible to determine on the basis of these studies whether the autonomic nervous system effects are all attributable to acute, intermittent nicotine exposure or to long-term modulation of autonomic function.

To determine whether SNA is elevated in smokers in the absence of acute smoke exposure, we directly measured resting SNA in young women who were habitual smokers but who had abstained from smoking for 12 h or ~6 nicotine half-lives, and in those who had never smoked. Because in women not taking oral contraceptive pills, muscle SNA varies during the

menstrual cycle, peaking during the high-hormone mid-luteal phase, and declining during the early follicular phase, we examined the influence of the ovarian cycle on muscle SNA in these groups (31). We confirmed this fluctuation in muscle SNA with the ovarian cycle in never-smokers, but found that it was abolished in women who smoked. Muscle SNA remained elevated during the early follicular phase in smokers, consistent with a greater sympathetic burden in premenopausal women who smoked (Figure 2). We recently extended these studies to former smokers and to women exposed to second-hand smoke (32). Interestingly, we found the same increased sympathetic burden in women exposed

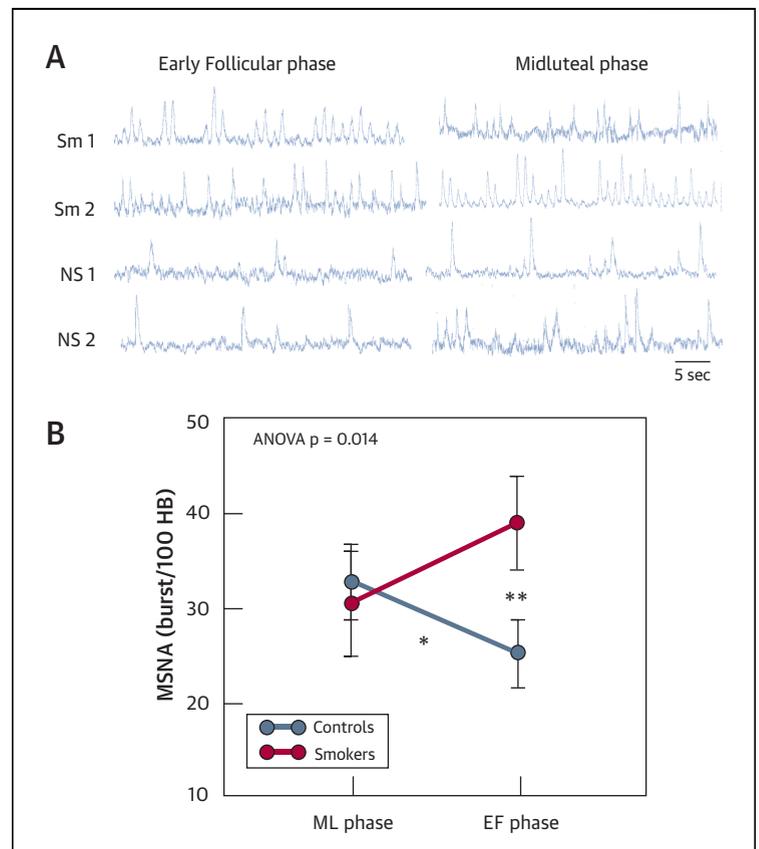


FIGURE 2 Elevated SNA During the Ovarian Cycle in Smokers

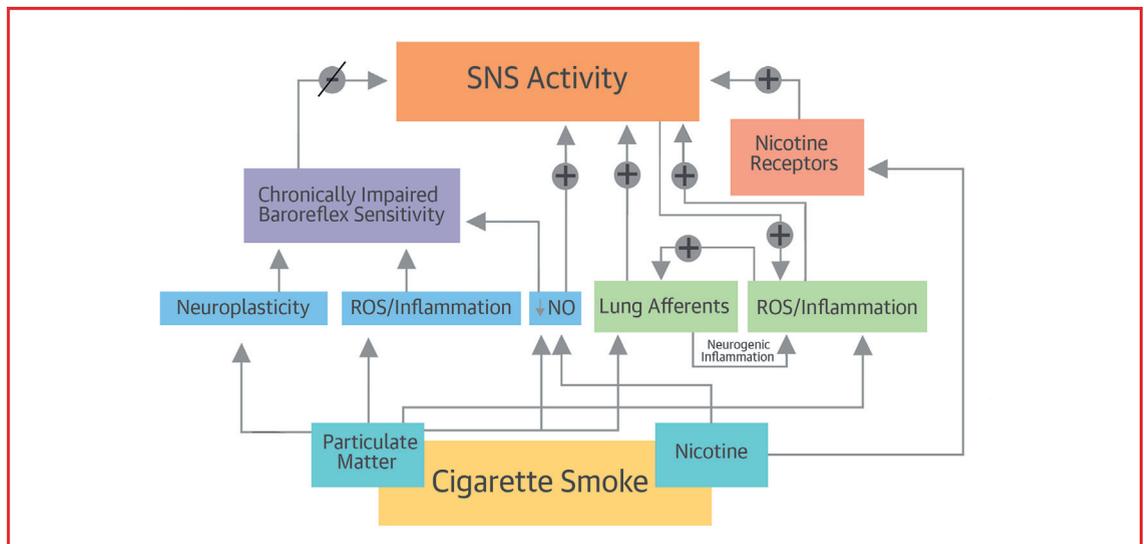
Sympathetic neurograms using microneurography of the original nerve recordings from two representative smokers (Sm) and two never-smokers (NS) during both the early follicular (EF) and midluteal (ML) phases of the ovarian cycle (A). In the never-smokers, sympathetic nerve activity (SNA) is higher in the ML phase and decreases in the EF phase, but in smokers, SNA remains elevated during the EF phase. Muscle SNA (MSNA) during the ML and EF phases of the ovarian cycle in smokers and never-smoker controls (B).

*Significant within-group difference for ML versus EF in controls. **Significant between-group difference during the EF phase. The overall analysis of variance *F*-test indicated a significant difference in the ovarian pattern of SNA between the two groups. HB = heartbeats. Adapted with permission from Park and Middlekauff (31).

