Influence of Cigarette Smoking on Human Autonomic Function

Otfried N. Niedermaier, MD; Michael L. Smith, PhD; Larry A. Beightol, MS; Zofia Zukowska-Grojec, MD, PhD; David S. Goldstein, MD, PhD; and Dwain L. Eckberg, MD

Background. Although cigarette smoking is known to lead to widespread augmentation of sympathetic nervous system activity, little is known about the effects of smoking on directly measured human sympathetic activity and its reflex control.

Methods and Results. We studied the acute effects of smoking two research-grade cigarettes on muscle sympathetic nerve activity and on arterial baroreflex-mediated changes of sympathetic and vagal neural cardiovascular outflows in eight healthy habitual smokers. Measurements were made during frequency-controlled breathing, graded Valsalva maneuvers, and carotid baroreceptor stimulation with ramped sequences of neck pressure and suction. Smoking provoked the following changes: Arterial pressure increased significantly, and RR intervals, RR interval spectral power at the respiratory frequency, and muscle sympathetic nerve activity decreased. Plasma nicotine levels increased significantly, but plasma epinephrine, norepinephrine, and neuropeptide Y levels did not change. Peak sympathetic nerve activity during and systolic pressure overshoots after Valsalva straining increased significantly in proportion to increases of plasma nicotine levels. The average carotid baroreceptor–cardiac reflex relation shifted rightward and downward on arterial pressure and RR interval axes; average gain, operational point, and response range did not change.

Conclusions. In habitual smokers, smoking acutely reduces baseline levels of vagal-cardiac nerve activity and completely resets vagally mediated arterial baroreceptor–cardiac reflex responses. Smoking also reduces muscle sympathetic nerve activity but augments increases of sympathetic activity triggered by brief arterial pressure reductions. This pattern of autonomic changes is likely to influence smokers’ responses to acute arterial pressure reductions importantly. (Circulation 1993;88:562-571)

Key Words • baroreceptors • vagal nerve • smoking

Cigarette smoking is a major risk factor for the development of atherosclerosis, coronary heart disease, acute myocardial infarction, and sudden cardiac death. Cessation of smoking is associated with reduced cardiovascular mortality and morbidity. Although smoking increases arterial pressure and heart rate acutely, the effects of smoking on sympathetic activity are not well understood. Smoking or nicotine infusions have been shown to decrease, to not change, or to increase plasma norepinephrine levels and to decrease or not change directly recorded muscle sympathetic nerve activity.

We conducted this study to answer several questions regarding the acute autonomic consequences of smoking: Does smoking increase human muscle sympathetic nerve activity? Does smoking decrease vagal-cardiac nerve activity (measured from the respiratory peak of heart rate power spectra)? What influence does smoking have on baroreflex sympathetic and vagal control mechanisms? Our results suggest that cigarette smoking provokes a complex pattern of acute autonomic changes: smoking reduces baseline levels of muscle sympathetic and vagal-cardiac nerve activity, completely resets vagally mediated baroreflex responses, and augments sympathetically mediated baroreflex responses. This study has been published in preliminary form.18

Methods

Subjects

Volunteers comprised five healthy male and three healthy female habitual smokers (ages, 19 to 44 years; mean, 30 years). This study was approved by the human research committees of the Hunter Holmes McGuire Department of Veterans Affairs Medical Center and the Medical College of Virginia, and each volunteer gave informed written consent before the study.

Measurements

Studies were conducted with subjects in the supine position. Room temperature was set at 25°C. All measurements were recorded by electrostatic and FM re-

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From the Departments of Medicine and Physiology, Hunter Holmes McGuire Department of Veterans Affairs Medical Center and Medical College of Virginia, Richmond (O.N.N., M.L.S., L.A.B., D.L.E.); the Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, DC (Z.Z.-G.); and the Clinical Neuroscience Branch, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Md (D.S.G.).

