Cigarette Smoking Augments Sympathetic Nerve Activity in Patients With Coronary Heart Disease

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SUMMARY

It has been shown that cigarette smoking increases blood pressure (BP) and heart rate (HR), and decreases muscle sympathetic nerve activity (MSNA) in healthy young smokers. The decrease in MSNA might be secondary to baroreflex responses to the pressor effect. We tested the hypothesis that cigarette smoking increases MSNA in smokers with impaired baroreflex function.

The effects of cigarette smoking on BP, HR, forearm blood flow (FBF), forearm vascular resistance (FVR), and MSNA were examined in 14 patients with stable effort angina (59 ± 3 years, group CAD) and 10 healthy smokers (23 ± 1 years, group C). In group CAD, the arterial baroreflex sensitivity (BRS) was significantly lower than in group C (4.7 ± 0.8 versus 15.1 ± 2.2 msec/mmHg, $P < 0.01$). In both groups, cigarette smoking increased the plasma concentration of nicotine, systolic and diastolic BP, HR, and FVR significantly ($P < 0.01$), but decreased FBF significantly ($P < 0.01$). After smoking, MSNA was decreased significantly in group C (from 35.2 ± 3.5 to 23.5 ± 3.2 bursts/100 beats, $P < 0.01$), but increased significantly in group CAD (from 48.8 ± 5.4 to 57.3 ± 5.5 bursts/100 beats, $P < 0.01$). There was significant correlation between BRS and changes in MSNA ($r = -0.62$, $P < 0.01$).

Cigarette smoking increased MSNA in smokers with impaired baroreflex function. This demonstrates that cigarette smoking stimulates sympathetic nerve activity by both a direct peripheral effect and a centrally mediated effect. (Int Heart J 2008; 49: 261-272)

Key words: Cigarette smoking, Nicotine, Coronary artery disease, Angina pectoris, Muscle sympathetic nerve activity, Sympathetic activity, Baroreflex sensitivity

Cigarette smoking is established as a major risk factor for coronary heart disease.1-5) This effect is caused by sympathetic activation,6-8) accelerated atherosclerosis,9) coronary vasoconstriction10-14) endothelial dysfunction,15-18) inflammation,19) hypercoagulability,19) and platelet activation20,21) due to cigarette smoking. There are many reports showing the acute sympathetic effects of cigarette smoking. Cigarette smoking increases heart rate (HR), blood pressure (BP), and plasma concentration of norepinephrine,6-8,22-24) but decreases muscle sympa-
thetic nerve activity (MSNA). Cigarette smoking acts mainly via direct stimulation of postganglionic sympathetic nerve endings rather than centrally mediated activation of efferent sympathetic nerves.

However, a recent clinical study demonstrated that there was a striking increase in MSNA when the blood pressure increase in response to smoking was blunted by nitroprusside infusion. Cigarette smoking has been shown to increase skin sympathetic nerve activity, which is not attenuated by increased BP or baroreflex activation. These data show that cigarette smoking increases sympathetic nerve outflow.

If the decrease in MSNA due to cigarette smoking is caused by baroreflex stimulation triggered by the smoking-related pressor response, the MSNA in the patients with impaired baroreflex function is increased by cigarette smoking, and there is a relationship between the percent changes of the MSNA and baroreflex sensitivity (BRS). On the basis of these considerations, we examined the effects of cigarette smoking in patients with stable effort angina who have impaired BRS as compared with otherwise healthy, habitual smokers. The relationship between the changes in MSNA and BRS were also tested.

**METHODS**

**Subjects:** We studied the effects of cigarette smoking in 14 stable effort angina subjects (group CAD) and 10 healthy volunteers (group C). All subjects were habitual cigarette smoking men with normal cardiac function. The mean age of group CAD was 59 ± 3 years (mean ± SEM; range, 34-72 years), and group C was 23 ± 1 years (mean ± SEM; range, 20-28 years). Myocardial ischemia was verified in the CAD group patients by treadmill stress electrocardiographic testing or thallium-201 myocardial scintigraphy. Coronary arterial narrowing was also confirmed by coronary angiography. Written informed consent was obtained from each subject after a detailed explanation of the purpose and procedures of the study. The protocol was approved by the Ethical Panel of the First Department of Internal Medicine, Kanazawa University.