to secondhand smoke as in habitual smokers. However, in former smokers, the SNA pattern was indistinguishable from the pattern seen in never-smokers, consistent with the notion that these effects of tobacco smoke are reversible. Hering *et al.* (33) used microneurography to directly compare resting sympathetic levels in the absence of acute nicotine exposure in hypertensive patients who were habitual smokers and in nonsmokers. Sympathetic levels were significantly greater in smokers, consistent with a chronic sympathoexcitatory effect attributable to habitual smoking (33). In summary, these findings are consistent with a sustained, chronic increase in SNA in habitual smokers, beyond the effects attributable to acute nicotine exposure. Furthermore, this pattern of increased SNA returns to normal with smoking cessation.

Potential mechanisms underlying this chronic increased sympathetic burden with smoking are depicted in the **Central Illustration**, and include: 1) activation of lung afferent C-fibers, which have an

excitatory influence on central sympathetic outflow, by $PM_{2.5}$, either directly or through the generation of reactive oxygen species; 2) direct nicotine interaction with nicotinic receptors, as well as a more enduring nicotine effect of nitric oxide depletion in the central nervous system, both excitatory; 3) persistent attenuation of the inhibitory baroreflex, so that it plays a permissive role; and 4) activation of peripheral arterial chemoreceptors, also excitatory. The remainder of this review will focus on roles of lung afferent C-fibers and the baroreflexes, including their interactions with oxidative stress/inflammation in mediating this sympathetic predominance in habitual smokers. Multiple studies have shown that smoking increases inflammation and oxidative stress both acutely and chronically (3). The increase in oxidative stress in the lungs leads to increased sympathetic activation via activation of lung afferent neurons. Chronic sympathetic activation leads, in turn, to further vascular oxidative stress, leading to a vicious cycle



CENTRAL ILLUSTRATION Proposed Model by Which Tobacco Smoke Exposure May Increase Central Sympathetic Outflow