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Correspondence to the Department of Medicine and Physiology, Hunter Holmes McGuire Department of Veterans Affairs Medical Center, 1201 Broad Rock Blvd, Richmond, VA 23249 (Dr. Eckberg).
corders. ECG lead II was monitored continuously, and RR intervals were derived from R-wave threshold crossings. Respiratory rate was monitored with an abdominal bellows connected to a strain-gauge pressure transducer. Beat-by-beat arterial pressure was estimated with a noninvasive finger photoplethysmograph (Finapres, Ohmeda, Englewood, Colo). The device we used provides reliable estimates of intra-arterial (particularly diastolic) pressures at rest and during Valsalva maneuvers.19,20

Postganglionic muscle sympathetic nerve activity was recorded with a microelectrode inserted into a peroneal nerve near the fibular head, as described earlier.21 Sympathetic activity was identified by its characteristic “bursting” quality, its relation to cardiac and respiratory activity, and its unresponsiveness to arousal stimuli or skin stroking (which elicit skin but not muscle sympathetic bursts). Acceptable nerve recordings were obtained from all eight subjects.

Blood samples were withdrawn through indwelling antecubital vein catheters, without use of tourniquets, into prechilled syringes. Each sample was transferred immediately to evacuated glass tubes containing ethylenediaminetetraacetate and reduced glutathione and placed on ice. The tubes were centrifuged under refrigeration (4°C) at 2000 rpm for 10 minutes, transferred to untreated silicone tubes, and frozen at −70°C. Plasma nicotine, cotinine, and catecholamine levels were measured with high-performance liquid chromatography as described previously.22,23 Neuropeptide Y levels were measured in unextracted plasma of four subjects by means of a highly specific radioimmunoassay as described previously.24 The antiserum used in this assay cross-reacts 100% with porcine neuropeptide Y and 50% with human neuropeptide Y. The data were not corrected for recovery. Intra-assay and interassay coefficients of variation for neuropeptide Y levels were 5% and 15%.

Valsalva straining was performed for 15 seconds at expiratory pressures of 10 and 20 mm Hg. Each subject blew into a mouthpiece connected to a Statham pressure transducer. The calibrated output of the pressure transducer and the respiratory tracing were displayed on a two-channel oscilloscope positioned to allow the subject to observe and control the level of expiratory pressure. A 25-gauge needle was inserted into the tubing that connected the mouthpiece to the pressure transducer; this created a small leak and thereby prevented closure of the glottis during straining.25 Subjects rested about 90 to 120 seconds between maneuvers. Measurements of responses were made during the four phases of the Valsalva maneuver defined by Hamilton et al.26; these include early straining during the arterial pressure elevation, late straining, release of straining, and poststraining during the arterial pressure overshoot.

Afferent carotid baroreceptor activity was modified by a stereotyped series of pressure changes delivered to a Silastic neck chamber.27 The chamber was attached to a pressure system containing a stepping motor-driven bellows that delivered very abrupt (>300 mm Hg/sec) R-wave-triggered pressure changes. During held expiration, a pressure of about 40 mm Hg was delivered to the neck chamber and sustained for 5 seconds. Then chamber pressure was lowered by successive R-wave-triggered 15-mm Hg decrements to −65 mm Hg. Thus, during this sequence, carotid sinuses were compressed initially and then stretched incrementally by fixed amounts in synchrony with the arterial pulse. Each pressure sequence was applied seven times, and responses were averaged. Carotid distending pressure was calculated as systolic minus neck chamber pressure. Responses were reduced to the following parameters for analysis: minimum and maximum RR intervals, maximum slope, and operational point position. Maximum slope was estimated with linear regression analyses applied to each set of three consecutive data pairs on the relation. The operational point position, which reflects subjects’ resting positions on the stimulus-response relation, was calculated as [(RR interval at 0 neck pressure minus minimum RR interval) divided by RR interval response range] times 100%.

Published and unpublished data indicate that responses to the neck pressure/suction sequence and Valsalva maneuvers used in this study are highly reproducible. First, the mechanical device we used27 delivers highly reproducible pressure changes to the neck.28 Second, although responses to individual neck pressure sequences are not reproducible, average responses to seven such sequences are highly reproducible over 24 hours.29 7 to 10 days, and 10 weeks.27 Third, unpublished data (M.L. Smith, L.A. Beightol, J.M. Fritsch, K.A. Ellenbogen, and D.L. Eckberg) indicate that increases of muscle sympathetic nerve activity during Valsalva straining and of systolic and diastolic pressure after release of straining are highly reproducible over 1-hour recording sessions.