**Measurements:** Subjects were studied in the supine position. HR was monitored with an electrocardiogram throughout the study. BP was measured directly and continuously in one arm. Forearm blood flow (FBF) was measured with a strain-gauge plethysmograph (MedaSonic, Mountain View, California) using a venous occlusion technique in another arm. The strain gauge was placed approximately 5 cm below the antecubital crease. The pressure in the venous occlusion cuff was set at 40 mmHg. FBF was taken as the average of 5 flow measurements. Forearm vascular resistance (FVR) was calculated by dividing the mean BP (diastolic BP plus one-third of the pulse pressure) by the FBF. A polyethylene catheter was
placed in the anticubital vein to take blood samples for measurement of plasma concentrations of norepinephrine and nicotine. Plasma concentrations of norepinephrine were measured by high-performance liquid chromatography with an electrochemical detector.\textsuperscript{27} Plasma concentrations of nicotine were determined by capillary column gas chromatography, with detection with electron impact mass spectrometry and selected ion monitoring according to methods similar to those described by Jacob, \textit{et al.}\textsuperscript{28} Multiunit postganglionic MSNA was recorded from a muscle nerve fascicle in the perineal nerve at the level of the fibular head using tungsten microelectrodes (FHC Inc., Bowdoinham, Maine) and micro-neurographic techniques.\textsuperscript{29,30} The electrodes were connected to a preamplifier with a gain of 1000 and an amplifier with a gain of 70. The signal was fed through a bandpass filter (700-2000 Hz) and a resistance-capacitance integrating circuit with a time constant of 0.1 second, to produce a mean voltage neurogram. The signal was fed through a loudspeaker, displayed on an oscilloscope, and recorded with a paper chart recorder (Nihon Koden, Tokyo). MSNA was identified on the basis of its relationship to cardiac and respiratory activity, its tendency to increase during the Valsalva maneuver, and its lack of change during arousal stimuli and skin stroking. Sympathetic bursts were determined by inspection of the filtered and mean voltage neurograms. Nerve activity is expressed in both bursts per minute (BR) and bursts per 100 heart beats (BI).

BRS was assessed as previously described.\textsuperscript{31} HR and BP were recorded continuously at a speed of 100 mm/sec. Phenylephrine (100 \(\mu\)g) was given intravenously as two or more bolus injections at intervals of least 5 minutes to raise systolic arterial pressure. The correlation between systolic arterial pressure and R-R interval on the electrocardiogram while raising the systolic arterial pressure was calculated. The slope of the line was defined as BRS when the correlation coefficient was greater than 0.70.

**Protocol and procedures:** This study was performed in the afternoon. All subjects were asked to avoid cigarette smoking for at least 6 hours before this study, and eating was not permitted for at least 3 hours before this study. They were permitted to take medicine as usual. Subjects were studied in the supine position, and the arterial and venous cannulas were inserted into the brachial artery and anticubital vein.

BP, HR, and MSNA were recorded continuously throughout the procedure. After 10 minutes of rest, baseline measurements and BRS were obtained. The subjects were then asked to smoke 2 cigarettes containing 2.2 mg of nicotine. The subjects were required to finish smoking within 5 minutes. Ten minutes after finishing the cigarettes, the measurements were repeated.

**Data analysis:** Data from individual subjects are expressed as the mean ± SEM. The significance of differences in hemodynamic and MSNA variables between
before and after cigarette smoking was assessed by Wilcoxon single-rank non-parametric analysis. The significance of differences in hemodynamic and MSNA variables between group CAD and group C was assessed with the Mann-Whitney U test. Correlations between changes in MSNA and BRS were tested by the Pearson correlation coefficient. Values of $P < 0.05$ were considered to indicate statistical significance.

**RESULTS**

**Baseline characteristics:** The baseline characteristics of the subjects are presented in Table I. There was no significant difference in body weight between the groups. Age, smoking period, and body mass index in group CAD were significantly larger than in group C. Height in group CAD was significantly smaller than in group C. Group C had no chronic disease and no medication. In group CAD, 9 patients had hypertension, 5 patients had diabetes mellitus, and 4, 6, 9, and 5 patients were treated with nitrates, beta-blockers, Ca-antagonists, and ACE inhibitors, respectively.

**Baroreflex sensitivity:** BRS in both groups is shown in Figure 1. The average BRS in group CAD was $4.71 \pm 0.75$ msec/mmHg, which was significantly lower than that in group C ($15.11 \pm 2.22$ msec/mmHg).

