Cigarette Smoking Increases Sympathetic Outflow in Humans

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Background—It is generally accepted that smoking increases blood pressure and inhibits muscle sympathetic nerve activity (SNA). The decrease in muscle SNA with cigarette smoking might be secondary to baroreflex responses to the pressor effect of smoking, thus obscuring a sympathetic excitatory effect of smoking. We tested the hypothesis that smoking increases sympathetic outflow.

Methods and Results—We examined the effects of sham smoking, cigarette smoking, and cigarette smoking in combination with nitroprusside on muscle (baroreflex-dependent) SNA in 10 healthy habitual smokers. The 3 sessions were performed in random order, each study on a separate day. In an additional study, we also investigated the effects of sham smoking and cigarette smoking on skin (baroreflex-independent) SNA in 9 subjects. Compared with sham smoking, cigarette smoking alone increased blood pressure and decreased muscle SNA. When the blood pressure increase in response to smoking was blunted by nitroprusside infusion, there was a striking increase in muscle SNA. Muscle SNA increased up to 3-fold the levels seen before smoking (P<0.001), accompanied by an increase in heart rate of up to 37±6 bpm. Cigarette smoking also induced a 102±22% increase in skin SNA (P=0.03).

Conclusions—These data provide the first direct evidence that cigarette smoking increases sympathetic outflow.

Key Words: smoking • blood pressure • heart rate • nervous system • baroreceptors

Cigarette smoking is a leading cause of cardiac and vascular disease. The mechanisms by which cigarette smoking may lead to cardiovascular events include endothelial dysfunction, accelerated atherosclerosis, increased platelet aggregation, coronary vasoconstriction, and increased carbon monoxide levels. Cigarette smoking is a strong risk factor for acute ischemic cardiac events such as myocardial infarction and sudden death, but it is much less a risk factor for chronic ischemic syndromes like angina pectoris. Acute sympathetic and hemodynamic responses to cigarette smoking may be implicated in the link between smoking and acute cardiovascular events. Studies of the acute effects of cigarette smoking show that smoking results in an increase in blood pressure and inhibition of muscle SNA. These findings have been cited as evidence that cigarette smoking does not elicit a centrally mediated activation of efferent sympathetic nerve traffic. Baroreflex responses to pressor effects of smoking may inhibit central sympathetic activity. When similar blood pressure increases as seen after cigarette smoking are induced by intravenous administration of phenylephrine, sympathetic activity is significantly lower than levels recorded during smoking. Smoking also augments the sympathetic neural responses to brief hypotension. Lower levels of exposure to cigarette smoke during passive smoking result in minimal blood pressure change but an increase in sympathetic activity. Hence, increased blood pressure in response to smoking, acting via the baroreflexes, may elicit sympathetic inhibition and thus may obscure any sympathetic excitatory property of cigarette smoke. On the basis of these considerations, we tested the hypothesis that cigarette smoking causes an increase in sympathetic outflow.

This hypothesis was tested in 2 ways. First, we examined the effects of sham smoking, cigarette smoking, and cigarette smoking in combination with a sodium nitroprusside infusion. Sodium nitroprusside was used to attenuate the blood pressure increase during cigarette smoking and thus permit identification of any smoking-associated increase in muscle sympathetic nerve outflow. Second, we investigated the effects of sham smoking and cigarette smoking on skin SNA. Skin sympathetic activity is not attenuated by increased blood pressure and baroreflex activation. Thus, we hypothesized that cigarette smoking in the absence of a substantial blood pressure increase would increase muscle SNA and that cigarette smoking, in contrast to sham smoking, would increase skin SNA.

Methods

Subjects
We studied the effects of smoking in 14 healthy normotensive habitual smokers (age, 22±7 years [mean±SD]; mean body mass...
chemical detection in a BAS Biophase ODF (C-18) column and a measured by high-performance liquid chromatography with electro-
smoking. The dose of nitroprusside used was 0.3 cigarette smoking to attenuate the blood pressure increase during separate day in which sodium nitroprusside was infused during
on muscle SNA were studied in 10 of these subjects, and the effects of smoking on muscle SNA were studied in 9 subjects. None of the subjects was taking any medication nor had any history of chronic disease. The studies were approved by the Institutional Review Board on Human Investigation, and written informed consent was obtained.