**Protocol**

The protocol, with approximate times for all measurements, is depicted in Fig 1. All studies were performed
in the morning after subjects had fasted, not smoked, and not drunk caffeinated beverages for at least 12 hours. Data were collected during three periods: (1) before smoking, (2) during and after smoking a low-nicotine research cigarette (0.24 mg/cigarette, No. 3A1, University of Kentucky Tobacco and Health Research Institute, Lexington, Ky), and (3) during and after smoking a medium-nicotine research cigarette (1.16 mg/cigarette, No. 1R3F). The interval between the end of smoking the first and the beginning of smoking the second cigarette averaged 30 to 45 minutes. Each cigarette was smoked to a butt length of 3.5 cm. The time required to smoke each cigarette varied among subjects and averaged 4.7 minutes (range, 3.7 to 5.8 minutes).

Vagal-cardiac neural outflow was estimated from RR intervals and RR interval spectral power at the respiratory frequency during frequency-controlled respiration (12 breaths per minute). Each data segment comprised 192 seconds and was sampled at a rate of eight times per second. RR interval power spectral density was estimated with DADiSP software (DSP Development Corp, Cambridge, Mass) and the periodogram method described by Chatfield.30 Blood samples were withdrawn for catecholamine determinations at the end of each period of controlled breathing, about 10 minutes after subjects completed smoking each cigarette. The timing of blood withdrawal was chosen to coincide with the collection of physiological data; this timing should have captured peak plasma epinephrine levels and should have slightly preceded peak norepinephrine and nicotine levels.

Subjects performed two Valsalva maneuvers at each of the two expiratory pressures in random sequence. There was a pause of at least 90 seconds between each two maneuvers. This sequence was repeated after each cigarette. Carotid baroreceptor stimulus-response relations were provoked during the presmoking period and 15 minutes (range, 12 to 20 minutes) after the subject began smoking the second cigarette.

Data Analysis
Data were analyzed off-line with data acquisition software that included custom programs for analysis of sympathetic nerve activity. Sympathetic bursts were identified by one investigator according to appearance, timing in relation to the R wave of the previous cardiac cycle, and in some instances, sounds on playback recordings. The heights of all sympathetic bursts were measured. In each subject, the largest burst occurring during the recording session was assigned a value of 1000, and all other bursts were normalized according to this standard. This transformation was done to allow comparisons to be made among different subjects.

Statistical Analyses
Because sample sizes were small, all variables were analyzed with nonparametric methods except where noted. Wilcoxon signed rank tests were used to test for differences from baseline data, changes during Valsalva maneuvers, and carotid baroreflex stimulus-response characteristics at different stages of the experiment. Tests for trends were carried out only on those variables with complete data at all levels, with a repeated-measures ANOVA performed with the rankings of values. Spearman's rank correlations were used for all correlations of interest. Numerical data are presented as mean±SEM. No corrections for multiple tests were done. Two-tailed tests for significance were used unless otherwise noted. Differences are considered significant when \( P<.05 \) for differences between single tests and when \( P<.025 \) for differences among tests during the presmoking period and during or after smoking low- or medium-nicotine cigarettes.

Trends of responses after smoking were identified with the cumulative-sum technique, a statistical method developed to discover and graphically portray subtle changes occurring in serial measurements.33 For these analyses, RR intervals, muscle sympathetic nerve activity, and systolic and diastolic pressures from each subject were averaged in 10-second bins. These values were then averaged for all subjects to derive one composite response. Measurements obtained during the 2-minute presmoking period were averaged, and differences of successive measurements from this average were added to obtain the cumulative algebraic sum of changes. The break point of each cumulative sum was determined with a method described by Eckberg and Jones and Molitoris.33 Briefly, the residual sums of squares for all points to the right and all points to the left of an arbitrarily defined break point were determined. Then this point was moved iteratively to the left and to the right of the original break point, and the residual sums of squares were calculated for each position. Finally, the residual sums of squares for each

![Graphs showing measurements obtained from one subject during the presmoking period and during (dashed lines) and after (solid lines) he smoked the low-nicotine cigarette (cig. 1). Data were averaged every 10 seconds. Muscle sympathetic nerve activity is given in arbitrary units (see "Methods").](http://circ.ahajournals.org/content/circulation/88/2/564.full.png)
point were plotted. The nadir of this relation was taken to be the break point.

Results

Effects of Smoking on Autonomic Outflow

The subjects we studied indicated that they smoked from 4 to 40 (mean, 19) cigarettes daily. Plasma cotinine levels, measured to obtain an independent index of chronic smoking levels, averaged 189±22 ng/mL (range, 17 to 419 ng/mL). There was a statistically significant correlation between historic smoking levels and measured cotinine levels (r=.60, P=.029). Fig 2 shows average autonomic responses of one subject to smoking the low-nicotine cigarette. RR intervals declined abruptly and then recovered slightly, muscle sympathetic nerve activity seemed to decline, and systolic and diastolic pressures increased slightly.