**Nicotine concentration:** The concentrations of nicotine before and after cigarette smoking in both groups are presented in Figure 2. After cigarette smoking, the concentrations of nicotine were increased significantly in both groups (group C, 14/0).

<table>
<thead>
<tr>
<th>Table I. Clinical Characteristics</th>
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<tbody>
<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>Gender (male/female)</td>
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<tr>
<td>Duration of smoking (years)</td>
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<tr>
<td>Height (cm)</td>
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<tr>
<td>Body weight (kg)</td>
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<tr>
<td>Body mass index (kg/m$^2$)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
</tr>
<tr>
<td>Diabetes mellitus (%)</td>
</tr>
<tr>
<td>Medication</td>
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<tr>
<td>Ca antagonist (%)</td>
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<td>ACE inhibitor (%)</td>
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</tbody>
</table>

Results are expressed as the mean ± SEM. Statistical difference between young healthy subjects and patients with coronary artery disease: $^*$, $P < 0.01$; $^\dagger$, $P < 0.05$.

ACE indicates angiotensin converting enzyme; and CAD, coronary heart disease.
Figure 1. Baroreflex sensitivity in young subjects (○) and patients with CAD (●). Side circles indicate the mean; Horizontal bars, ± SEM; and CAD, coronary artery disease.

Figure 2. Plasma concentration of nicotine at the baseline and after smoking in healthy young subjects (○) and in patients with CAD (●). Side circles indicate the mean; Horizontal bars, ± SEM; and CAD, coronary artery disease.
from 21.8 ± 1.4 μg/L to 41.2 ± 3.2 μg/L; *P < 0.05; group CAD, from 17.0 ± 1.6 μg/L to 25.8 ± 2.2 μg/L; *P < 0.05).

**Hemodynamic effects of cigarette smoking:** The hemodynamic effects of cigarette smoking are shown in Table II. In group C, cigarette smoking caused significant (*P < 0.01) increases in HR (by +34.7 ± 4.1%), systolic BP (by +11.7 ± 2.5%), and diastolic BP (by +16.6 ± 1.7%). In group CAD, cigarette smoking caused significant (*P < 0.01) increases in HR (by +8.3 ± 2.1%), systolic BP (by +9.3 ± 1.7%), and diastolic BP (by +11.3 ± 1.6%). The peripheral hemodynamic effects of cigarette smoking were a significant (*P < 0.01) decrease in FBF (by -31.4 ± 7.1% in group C, and by -28.2 ± 4.1% in group CAD), and a significant (*P < 0.01) increase in FVR (by +95.1 ± 33.1% in group C, and by +62.1 ± 12.2% in group CAD).

### Table II. Hemodynamic Effects of Cigarette Smoking in Young Subjects and Patients With CAD

<table>
<thead>
<tr>
<th>Hemodynamic parameter</th>
<th>Young subjects</th>
<th></th>
<th>Patients with CAD</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After smoking</td>
<td>Baseline</td>
<td>After smoking</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td>64.0 ± 1.7</td>
<td>85.9 ± 2.3*</td>
<td>60.2 ± 1.7</td>
<td>65.5 ± 2.7*</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>106.3 ± 3.6</td>
<td>118.2 ± 2.9*</td>
<td>129.5 ± 6.0</td>
<td>140.9 ± 5.7*</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>64.0 ± 1.8</td>
<td>74.4 ± 1.9*</td>
<td>65.0 ± 2.8</td>
<td>72.1 ± 2.7*</td>
</tr>
<tr>
<td>Mean blood pressure (mmHg)</td>
<td>78.1 ± 2.3</td>
<td>89.0 ± 2.1*</td>
<td>86.5 ± 3.5</td>
<td>95.0 ± 3.2*</td>
</tr>
<tr>
<td>Forearm blood flow (mL/100 mL*minute-1)</td>
<td>10.14 ± 1.20</td>
<td>7.10 ± 1.14*</td>
<td>7.90 ± 1.19</td>
<td>5.27 ± 0.50*</td>
</tr>
<tr>
<td>Forearm vascular resistance (units)</td>
<td>8.66 ± 0.96</td>
<td>17.45 ± 4.09*</td>
<td>13.55 ± 1.75</td>
<td>20.35 ± 2.22*</td>
</tr>
</tbody>
</table>

Results are expressed as the mean ± SEM. Statistical difference between baseline and after smoking ; *, *P < 0.01. CAD indicates coronary artery disease.