Measurements
Subjects were studied in the supine position. Heart rate was measured continuously by an ECG. Blood pressure was measured each minute by an automatic sphygmomanometer (Life Stat 200, Physio-
Control Corp). In 7 of the 10 subjects in the muscle SNA study, measurements of CVP were also obtained during smoking with and without nitroprusside by a catheter inserted percutaneously into an antecubital vein and advanced into an intrathoracic vein.
Multitunit postganglionic SNA was recorded with tungsten micro-
electrodes (shaft diameter, 200 μm, tapering to an uninsulated tip of 1 to 5 μm) inserted selectively into muscle or skin fascicles of the peroneal nerve.14 A subcutaneous reference electrode was first inserted 2 to 3 cm away from the recording electrode, which was itself inserted into the nerve fascicle. The neural signals were amplified, filtered, rectified, and integrated to obtain a voltage display of sympathetic nerve activity. Carboxyhemoglobin levels were determined by spectrophotome-
try with an OSM3 Hemoximeter (Radiometer America Inc). Plasma nicotine levels were determined through capillary column gas chromatography, with detection on electron impact mass spectrom-
etry and selected ion monitoring according to methods similar to those described by Jacob et al.15 Plasma norepinephrine levels were measured by high-performance liquid chromatography with electro-
chemical detection in a BAS Biophase ODF (C-18) column and a BAS LC-4B detector (Bio Analytical Systems). Interassay and intra-assay coefficients in our laboratory are 3.8% and 3.6%, respectively.22 Blood samples were obtained at the outset of the study and 3 minutes after completion of each of the second and third cigarettes (3 blood samples per session).

Protocol and Procedures
All subjects were asked to avoid smoking for at least 12 hours before each study. Subjects were studied in the supine position.

Protocol 1: Muscle Sympathetic Nerve Responses to Smoking
The effect of smoking on muscle sympathetic nerve discharge was determined in 10 subjects. The study design was randomized and placebo controlled with 3 experimental sessions (sham smoking, smoking alone, and smoking in combination with the intravenous infusion of sodium nitroprusside). The sessions were performed in random order, each session on a separate day.
After 15 minutes of rest, baseline measurements were obtained. The subjects were then asked to smoke 2 cigarettes containing 1.1 mg nicotine or simulate smoking with a drinking straw with a filter (sham smoking).15 The 2 cigarettes were separated by 5 minutes. Forty-five minutes after finishing the second cigarette, subjects smoked a third cigarette or sham cigarette.
Subjects also underwent an identical experimental session on a separate day in which sodium nitroprusside was infused during cigarette smoking to attenuate the blood pressure increase during smoking. The dose of nitroprusside used was 0.3 μg ⋅ kg⁻¹ ⋅ min⁻¹; increased as required to minimize the blood pressure increase during smoking. Nitroprusside infusion was carried out during smoking of each of the 3 cigarettes and was initiated at the start of smoking. Special care was taken not to lower blood pressure below the presmoking values. Nitroprusside was administered only during smoking and was directed at maintaining blood pressure during each cigarette at the same level as that just before that particular cigarette was smoked. Nitroprusside was discontinued on cessation of smoking. We noted a sustained increase in blood pressure after smoking.
We did not use nitroprusside to lower blood pressure to the levels recorded at the outset of the study, ie, before any cigarettes were smoked. Nitroprusside was used during smoking only to lower blood pressure to the level immediately before each cigarette smoking session.
Because of a slightly but significantly lower CVP during smoking plus nitroprusside compared with smoking alone (data not shown), we also examined the effects of decreasing CVP in 7 normal subjects (age, 27±7 years). These subjects underwent 5 minutes of LBNP at −5 mm Hg to examine the effect of lower CVP on muscle SNA and heart rate.