Fig 3 shows cumulative-sum plots of autonomic responses of all subjects to the medium-nicotine cigarette. Within <2 minutes, RR intervals and muscle sympathetic nerve activity began to decline, and systolic and diastolic pressures began to rise. Increases of systolic pressure were slightly larger than increases in diastolic pressure. Response patterns were nearly identical after subjects smoked the low- and medium-nicotine cigarettes. Average net changes of these measures after both cigarettes are given in Table 1.

Fig 4 shows average changes of antecubital vein plasma nicotine, norepinephrine, and epinephrine levels. As expected, plasma nicotine levels were low in the presmoking period (3.27±3.07 μg/L) and increased

<table>
<thead>
<tr>
<th>Table 1. Baseline Effects of Smoking</th>
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<tr>
<td>Before smoking</td>
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<tr>
<td><strong>Systolic pressure (mm Hg)</strong></td>
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<td>cig. 1</td>
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<td>cig. 2</td>
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<td><strong>Diastolic pressure (mm Hg)</strong></td>
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<td>cig. 2</td>
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<td><strong>Heart rate (bpm)</strong></td>
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<td>cig. 1</td>
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<td>cig. 2</td>
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<tr>
<td><strong>RR interval std dev (ms)</strong></td>
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<td>cig. 1</td>
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<td>cig. 2</td>
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<tr>
<td><strong>Sympathetic activity (bursts per min)</strong></td>
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<tr>
<td>cig. 1</td>
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<tr>
<td>cig. 2</td>
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<tr>
<td><strong>Sympathetic activity (bursts per 100 beats)</strong></td>
</tr>
<tr>
<td>cig. 1</td>
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<tr>
<td>cig. 2</td>
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</table>

*Significant difference from control (P<.05).

Cig. 1, low nicotine cigarette; Cig. 2, medium-nicotine cigarette; bpm, beats per minute; Std dev, RR interval standard deviation.

**Fig 3.** Graphs showing cumulative-sums analysis of responses of seven subjects to smoking the medium-nicotine cigarette (cig. 2). (One subject was excluded from these analyses because of loss of nerve signal after the medium-nicotine cigarette.) The onset of smoking is designated as 0 time. The end of smoking varied among subjects; the average times that smoking ended are denoted by the dashed lines. In the upper panels, average measurements from all subjects are indicated by circles. Calculated least-squares linear regression slopes to the left and right of the bending point identified by this analysis are indicated by straight lines. In the lower panels (see "Methods" 35), the vertical axis is derived as follows: the computer iteratively computes the residual sum of squares (rss) to the left and the right of each point on the relation; at the "bending point," this value is minimal (rss_min) (mse, rss divided by the number of observations less four degrees of freedom.) Vertical dashed lines on the bending point analyses estimate the times after the onset of smoking that the measured parameters changed.
FIG 4. Bar graphs showing average (+SEM) changes of antecubital vein plasma nicotine and catecholamine levels. Cig. 1, low-nicotine cigarette; cig. 2, medium-nicotine cigarette. *P<.05 (presmoking vs smoking levels).

significantly after the low-nicotine (to 7.09±2.81 μg/L, \(P=.005\)) and medium-nicotine cigarettes (to 16.36±4.34 μg/L, \(P=.004\) from the low-nicotie cigarette). An overall trend also was statistically significant (\(P=.0006\)). Decreases of plasma norepinephrine and increases of plasma epinephrine were not significant. Plasma nicotine levels measured in the presmoking period correlated significantly with muscle sympathetic nerve activity \(r=.83, P=.021\); there was no significant correlation between plasma nicotine levels and sympathetic activity after the low- and medium-nicotine cigarettes \(r=-.71, P=.076, \) and \(r=-.44, P=.33\). Neuropeptide Y levels in four subjects (not shown) averaged 49.9±0.1 pmol/L before smoking and 51.1±0.1 and 51.3±0.3 pmol/L after the low- and medium-nicotine cigarettes, respectively. In these subjects, there was no significant correlation between changes of plasma neuropeptide Y and norepinephrine levels.