Fine particulate matter $<2.5 \mu\text{m}$ in hydrodynamic diameter ($PM_{2.5}$) in tobacco smoke stimulates lung afferent C-fibers, either directly or through generation of oxidative stress, which then initiates neurogenic inflammation, further stimulating lung afferents. Lung afferents reflexively increase systemic (specifically cardiac) sympathetic nerve activity (SNA), which then increases cardiac inflammatory oxidation, further increasing cardiac SNA in a positive feedback loop. Nicotine in tobacco smoke stimulates nicotinic receptors in the rostral ventrolateral medulla, and decreases nitric oxide production centrally, thereby increasing central sympathetic outflow. Baroreflex suppression of sympathetic activation is attenuated in habitual smokers by 3 potential mechanisms: 1) neuroplasticity ($PM_{2.5}$ in tobacco smoke may induce neuroplasticity in the nucleus tractus solitarius, the first synapse of the baroreceptor afferents, thereby directly altering baroreflex responsiveness in smokers [34,35]); 2) oxidative stress (cigarette smoke, through particulate matter and/or nicotine, is known to generate oxidative stress [3]; in animal models, free radicals attenuated baroreceptor activity, while oxyradical scavengers increased baroreceptor activity [36,37]); and 3) endothelial dysfunction (chronic active and passive tobacco exposure is associated with increased vascular stiffness; vascular reactivity mediated by nitric oxide is impaired [38,39]; thus, blood pressure fluctuations transmitted to the baroreceptors through changes in stretch of the vascular wall are dampened). NO = nitric oxide; ROS = reactive oxygen species; SNS = sympathetic nervous system.

that results in sustained sympathoexcitation. This model also has important implications for other emissions, including marijuana, e-cigarettes, hookahs, and air pollution.

MECHANISMS OF SYMPATHETIC ACTIVATION WITH TOBACCO SMOKE EXPOSURE

STIMULATION OF LUNG AFFERENT C-FIBERS. Airways are lined with vagal afferent nerve fibers, including nonmyelinated afferent C-fibers sensitive to noxious chemicals (29). A subset of these vagal C-fibers express the acid-sensitive transient receptor potential (TRP) channels, which, when exposed to irritants, release neuropeptides locally, resulting in a local inflammatory response. This inflammatory response is characterized by the cough reflex, mucous secretion, and bronchoconstriction and thereby defends against inspired toxicants (29,40). This neurogenic inflammation creates a more sustained inflammatory oxidative environment, which further stimulates lung afferent fibers, thus reflexively increasing efferent SNA (40-43). In addition to neurogenic inflammation, toxicants in cigarette smoke and diesel exhaust may also directly stimulate acid-sensitive TRP vanilloid 1 (TRPV1) or ankyrin 1 (TRPA1) receptors on lung afferent C-fibers, thereby directly stimulating the lung afferents, which, in turn, are integrated centrally and reflexively increase efferent SNA, including cardiac SNA (29,40-50). The resultant increase in efferent cardiac SNA generates further inflammation and oxidative stress in the heart in a positive feedback loop (29,42). The reflex increase in SNA mediated by PM_{2.5} activation of TRPV1 receptors also increases cardiac vulnerability to arrhythmias in this animal model (47) (**Central Illustration**).

In summary, in animal studies of inhaled toxicants in tobacco smoke and diesel exhaust, PM_{2.5} generates lung oxidative stress and stimulates TRPV1 and TRPA1 receptors present on lung afferent C-fibers, leading to reflexively increased efferent cardiac SNA. Increased cardiac SNA causes further generation of cardiac oxidative stress, as well as increased susceptibility to arrhythmias. Whether this reflex sequence occurs in humans is unknown and mandates further study.

DIRECT AND INDIRECT (VIA NITRIC OXIDE SYNTHASE) NICOTINE EFFECTS. Studies to explain the chronic changes in SNA mediated by a central neural action of tobacco smoke have focused on two potential mechanisms (Figure 3): 1) a direct effect of nicotine on receptors in the central nervous system,