### Table III. Effects of Cigarette Smoking on Sympathetic Nervous System in Young Subjects and Patients With CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Young subjects</th>
<th></th>
<th>Patients with CAD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After smoking</td>
<td>Baseline</td>
<td>After smoking</td>
</tr>
<tr>
<td>Burst rate (bursts/minute)</td>
<td>22.2 ± 1.9</td>
<td>20.0 ± 2.6</td>
<td>29.7 ± 3.7</td>
<td>37.5 ± 4.3*</td>
</tr>
<tr>
<td>Burst incidence (bursts/100 beats)</td>
<td>35.2 ± 3.5</td>
<td>23.5 ± 3.2*</td>
<td>48.8 ± 5.4</td>
<td>57.3 ± 5.5*</td>
</tr>
<tr>
<td>Plasma norepinephrine concentration (mg/mL)</td>
<td>0.187 ± 0.027</td>
<td>0.142 ± 0.020</td>
<td>0.137 ± 0.021</td>
<td>0.134 ± 0.020</td>
</tr>
<tr>
<td>Plasma epinephrine concentration (ng/mL)</td>
<td>0.026 ± 0.004</td>
<td>0.096 ± 0.024</td>
<td>0.023 ± 0.004</td>
<td>0.057 ± 0.022</td>
</tr>
</tbody>
</table>

Results are expressed as the mean ± SEM. Statistical difference between baseline and after smoking ; *, *P < 0.01. CAD indicates coronary artery disease.
**Sympathetic effects of cigarette smoking:** The sympathetic effects of cigarette smoking are shown in Table III. Cigarette smoking caused significant ($P < 0.01$) increases in BR (by $+7.8 \pm 1.2$ bursts/minute) and BI (by $+8.5 \pm 2.0$ units) in group CAD. In group C, cigarette smoking caused a significant ($P < 0.01$) decrease in BI (by $-11.7 \pm 1.0$ units), but there was no significant change in BR.

The percentage changes in MSNA between before and after cigarette smoking are shown in Figure 3. In group CAD, the change in BR was $+29.5 \pm 5.4\%$, which was significantly ($P < 0.01$) higher than that in group C ($-10.3 \pm 9.3\%$). In group CAD, the change in BI was $+20.3 \pm 5.8\%$, which was significantly ($P < 0.01$) higher than that in group C ($-32.8 \pm 7.0\%$).

Cigarette smoking caused no significant change in the plasma concentration of norepinephrine or epinephrine between before and after cigarette smoking in both groups.

**Correlations between changes in MSNA and baroreflex sensitivity:** The relationships between changes in MSNA and BRS at baseline are shown in Figure 4 (BR and BRS) and Figure 5 (BI and BRS). There was significant ($P < 0.01$) correlation between BRS at baseline and changes in BR ($r = -0.53$), and between BRS at baseline and changes in BI ($r = -0.62$).
Figure 4. Relation between the change in burst rate after cigarette smoking and baroreflex sensitivity. Open circles indicate young subjects and filled circles denote patients with coronary artery disease.

$y = -2.3x + 33.8$
$r = -0.53$
$P < 0.01$

Figure 5. Relation between the change in burst incidence after cigarette smoking and baroreflex sensitivity. Open circles indicate young subjects and filled circles denote patients with coronary artery disease.

$y = -3.0x + 25.1$
$r = -0.62$
$P < 0.01$
DISCUSSION

Our study is the first report that shows the sympathetic effects of cigarette smoking in subjects with impaired baroreflex function. Many reports have examined the sympathetic effects of cigarette smoking in young healthy smokers and animals. In healthy subjects, cigarette smoking has been found to increase HR, BP, and the plasma concentration of norepinephrine. These changes are attenuated markedly by alpha-adrenergic and beta-adrenergic blockade, indicating that these hemodynamic effects of cigarette smoking are derived from sympathetic activation. However, the mechanisms of cigarette smoking-mediated sympathoexcitation are unclear.