FIG 5. Graph showing average RR interval spectral power for all subjects. During the period of measurement, subjects breathed at a frequency of 0.2 Hz (12 breaths per minute). Cig. 1, low-nicotine cigarette; cig. 2, medium-nicotine cigarette. See “Results” for statistical analyses.

the medium-nicotine cigarette and before and after the medium-nicotine cigarette were significant (both \(P=.027\)). (It seems likely that some of the effects we observed resulted directly from nicotine, since other workers have made related observations after subjects were given intravenous injections of nicotine or nicotine chewing gum.10,11,17 However, we cannot exclude the possibility that other active substances in the test cigarettes we used contributed to the autonomic changes we observed.)

Responses to Valsalva Maneuvers

FIG 6 illustrates representative trials from one subject with expiratory Valsalva pressures of 20 mm Hg before and after he smoked the medium-nicotine cigarette. In this subject, smoking augmented sympathetic responses to straining and arterial pressure increases after straining. After release of straining, sympathetic activity was silenced.

FIG 7 shows arterial pressures and RR intervals before (phase 0) and during each stage of Valsalva maneuvers. Systolic pressures and RR intervals during phases 1 and 2 (early and late straining) and 3 (release of straining) were comparable \(P>.05\) before and after smoking. Systolic pressure increases after release of straining (upper panel, right) were significantly greater after each cigarette for both 10 mm Hg \(P=.04\) and \(P=.02\) for the first and second cigarettes) and 20 mm Hg \(P=.03\) and \(P=.01\) (expiratory pressures. Increases of systolic pressure after 20 mm Hg straining averaged 21±5 mm Hg before smoking and 24±3 and 31±3 mm Hg after smoking low- and medium-nicotine cigarettes. Diastolic pressure increases after release of straining were comparable during the presmoking period and after smoking the low- and medium-nicotine cigarettes. RR intervals during phase 4 were not significantly different after either cigarette \(P>.05\).
Fig 6. Direct recordings during Valsalva maneuvers for one subject during presmoking conditions (left) and after (right) he smoked the medium-nicotine cigarette. This subject’s poststraining RR interval increase was minimal in this trial; it was larger in other trials.

Fig 8 shows average changes of sympathetic nerve activity from before to during Valsalva straining. Average responses to straining were comparable during the presmoking period and after the low-nicotine cigarette but were augmented significantly after the medium-nicotine cigarette (P=.007 for both 10 and 20 mm Hg maneuvers). Significant trends were also found for both maneuvers (P=.002 and P=.001 for 10 and 20 mm Hg maneuvers). Peak increases of sympathetic activity during Valsalva maneuvers correlated weakly but significantly with plasma nicotine levels (r=.36, P=.01).

**Carotid Baroreflex Stimulus-Response Relations**

Fig 9 illustrates average carotid distending pressure-RR interval relations and their first derivatives during the presmoking period and after the medium-nicotine cigarette. After smoking, the position of the relation was shifted to lower RR intervals and higher arterial pressure ranges; minimum and maximum RR intervals were lower (P=.002 and P=.007); and maximum slopes (P=.45), operational points (P=.32), and ranges of responses (P=.42) were comparable. The latter results are summarized in Table 2.

**Discussion**

Our study suggests new insights into the effects of cigarette smoking on baseline levels and baroreflex-mediated changes of sympathetic and vagal neural activity in healthy habitual smokers. First, smoking reduces baseline sympathetic nerve traffic to the muscle vascular bed but exaggerates baroreflex-mediated increases of sympathetic activity and resulting increases of pressure. Second, smoking substantially reduces baseline vagal-cardiac nerve activity but preserves the ability of baroreflex mechanisms to...
mediate further vagal withdrawal. The complex change of autonomic responses provoked by smoking may have important practical consequences, particularly including modification of smokers’ responses to abrupt arterial pressure reductions.

**TABLE 2.** Characteristics of Carotid Baroreflex Stimulus-Response Relation Parameters Before and After Smoking

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before smoking</th>
<th>After smoking</th>
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<tbody>
<tr>
<td>Maximum gain (ms/mm Hg)</td>
<td>4.1±0.9</td>
<td>3.7±0.5</td>
</tr>
<tr>
<td>Response range (ms)</td>
<td>180±24</td>
<td>184±18</td>
</tr>
<tr>
<td>Operational position (% of range)</td>
<td>47±6</td>
<td>41±6</td>
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</table>

Average measurements taken from carotid distending pressure–RR interval relations before and after subjects smoked the second cigarette. Maximum gain is maximum slope obtained from three consecutive data points on stimulus-response relation. Response range is the total RR interval change during a complete sequence of neck pressure changes. Operational position is the position of the RR interval at 0 neck pressure relative to the entire relation.