Protocol 2: Effects of Smoking on Skin Sympathetic Activity
We compared the response of skin sympathetic activity during the smoking of 1 cigarette with that evoked by sham smoking in 9 subjects. Smoking and sham smoking were performed in a random-
ized order, separated by a 15-minute recovery, on the same day. Nitroprusside was not used in studies of skin sympathetic activity.

Analyses
Tracings of ECG, muscle and skin SNA, and CVP were recorded on a Gould 2800S recorder and with a MacLab data acquisition system (AD Instruments) on a Macintosh Computer (Apple Inc). Sympa-
thetic bursts were identified by careful inspection of the voltage neurogram. The amplitude of each burst was determined, and muscle sympathetic activity was calculated as bursts per minute multiplied by mean burst amplitude and expressed as units per minute. Skin sympathetic activity was calculated as area under the curve and expressed as units times seconds. The intraobserver and interob-
server variabilities in our laboratory have been reported to be 4.3±0.3%23 and 5.4±0.5%,24 respectively. Measurements of nerve activity, heart rate, and blood pressure were obtained at baseline before each cigarette was smoked. Changes in SNA, MAP, and heart rate were calculated for the last 2 minutes of smoking, when the pressor effects of smoking are especially marked.25 SNA was expressed as a percentage of changes from baseline.
Data were analyzed by repeated-measures ANOVA with time (before versus during smoking) as the within factor and session (sham smoking, cigarette smoking alone and cigarette smoking with nitroprusside infusion) as the between factor. P values for differ-
ences within a session were obtained by post hoc tests (planned contrasts). Results are expressed as mean±SEM. P<0.05 was considered significant.

Results

Protocol 1: Smoking and Muscle Sympathetic Activity
At the start of the study on each of the days during which sham smoking, smoking alone, and smoking plus nitroprusside were studied, baseline plasma nicotine averaged 1.8±0.4, 1.6±0.4, and 1.6±0.4 ng/mL, respectively (P=NS). Carboxyhemoglobin measures at the onset of the study on each of these 3 days averaged 1.6±0.3%, 1.8±0.3%, and 1.8±0.3%, respectively (P=NS), and plasma norepinephrine levels averaged 170±12, 171±19, and 180±9 pg/mL, respectively (P=NS). Plasma nicotine, car-
boxyhemoglobin, and norepinephrine levels during smoking alone and smoking plus nitroprusside are shown with corre-
sponding blood pressure and heart rate changes in Table 1.
Sham smoking did not change plasma norepinephrine levels (data not shown).

Figures 1 and 2 show individual changes in MAP and muscle SNA during smoking, both alone and with nitroprusside infusion. Group data for MAP, heart rate, and muscle SNA are shown in Figure 3. Smoking the first cigarette was associated with a marked increase in both MAP and heart rate, with a decrease in muscle SNA (Figures 1 and 3). The increase in MAP and heart rate and the muscle SNA inhibition during smoking of the second and third cigarettes were less pronounced (Figure 3).

When the smoking-induced elevation in blood pressure was attenuated with nitroprusside, muscle SNA increased strikingly (Figures 2 and 3). The increase in muscle SNA was evident during smoking of each of the 3 cigarettes and was especially evident during the third cigarette when muscle

<table>
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<tr>
<th>Measurement</th>
<th>Smoking-Only Session</th>
<th>Smoking-Plus-Nitroprusside Session</th>
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<td>Outset of Study</td>
<td>After 2nd Cigarette</td>
<td>After 3rd Cigarette</td>
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<tr>
<td>Plasma nicotine levels, ng/mL</td>
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<td>Carboxyhemoglobin, %</td>
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<td>Plasma norepinephrine levels, pg/mL</td>
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<td>189±27</td>
<td>214±33†</td>
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<tr>
<td>Heart rate, bpm</td>
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<tr>
<td>MAP, mm Hg</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>64±2</td>
<td>68±2†</td>
<td>73±2*</td>
</tr>
</tbody>
</table>

P values are for time × session (smoking only vs smoking plus nitroprusside) interaction term (ANOVA). Values are mean±SEM.