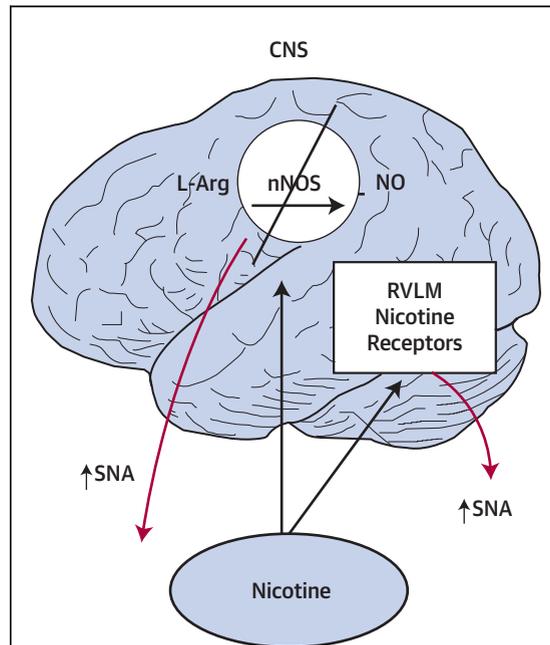


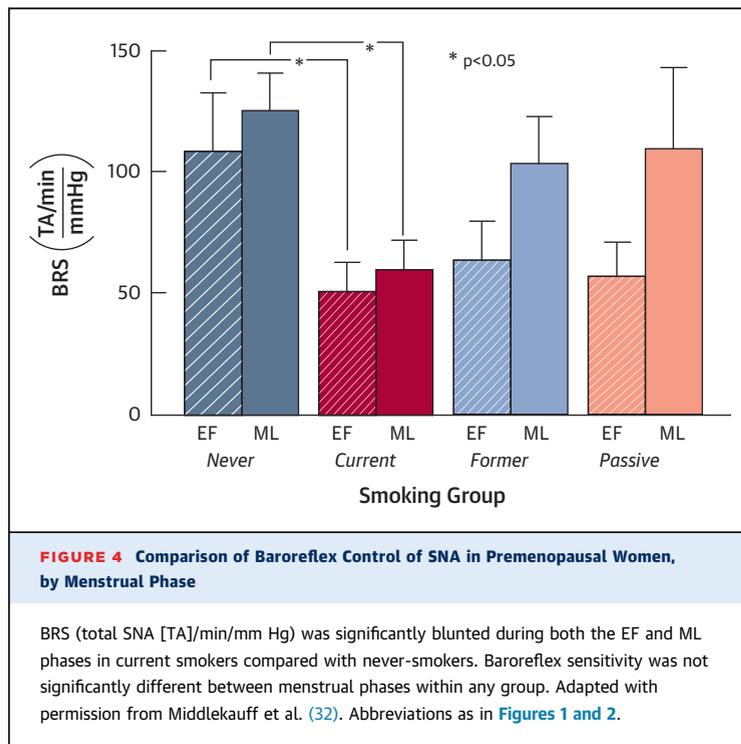
FIGURE 3 Direct and Indirect (via nNOS) Sympathomimetic Effects of Nicotine From Tobacco Smoke Exposure

There are at least two plausible mechanisms by which cigarette smoke may directly interact with the central nervous system and increase central sympathetic outflow: 1) stimulation of excitatory nicotinic receptors; and/or 2) inhibition of the inhibitory neurotransmitter nitric oxide. CNS = central nervous system; L-Arg = L-arginine; nNOS = neuronal nitric oxide synthase; NO = nitric oxide; RVLM = rostral ventrolateral medulla; SNA = sympathetic nerve activity.

and 2) nicotine-mediated inhibition of neuronal nitric oxide synthase, which decreases central nitric oxide availability, thereby removing its tonic inhibitory effect on central sympathetic outflow. The relative importance of these mechanisms in humans remains uncertain.

ATTENUATED BAROREFLEX SENSITIVITY AND DISRUPTION OF NEGATIVE FEEDBACK LOOP.

Blunted baroreflex sensitivity can lead to chronic sympathetic nervous system activation at baseline, and exaggerated increases in SNA acutely during smoking if the activation of baroreceptors fails to appropriately suppress central sympathetic neural output. In most studies of the baroreflex in smokers, they abstained from smoking for several hours, during which time nicotine levels and tolerance subsided. Acute smoking was then reintroduced as the blood pressure stimulant to test the baroreflex, potentially confounding any chronic impairment of the baroreflex with the effects of acute smoke exposure. With



this approach, baroreflex control of heart rate was consistently blunted in smokers compared with otherwise-matched nonsmokers (51-54). Nonetheless, it remains difficult to distinguish acute hemodynamic and neural effects mediated by nicotine from those potentially mediated by a chronic impairment of the baroreflex.

We reported the first direct recordings of muscle SNA during pharmacological baroreflex testing in active smokers who had abstained from smoking for ≥ 12 h compared with never-smokers to determine whether baroreflex control of muscle SNA is chronically impaired in habitual smokers (32). We found that in women who were habitual smokers, baroreflex control of muscle SNA was significantly blunted compared with that in never-smokers (Figure 4). Interestingly, we found that in women who had stopped smoking >1 year, baroreflex control of muscle SNA was no different from that of never-smokers, consistent with the reversibility of this adverse smoking effect. Whether baroreflex control of muscle SNA in men who smoke is also impaired is unknown and is an active area of research in our laboratory. Attenuation of the baroreflex inhibition in smokers may stem from one or more plausible mechanisms: 1) oxidative stress; 2) endothelial dysfunction; and/or 3) neuroplasticity (Central Illustration).