**Sympathetic Responses**

Some[7,14,38,39] but not all[9,12,13] earlier studies show that smoking increases venous pressure levels of the principal sympathetic neurotransmitter, norepinephrine. Increases of norepinephrine (and epinephrine) levels are taken as evidence for a generalized increase of sympathetic nerve activity. Our study suggests that increases of sympathetic activity during and after smoking are differentiated rather than generalized.

Sympathetic traffic to the skeletal muscle vascular bed, which composes about 42% of body mass,[40] is reduced by smoking. Others have reported that smoking or nicotine infusion reduces[15] or does not alter[6,17] the level of muscle sympathetic nerve activity. We found that reductions of sympathetic nerve activity provoked by smoking one low- or one medium-nicotine cigarette are readily apparent when data are plotted with the cumulative-sums technique (Fig 3 illustrates responses after the medium-nicotine cigarette).[33] Our conclusion that smoking reduces muscle sympathetic nerve activity does not hinge on use of the cumulative-sums technique, however. Grassi and coworkers[15] used more conventional methods for plotting data and also documented reductions of muscle sympathetic nerve activity after their subjects smoked only one (medium-, not low-nicotine) cigarette.

Our findings do not contradict the well-established view that smoking increases sympathetic outflow to the heart and other vascular beds in humans. Smoking increases directly measured sympathetic traffic to the cutaneous vascular bed[41] and provokes dramatic skin vasoconstriction.[10,42] Smoking also causes cardioacceleration, which is reduced by pretreatment with β-adrenergic blocking drugs,[46] and coronary vasoconstriction, which is intensified by blockade of vasodilator β-adrenergic receptors and largely prevented by blockade of vasoconstrictor α-adrenergic receptors.[43,44] Furthermore, preliminary data[45] indicate that smoking increases coronary sinus norepinephrine spillover, an indirect index of sympathetic nerve traffic to the heart. Others have shown that smoking increases plasma levels of adrenally released epinephrine.[7,9,12,14,39] We found that plasma epinephrine levels increase insignificantly with smoking (Fig 4, bottom panel). We suspect that the changes of epinephrine we observed might have been statistically significant if we had studied more subjects and delivered higher doses of nicotine.

Thus, published information and the present study indicate that smoking differentially affects sympathetic outflow to different target organs. Smoking increases sympathetic traffic to the skin, heart, and adrenal glands but reduces sympathetic traffic to muscle. We assume that reductions of muscle sympathetic nerve activity after smoking are mediated by increased baroreceptor activity triggered by arterial pressure elevations. If this speculation is correct, it follows that smoking differentially affects baroreceptor control of sympathetic outflow to different vascular beds.

Our results may explain why many workers have not found increased antecubital vein plasma norepinephrine levels after smoking; such samples are dominated by norepinephrine overflow from skeletal muscle.[46] In our study, there was a highly significant correlation
between reductions of plasma norepinephrine and muscle sympathetic nerve activity after smoking.

Although baseline muscle sympathetic nerve activity is reduced slightly by smoking, sympathetic responses to brief reductions of arterial pressure are exaggerated (Fig 8). Augmented surges of sympathetic activity during nearly identical pressure reductions after smoking appeared to be functionally important, since elevations of systolic pressure after Valsalva straining also were significantly greater after smoking than before (Fig 7). Healthy resting humans operate on the linear portion of their arterial pressure–muscle sympathetic nerve response relations.\(^{47,48}\) Experimental results reported in preliminary form\(^ {49}\) suggest that when arterial pressure is increased modestly (as it is after the smoking of one low-nicotine cigarette), baseline sympathetic nerve activity decreases, but sympathetic responses to sudden arterial pressure reductions increase. Such augmented sympathetic responses may result because when baseline sympathetic activity is reduced, the potential for sympathetic activity to increase is augmented. It is likely that responses to hypertension are augmented in other sympathetic outflows also, since arterial baroreflex-mediated changes of sympathetic activity are directionally similar in renal, splanchnic, and cardiac sympathetic nerves.\(^ {50}\)