*P<0.001, †P<0.05, ‡P<0.01 vs outset of study (planned contrasts).

Figure 1. Recordings of muscle SNA before and during smoking in 1 subject. Smoking the first cigarette was associated with a marked increase in MAP and a decrease in muscle SNA. Baseline blood pressure was higher and the increase in MAP and consequent inhibition of muscle SNA was less pronounced during smoking of the second and third cigarettes, probably because of a sustained increase in pressure after the first cigarette.

Figure 2. Recordings of muscle SNA before smoking and during smoking with infusion of nitroprusside (same subject as in Figure 1). When the smoking-induced elevation in blood pressure was attenuated with nitroprusside, muscle SNA increased strikingly. Baseline blood pressures before the second (82 mm Hg) and third (86 mm Hg) cigarettes are higher than the first baseline blood pressure at the outset of the study before any cigarettes were smoked (79 mm Hg) because of a sustained increase in blood pressure after smoking. Nitroprusside was infused only during smoking and was directed at maintaining blood pressure close to levels immediately before that particular cigarette.
Smoking-induced tachycardia was significantly greater during the session when intravenous infusion of sodium nitroprusside was used to minimize the blood pressure increase during cigarette smoking (P<0.05 for both the first and second cigarettes, P<0.01 for the third cigarette) (Figure 3). Sham smoking had no significant effect on heart rate (Figure 3). MAP decreased slightly during the second and the third sham smoking, and muscle SNA decreased during the second sham smoking (Figure 3). CVP was unchanged during sham smoking.

CVP changes during smoking and smoking plus nitroprusside were similar for the first cigarette (data not shown); however, CVP decreased slightly more during smoking and nitroprusside compared with smoking alone for the second (~1.0±0.2 versus ~0.1±0.2 mm Hg, respectively) and third (~1.9±0.4 versus ~0.7±0.3 mm Hg, respectively) cigarettes (both P<0.05).

To determine the potential effect of the slightly lower CVP, we examined the effect of 5 minutes of LBNP at ~5 mm Hg. LBNP decreased CVP by 2.1±0.3 mm Hg (P<0.001) and decreased MAP by 1.9±0.9 mm Hg (P=0.05). Heart rate was unchanged. Muscle SNA increased by only 41±19% (P=0.05) in response to the decrease in CVP and blood pressure.

Consistent with findings of other investigators,15 we noted a sustained increase in blood pressure and heart rate after smoking. These changes and accompanying levels of muscle SNA are shown in Table 2. After sham smoking, there was no evidence of any sustained increases in blood pressure or heart rate (2.2±1.3 mm Hg and 0.6±0.6 bpm; both P=NS).

**Protocol 2: Effects of Smoking on Skin Sympathetic Activity**
Sham smoking of 1 cigarette did not change MAP (82±2 mm Hg before and 80±2 mm Hg after sham smoking; P=0.08). Actual smoking of a single cigarette increased MAP from 80±2 to 88±3 mm Hg (P=0.003). Smoking caused a marked increase in skin SNA (P<0.001), far greater than that observed during sham smoking (P=0.03) (Figures 4 and 5). Nicotine, carboxyhemoglobin, and norepinephrine levels were not measured during studies of skin sympathetic activity.

**Discussion**
These studies provide direct evidence that cigarette smoking increases sympathetic outflow to skin and muscle blood vessels. The novel findings in our study are, first, that when the blood pressure increase in response to cigarette smoking is blunted by simultaneous infusion of sodium nitroprusside, there is a striking increase in sympathetic nerve traffic. Levels of sympathetic activity may reach 3-fold the levels seen before smoking. Second, the increase in sympathetic nerve traffic to muscle blood vessels is accompanied by tachycardia, with increases in heart rate of up to 37 bpm. Third, skin SNA, which is not inhibited by an increase in blood pressure, is also increased during smoking.