In summary, sustained attenuation in baroreflex inhibition of central sympathetic outflow, mediated by $PM_{2.5}$, and possibly nicotine, likely plays a permissive role, allowing for increased sympathetic outflow in habitual smokers.

AUGMENTED ARTERIAL CHEMOREFLEX SENSITIVITY. Acute activation of peripheral arterial chemoreceptors, located on carotid and aortic bodies, leads to acute increases in SNA, as well as rate and volume of breathing; chronic arterial chemoreflex sensitization in smokers could lead to sustained sympathetic activation. Arterial chemoreceptors are activated by hypoxia, to which habitual smokers are susceptible due to underlying lung damage and exposure to carbon monoxide in tobacco smoke. However, to date, there is no evidence for augmented arterial chemoreceptor sensitivity in habitual smokers (31,55).

NONTOBACCO CIGARETTE SMOKE EMISSIONS. For the emissions of each nontobacco cigarette product (Table 2), we will address two questions: 1) What is the evidence that the emission increases cardiovascular risk?; and 2) Given the proposed model, does the emission have known or potential effects on the autonomic nervous system?

Marijuana. Marijuana is the most widely used illicit drug in the United States, and its use is increasing (56); several states have legalized its use for medical and/or recreational purposes, contributing to the misperception that it is safe. Large epidemiological studies reporting the cardiac risk associated with marijuana are lacking, but case reports and cohort studies have reported that smoking marijuana is associated with an increased risk for triggering an acute myocardial infarction (57).

Marijuana may be expected to have significant interactions with the autonomic nervous system because marijuana smoke is generated from the combustion of organic materials and thus contains many of the same gases and $PM_{2.5}$ emissions, but in even greater concentrations than those found in tobacco smoke (58). The proinflammatory and sympathoexcitatory effects of these $PM_{2.5}$ emissions may be modulated, however, by the presence of delta-9-tetrahydrocannabinol, the main active ingredient in marijuana that binds to cannabinoid (CB) receptors 1 and 2. CB1 and CB2 receptors are found throughout the autonomic nervous system, including on sympathetic afferents. The activation of presynaptic CB1 receptors localized to sympathetic efferent neurons inhibits catecholamine release (59,60) and thus opposes the deleterious, sympathoexcitatory effects of particulates. Furthermore, CB1 and TRPV1

TABLE 2 Hemodynamic and Autonomic Effects of Noncigarette Emissions Exposure

Exposure	Key Constituents	Hemodynamic Characteristics	ANS	Cardiac Risk
Marijuana (inhaled)	PM, Δ9-THC gases (e.g., CO)	↑ BP, ↑ HR, orthostatic hypotension	↑ HRV	↑ MI risk
E-cigarettes	PM, nicotine	Unknown	Unknown	Unknown
Waterpipe (hookah)	PM, nicotine, gases (e.g., CO)	↑ BP, ↑ HR	↓ BRS, ↓ HRV	Unknown, but likely similar to cigarette smoke
Air Pollution	PM, gases (e.g., CO)	Unknown	↓ HRV	↑ CV risk short-/long-term

ANS = autonomic nervous system; BRS = baroreflex sensitivity; CO = carbon monoxide; CV = cardiovascular; E = electronic; HRV = heart rate variability; MI = myocardial infarction; PM = particulate matter; Δ9-THC = delta-9-tetrahydrocannabinol.

are co-expressed on vagal C-afferents and have opposing effects on neural function (61,62). CB1 activation by delta-9-tetrahydrocannabinol inhibits neurotransmission and neurogenic inflammation (59,60). In the only published report of the effects of marijuana on the autonomic nervous system, HRV was compared between 72 chronic marijuana users and 72 nonusers, and somewhat surprisingly, an increase in HRV was reported, consistent with an increase in vagal over sympathetic tone (62). Confirmatory studies are warranted.