**Vagal Activity**

Most of the cardiovascular effects of smoking are thought to be mediated by sympathetic stimulation. However, the finding that pretreatment with \(\beta\)-blockers does not entirely prevent cardioacceleration after smoking\(^ {46}\) supports the notion that smoking speeds heart rate in part by reducing vagal restraint. Other more direct proof comes from the study of Hayano and coworkers,\(^ {51}\) whose findings we confirm. That group, and now ours (Fig 5), showed that RR interval spectral power at the respiratory frequency (widely accepted as a noninvasive index of vagal-cardiac activity\(^ {52,53}\)) is reduced by smoking. However, smoking does not alter the relation between baroreceptor input and vagal output; it merely shifts ("resets")\(^ {54}\) this relation to operate at higher than normal arterial pressures and shorter RR intervals. We found that resetting is complete; that is, maximum slopes, operational points, and response ranges were similar before and after smoking. Therefore, even though smoking reduces baseline levels of vagal-cardiac nerve activity, the ability of pressure reductions to reduce vagal outflow further is preserved.

**Clinical Implications**

Our conclusion that smoking acutely modifies autonomic responses to sudden changes of baroreceptor input may have practical importance. One change of baroreceptor input that may be of particular interest is the abrupt pressure reduction that occurs during ventricular rhythms. Welch et al\(^ {55}\) and Smith et al\(^ {56}\) showed that hypotension caused by isolated premature ventricular beats or ventricular tachycardia elicits surges of muscle sympathetic nerve activity in proportion to the degree of hypotension. Our finding that smoking exaggerates sympathetic responses to pressure reductions makes it likely that smoking augments sympathetic neural responses to ventricular tachycardia, a rhythm that commonly precedes ventricular fibrillation.\(^ {57}\) Augmented sympathetic responses to ventricular tachyca-

dia could be helpful, in the sense that sympathetic vasoconstrictor activity restores coronary and cerebral perfusion pressures toward normal,\(^ {58}\) or they could be harmful, in the sense that sympathetic myocardial stimulation promotes mechanisms responsible for ventricular fibrillation, including reentry, increased automaticity, and triggered activity.\(^ {58}\)

**Potential Limitations**

Although we did not study the effects of sham smoking (such as smoking a drinking straw), others have. Cryer and coworkers\(^ {7}\) reported that sham smoking does not significantly increase average heart rate, arterial pressure, or plasma norepinephrine and epinephrine levels, and Grassi et al\(^ {59}\) reported that sham smoking does not alter muscle sympathetic nerve activity. We did not measure cardiac chamber pressures, which may exert a strong influence on human muscle sympathetic nerve activity.\(^ {59}\) We cannot exclude the possibility that the timing of blood withdrawals and physiological interventions in our study (see "Methods") was such that we missed peak increases of plasma norepinephrine levels and peak changes of physiological responses. This question may be moot, however, since we measured sympathetic nerve activity directly and continuously before and during smoking, and the hemodynamic changes we found were highly significant. It seems likely that augmented sympathetic responses to Valsalva straining are mediated by baroreflex mechanisms. However, we did not evaluate the effects of other sympathoexcitatory maneuvers, including the cold pressor test and exercise, and therefore, we do not know whether the effects we observed are specific for baroreflex mechanisms.

We do not know whether responses of smokers to the same stimuli are different from those of nonsmokers; we limited our study to smokers because they constitute the population for which our findings have the greatest relevance. However, Hofstetter et al\(^ {60}\) and Perkins et al\(^ {61}\) showed that cardiovascular responses and energy expenditures during exercise are exaggerated in smokers. Their results suggest that autonomic function of smokers is different from that of nonsmokers at baseline, before they smoke. Conceivably, such differences in baseline autonomic activity contribute further to the abnormal responses we observed after smoking. Finally, we do not know whether nicotine withdrawal contributed to the responses we measured; we obtained our measurements in smokers after overnight deprivation because of known functional habituation to the cardiovascular effects of smoking.\(^ {62}\)

In summary, we measured the acute autonomic cardiovascular effects of smoking in healthy habitual smokers. We found that smoking increases arterial pressure, reduces baseline levels of muscle sympathetic and vagal-cardiac nerve activity, and augments sympathetic responses to brief arterial pressure reductions. This pattern of changes is likely to modulate smokers’ autonomic responses to acute arterial pressure changes importantly.

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