We can assume 3 different mechanisms underlying activation of the sympathetic nervous system due to cigarette smoking. First, a direct effect on the central nervous system; second, a stimulatory effect on ganglionic sympathetic transmission that leads to a subsequent increase in postganglionic efferent sympathetic nerve activity; and third, a direct effect on peripheral sympathetic nerve endings. It has been shown that cigarette smoking stimulates the release of catecholamine directly from postganglionic peripheral sympathetic nerve endings. However, the mechanism of the effect of cigarette smoking on the central nervous system is still controversial.

Animal studies have shown that local injection of nicotine in several brain-stem areas caused hypotension and bradycardia, suggesting that cigarette smoking may inhibit central sympathetic nerve activity. Other studies reported that local injection of nicotine in other brain-stem areas had a pressor effect, suggesting that cigarette smoking may stimulate central sympathetic nerve activity.

In healthy smokers, cigarette smoking decreases MSNA, which suggests that cigarette smoking acts mainly via direct stimulation of postganglionic sympathetic nerve endings rather than centrally mediated activation of efferent sympathetic nerves. In contrast to young healthy smokers, cigarette smoking increased the MSNA significantly in subjects with stable effort angina with impaired baroreflex function. Our data support the opinion that cigarette smoking stimulates centrally mediated sympathetic nerve activity. The decrease in MSNA due to cigarette smoking in young healthy smokers, which gives us the impression that cigarette smoking inhibits central sympathetic nerve activity, is derived from baroreflex stimulation triggered by the smoking-related pressor response. Actually, there was significant correlation between changes in MSNA and BRS at baseline.

The same conclusion was reached in another study. There was a striking increase in MSNA when the BP increase in response to smoking was blunted by nitroprusside infusion, and cigarette smoking increased skin sympathetic nerve
activity,\textsuperscript{26} which is not attenuated by increased BP or baroreflex activation.

Furthermore, cigarette smoking impairs the baroreflex function both acutely and chronically.\textsuperscript{39,40} According to our study, the impaired baroreflex function at baseline stimulates the activation of the sympathetic nervous system due to cigarette smoking even more. This results in a vicious circle in smokers, especially those with impaired baroreflex function. We must break this vicious circle by clinical treatment designed to help the person stop cigarette smoking. It has been shown that cardiac events and mortality are lower in subjects who have given up smoking than in subjects who continued to smoke.\textsuperscript{41-44}

However, in contrast to many studies,\textsuperscript{6,7} our study showed that there was no change in the plasma concentration of norepinephrine or epinephrine between before and after cigarette smoking in either group. The reasons for this result are that it is too short a time to take a sample, and it is too short a time to smoke, because it has been shown that the plasma concentration of catecholamine begins to rise 10 minutes after starting to smoke a cigarette.\textsuperscript{7}

This study has several limitations. First, we did not make our subjects smoke sham cigarettes. The plasma concentration of nicotine after cigarette smoking was significantly higher than before smoking. Thus, we are able to discuss the sympathetic effects of cigarette smoking, but there was no control condition. Second, our patients with stable effort angina were taking some medication. In our study, 64\% of patients took a Ca antagonist and 36\% took an ACE inhibitor. It has been shown that the MSNA was reduced and the baroreflex sensitivity was enhanced by chronic treatment with an ACE inhibitor in patients with heart failure.\textsuperscript{45,46} It has also been shown that baroreflex sensitivity was increased significantly by chronic treatment with a Ca antagonist in patients with hypertension\textsuperscript{47} and some Ca antagonists inhibited sympathetic nerve activity.\textsuperscript{48,49} Therefore, in patients with stable effort angina and with impaired BRS, the same mechanisms might be observed with an ACE inhibitor or a Ca antagonist. These medications might alter the effect of cigarette smoking. Third, our control group did not match group CAD in terms of age and risk factors. It has been demonstrated that baroreflex sensitivity becomes impaired with advancing age,\textsuperscript{50} and that patients with hypertension or diabetes mellitus have sympathetic hyperactivity.\textsuperscript{51} Therefore, these conditions might influence our results at baseline.

In conclusion, cigarette smoking stimulates activation of the sympathetic nervous system by a direct peripheral effect and a centrally mediated effect. The decrease in MSNA in healthy smokers with normal BRS is derived from baroreflex stimulation triggered by the smoking-related pressor response. In patients with impaired BRS, cigarette smoking increases the MSNA, showing that cigarette smoking increases sympathetic outflow directly. There was significant correlation between BRS and changes in MSNA.
REFERENCES