In summary, case reports and cohort studies suggest that smoking marijuana carries an increased risk for triggering an acute infarct. Sympathoexcitatory effects of PM_{2.5} may be countered by delta-9-tetrahydrocannabinol interactions with CB1 receptors on efferent nerve terminals, and CB1 co-expression with TRPV1 receptors on vagal C-afferents. Considering the widespread and increasing use of marijuana, physiological studies of its acute and chronic autonomic effects and long-term cardiovascular sequelae in humans are needed.

Electronic (e)-cigarettes. Relatively recently, a new source of emissions, the e-cigarette, was introduced and is gaining unprecedented popularity, especially among young people. Although e-cigarettes are not cigarettes at all (no tobacco, no smoke), they are similar to tobacco cigarettes as a source of gases, PM_{2.5}, and nicotine. Whether they too activate the sympathetic nervous system and generate increased oxidative stress and inflammation, leading to an increased risk for cardiovascular disease, remain unknown. Because they are relatively new, and perhaps unfamiliar, a little background is warranted. An e-cigarette is a nicotine-dispensing device in which a mixture of chemicals (“e-liquid”) in a chamber is intermittently heated and aerosolized when a battery-powered heating unit is triggered by an inhalation (“puff”). There is almost a complete overlap in PM_{2.5} size and concentration between tobacco smoke and e-cigarette vapor, but tobacco

smoke differs fundamentally from e-vapor in that only tobacco smoke is produced by the combustion of organic material, and it is the combusted organic PM_{2.5} that confers the greatest toxicity (28). In the few available reports, mainstream e-vapor is void of carbon monoxide and other toxic gases and has trace to no detectable toxicants, including volatile organic compounds, carbonyls, tobacco specific nitrosamines, polycyclic aromatic hydrocarbons, and metals (63); the concentrations of these toxicants, if detected, are 9 to 450 times lower in e-vapor than in mainstream smoke from tobacco cigarettes (63).

E-liquid usually contains nicotine, although this is not obligatory, as well as an excipient, for example, propylene glycol (antifreeze) and/or glycerin, and flavors. Nicotine exposure in mainstream or secondhand e-vapor depends on the nicotine content in the e-liquid, but the nicotine concentration in even the most nicotine-concentrated e-liquid is less than that in tobacco cigarettes measured at 5 and 20 min of ad lib use (64). The principle component of e-liquid and e-vapor is propylene glycol, classified as “generally recognized as safe” by the U.S. Food and Drug Administration (FDA) and present in many common, FDA-approved injectable medications.

Unfortunately, at present, there are no animal or human data on the health effects of e-cigarettes, and extrapolation for other forms of nicotine replacement therapy is hazardous, because oral and transcutaneous formulations do not contain PM_{2.5}. Further, nicotine replacement therapy has been compared to tobacco cigarettes only for short durations; but in these short-term comparisons, it does not increase cardiac risk, even in patients with known coronary artery disease (65). Nonetheless, nicotine increases SNA, which should raise concern over long-term e-cigarette use, especially in young people who are nonsmokers.

In summary, the absence of combustion and organic substrates, and the knowledge that

propylene glycol is used safely as an injectable, are reassuring. However, the lack of *e*-liquid regulation, the presence of nicotine as well as detectable levels of toxicants and metal “impurities” (potentially from the device itself [66]), and the virtually complete overlap in PM_{2.5} size and concentration with tobacco smoke, coupled with reports that even low exposures to PM_{2.5} confer significant cardiac risk, are concerning and warrant further investigation into the physiological effects of these exposures.

Waterpipes (hookahs). Although waterpipe tobacco smoking has existed for centuries, its resurgence, especially among young people, is high; approximately one in five of all American college students admits to waterpipe smoking in the past year (67). This increase has been attributed to the social acceptance of waterpipe smoking, social bonding while sharing a waterpipe, and the misperception that waterpipe smoking is safe. The cardiac risks of waterpipe smoking have not been systematically studied but are likely to be significant.

Compared with tobacco cigarette smoking, waterpipe tobacco smoking has been associated with greater smoke exposure and increased nicotine and carbon monoxide blood levels. The effects of waterpipe tobacco smoking on the autonomic nervous system can be assumed to be virtually the same as those with cigarette smoking, and emerging evidence supports this assumption (68,69). Acute waterpipe tobacco smoking markedly impairs baroreflex control of the heart rate in otherwise healthy chronic waterpipe users (70). Not surprisingly, HRV is acutely decreased during waterpipe tobacco smoking (71). Importantly, HRV is also decreased when a waterpipe is used to smoke a nontobacco, non-nicotine, product, supporting the concept that the PM_{2.5} and gaseous components of smoking, not just the nicotine, interact adversely with the autonomic nervous system (71).