The increases in sympathetic activity and heart rate were evident even though blood pressure during smoking plus sodium nitroprusside increased by between 1 and 5 mm Hg over the presmoking baseline levels. These studies were

| TABLE 2. MAP, Heart Rate, and Muscle SNA Before the 1st, 2nd, and 3rd Cigarettes During the Smoking-Only and Smoking-Plus-Nitroprusside Sessions, Demonstrating Sustained Pressor Effect of Smoking |
|-------------------------------------------------|--|-------------------------------------------------|--|-------------------------------------------------|--|-------------------------------------------------|---|
| MAP, mm Hg | 80±1 | 84±1* | 87±2† | 79±1 | 82±1* | 85±2† | 0.79 |
| Heart rate, bpm | 59±2 | 79±3† | 70±3† | 62±2 | 84±3† | 74±3† | 0.85 |
| Muscle SNA, U/min | 77±139 | 641±126* | 660±100 | 764±112 | 609±111* | 660±129 | 0.75 |

*P values are for time×session (smoking only vs smoking plus nitroprusside) interaction term (ANOVA). Values are mean±SEM. *P<0.05, †P<0.001 vs outset of study (planned contrasts).
conducted in young, healthy subjects in whom even small increases in blood pressure will cause a marked suppression in sympathetic nerve traffic and slowing of heart rate. Thus, cigarette smoke appears to be a powerful sympathetic excitatory influence, with its effects evident despite higher blood pressures.

Smoking resulted in increases in plasma norepinephrine levels, consistent with findings of other investigators.15,25 This may be explained in part by the direct effects of nicotine on sympathetic nerve endings, increasing catecholamine release. Nitroprusside did not increase norepinephrine levels further, despite the increase in muscle SNA. This is in keeping with studies by Grassi et al26 showing that during known changes in sympathetic cardiovascular drive, changes in muscle SNA are more clearly evident than changes in plasma norepinephrine levels.

Despite the higher blood pressures and muscle sympathetic nerve inhibition, smoking alone resulted in significant increases in heart rate. This may result because smoking has a greater effect on increasing sympathetic drive to the heart than to peripheral blood vessels. A direct effect of nicotine on heart rate via stimulation of intracardiac sympathetic nerves27,28 cannot be excluded, because a sympathetic stimulatory effect of nicotine has been demonstrated in centrally denervated, incubated cardiac tissue.29 Alternatively, smoking may itself impair arterial baroreflex function,15,30 perhaps by reducing arterial distensibility acutely.31 Simultaneous tachycardia and inhibition of sympathetic traffic to muscle blood vessels suggests a differential baroreflex impairment affecting regulation of heart rate more than regulation of sympathetic traffic to muscle blood vessels.

We also noted a sustained increase in blood pressure and heart rate 30 minutes after smoking the first 2 cigarettes.13 Nitroprusside was used only during actual smoking and only to lower blood pressure to approach levels recorded just before each cigarette. Nitroprusside was discontinued on cessation of smoking. Because of the sustained blood pressure increase after smoking, baseline blood pressure before the third cigarette was higher (by ≈7 mm Hg) than that recorded at the outset of the study, before any cigarettes were smoked. If blood pressure had been lowered further to levels recorded before any cigarettes were smoked, the increases in sympathetic activity and heart rate after smoking would be even greater than is evident in these data. Our results suggest that the arterial baroreflexes, responding to increases in blood pressure during smoking, exert a protective effect by inhibiting the sympathetic activation and tachycardia that result from cigarette smoke. Thus, in those patients with cardiovascular disease who have impaired baroreflex sensitivity, such as patients with hypertension32 and heart failure,33 impaired baroreflex function may result in significant tachycardia and sympathetic activation during cigarette smoking. Indeed, previous studies indicate that the increase in ambulatory blood pressure seen after smoking is more pronounced in elderly hypertensive patients.34,35

Apart from an anecdotal uncontrolled report suggesting that smoking may increase skin sympathetic activity,36 the effect of cigarette smoking on sympathetic activity to skin has not previously been studied. Sham smoking alone caused an increase in sympathetic discharge to skin, probably because of the alerting response to the maneuver. However, cigarette smoking caused a more marked increase in skin sympathetic discharge, even though we did not seek to maintain blood pressure...
pressure at baseline levels by sodium nitroprusside. Skin sympathetic activity, in contrast to muscle sympathetic activity, is unlikely to be inhibited by blood pressure changes.18,19 Thus, the sympathetic excitatory effect of cigarette smoke is evident in measures of skin sympathetic activity even in the absence of sodium nitroprusside infusion.