In summary, the long-term cardiovascular consequences of waterpipe tobacco smoking in the United States have not been studied, largely because usage has only recently increased. However, given the similarities between waterpipe tobacco smoke and cigarette tobacco smoke, and the available studies reporting increased SNA and attenuated baroreflex control, the potential cardiovascular risks are cause for concern.

Air pollution. As noted earlier, the constituents and size of PM_{2.5} in air pollution (27) are remarkably similar to those in cigarette smoke, although at differing concentrations. The concentration of PM_{2.5} in mainstream smoke is several-fold greater, but

concentrations in secondhand smoke are on par with those in air pollution, and of course, exposure to even low levels of PM_{2.5} has been associated with a significantly increased cardiac risk (27). In fact, exposure to PM_{2.5} in air pollution is recognized to increase cardiovascular risk and mortality worldwide, underlying almost 1 million premature deaths per year (28). Short-term (days to weeks) exposure to PM_{2.5} can trigger fatal and nonfatal myocardial infarction, and long-term (years) exposure increases cardiovascular mortality (reviewed by Brook *et al.* [28]).

Evidence supports the concept that adverse affects on the autonomic nervous system contribute to this increased cardiac risk (28,29,42,47). As reviewed earlier, in animal models, exposure to PM_{2.5} from diesel exhaust increased efferent cardiac SNA through the generation of reactive oxygen species and the activation of TRPV1 receptors present on vagal afferent C-fibers in the lungs (29,42). In a meta-analysis of data from 20 studies that included over 18,000 people, particulate air pollution was associated with a significant reduction in HRV, consistent with a sympathetic predominance (72). Unfortunately, direct microneurographic recordings of SNA and measurements of baroreflex function in humans exposed to air pollution have not been performed to date and are needed to further elucidate mechanisms.

In summary, air pollution increases short-term and long-term cardiac risk, likely through the activation of lung afferent C-fibers and subsequent reflex stimulation of efferent cardiac SNA; air pollution and cigarette smoke (except for the nicotine) share considerable mechanistic overlap.

CLINICAL IMPLICATIONS

Understanding the mechanisms leading to the sympathetic predominance that accompanies exposures to nicotine and PM_{2.5} will lead to therapies to counter adverse cardiac sequelae. Beta-adrenergic blockers are already widely used to decrease cardiac risk in patients with known cardiac disease, but whether they should be used (and at what threshold) in habitual smokers without known cardiac disease is unknown. Similarly, antioxidant therapy, although disappointing in many established cardiac populations, may be more effective in smokers without established cardiac disease but who had oxidative stress increase (73). Finally, the development of agonists to CB1 receptors and antagonists to TRPV1 and TRPA1 receptors may prove a novel therapeutic strategy (74).

CONCLUSIONS

Acute and long-term exposure to cigarette smoke, in either active or passive smokers, leads to acute and chronic changes in the balance of the autonomic nervous system, resulting in sympathetic predominance. Acute sympathetic activation during cigarette smoke exposure has been attributed to nicotine interactions with the autonomic nervous system, with a contribution by PM_{2.5}. Chronic, sustained effects are likely principally mediated by lung afferent C-fibers, either directly through TRPV1 receptors and/or by generation of oxidative stress. Nicotine uncoupling of neuronal nitric oxide synthesis in the central nervous system, either acutely or long-term, has not

been investigated in humans but may also contribute to sympathetic activation. The baroreflex, which suppresses sympathetic activation, is attenuated in habitual smokers and plays a permissive role in this sustained sympathetic activation. Nong cigarette emissions (e.g., marijuana, e-cigarettes, waterpipes, and air pollution) also interact with the autonomic nervous system but are understudied.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Holly R. Middlekauff, Division of Cardiology, Department of Medicine, University of California-Los Angeles, 10833 LeConte Avenue, CHS A2-237, Los Angeles, California 90095. E-mail: hmiddlekauff@mednet.ucla.edu.

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APPENDIX For supplemental references, please see the online version of this article.