Bernardi et al27 have recently shown that skin microcirculation is modulated by the arterial baroreflex. Even if the baroreflex did have any inhibitory influence on skin SNA, the sympathetic-excitatory effects of smoking override any such inhibition. The increase in skin sympathetic activity is consistent with earlier studies by Coffman34 showing cutaneous vasoconstriction during smoking. The increases in muscle SNA, skin sympathetic activity, and heart rate with smoking suggest that cigarette smoke may act at a central level to cause a uniform increase in sympathetic nerve traffic to blood vessels, skin, and the heart.

How does cigarette smoke increase sympathetic outflow and blood pressure? Carbon monoxide is unlikely to be involved in this response.9 Nicotine or 1 or more toxic agents in cigarette smoke may be implicated.8 Although tachycardia during smoking contributes to the increase in blood pressure, other mechanisms by which cigarette smoking may raise blood pressure include $\alpha_1$-adrenoceptor–mediated vasoconstriction,25 vasopressin release,40 and possibly direct effects on endothelial function.7

The use of sodium nitroprusside to lower blood pressure may have influenced our findings. Musialek et al41 have shown that nitroprusside infusion has a direct effect on increasing sinus node firing; hence, we may have overestimated the effects of smoking on heart rate. Conversely, baroreflex responses to vasoactive agents may also reflect changes in wall dimension and wall tension.42 Increased distensibility of baroreceptor areas in the carotid sinus and aortic arch due to nitroprusside may increase baroreceptor firing and cause an underestimation of the heart rate and muscle SNA responses to smoking.

For the following reasons, it is unlikely that our findings of increased sympathetic activity during smoking plus nitroprusside are explained by changes in CVP during sodium nitroprusside infusion. First, during the first cigarette, blood pressure increased by 5 mm Hg despite nitroprusside infusion during cigarette smoking. In addition, for the first cigarette, CVP was not different between the smoking plus nitroprusside session and the smoking only session. Despite the absence of any difference in CVP and despite the increase in blood pressure during smoking plus nitroprusside, sympathetic activity increased by >50% from baseline levels, and heart rate increased by 37 bpm. Second, the sympathetic excitatory effects of cigarette smoke are further confirmed by increases in skin sympathetic activity, which are evident despite an increase in blood pressure, and in the absence of any infusion of sodium nitroprusside. Third, the differences in CVP between smoking alone and smoking with nitroprusside was very small, $\approx$ 1 mm Hg. Combined reductions of CVP by 2 mm Hg and MAP by 2 mm Hg during LBNP elicited no change in heart rate and an increase in muscle sympathetic traffic by only $\approx$ 40% compared with an increase of $\approx$ 200% during smoking plus nitroprusside.

Similar changes in nicotine and carboxyhemoglobin levels during smoking alone and smoking plus nitroprusside indicate (1) the equivalence of smoke exposure in both sessions and (2) that neither of these variables explains the difference in sympathetic activation and tachycardia in the 2 sessions.

In conclusion, cigarette smoking has a powerful sympathetic excitatory effect, influencing sympathetic drive to muscle blood vessels, to skin, and to the heart. In young, healthy subjects, the baroreflexes, responding to the blood pressure increase from cigarette smoking, prevent the increase in muscle SNA and blunt the increase in heart rate. We speculate that in patients in whom baroreflex function is impaired, cigarette smoking may induce overt sympathetic excitation. These findings may have implications for our understanding of the mechanisms linking smoking to acute cardiovascular events.

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