Effects of Long-term Smoking on Myocardial Blood Flow, Coronary Vasomotion, and Vasodilator Capacity

Roxana Campisi, MD; Johannes Czernin, MD; Heiko Schöder, MD; James W. Sayre, PhD; Fernando D. Marengo, PhD; Michael E. Phelps, PhD; Heinrich R. Schelbert, MD

Background—The effect of long-term smoking on coronary vasomotion and vasodilator capacity in healthy smokers is unknown.

Methods and Results—Myocardial blood flow (MBF) was quantified with $^{[13]}$Nammonia and positron emission tomography (PET) at rest, during cold pressor testing (endothelium-dependent vasomotion), and during dipyridamole-induced hyperemia in 16 long-term smokers and 17 nonsmokers. MBF at rest did not differ between the 2 groups. Cold induced similar increases in rate-pressure product (RPP) in smokers and nonsmokers. However, MBF increased only in nonsmokers and was, during cold, higher than in smokers ($0.91 \pm 0.18$ versus $0.78 \pm 0.14$ mL $\cdot$ g$^{-1}$ $\cdot$ min$^{-1}$, $P<0.05$).

Conclusions—The normal hyperemic response to dipyridamole in long-term smokers indicates a preserved endothelium-dependent coronary vasomotion, whereas the abnormal response to cold suggests a defect in coronary vasomotion likely located at the level of the coronary endothelium. Its severity depends on the total exposure time to smoking. (Circulation. 1998;98:119-125.)

Key Words: blood flow ■ smoking ■ tomography ■ cold pressor test

Long-term smoking alters the peripheral vascular endothelial function.$^{1,2}$ However, the effects of long-term smoking on the coronary endothelial function remain controversial.$^{3,4}$ Cigarette smoking increases the risk for obstructive coronary artery disease. Coronary endothelial dysfunction might precede epicardial, obstructive atherosclerosis in long-term smokers and other individuals at risk for coronary artery disease.$^{4}$

Until recently, assessment of coronary endothelial function in humans required intracoronary administration of acetylcholine. However, Zeiher et al$^{5}$ reported a significant correlation between the vasomotor responses to intracoronary acetylcholine and cold pressor testing in patients with mild atherosclerosis, suggesting that cold pressor testing might be useful for probing endothelium-dependent coronary vasomotion.$^{5}$ Dynamic, high spatial and temporal resolution positron emission tomography (PET) imaging permits the noninvasive quantification of myocardial blood flow. Thus, the effects of interventions such as cold pressor testing or intravenous dipyridamole as probes of coronary vasomotor function can be evaluated noninvasively. The myocardial blood flow responses to these interventions might serve as indexes of endothelium-dependent and -independent coronary vasomotion.

Therefore, the aim of the current study was to determine noninvasively with $^{[13]}$Nammonia PET imaging whether long-term smoking affects coronary vasomotion and vasodilator capacity in smokers without evidence of epicardial coronary artery disease.

Methods

Study Population

Thirty-three individuals (16 healthy long-term smokers and 17 nonsmokers) were enrolled in this study. The group of smokers consisted of 13 men and 3 women with a mean age of 46$\pm$10 years (range, 36 to 68 years) who had been smoking cigarettes for 23$\pm$8 years (range, 11 to 39 years; 27$\pm$13 pack-years). None of the study participants had a history of hypertension, diabetes mellitus, or familial hyperlipidemia or was on any medication. All had normal ECGs at rest and during pharmacological stress. All had a normal stress/rest myocardial perfusion by PET polar map analysis. The group of 17 healthy lifelong nonsmokers (10 men, 7 women; age, 49$\pm$9 years; range, 37 to 64 years) had no known risk factors for coronary artery disease and served as control subjects.
All individuals refrained from intake of caffeine-containing food or beverages for at least 24 hours before the PET study. The smokers abstained from smoking for at least 4 hours before the PET study. Each participant signed an informed consent form approved by the Human Subject Protection Committee of the University of California, Los Angeles.

**Positron Emission Tomography**

Myocardial blood flow was quantified at rest, during cold pressor testing, and during dipyridamole-induced hyperemia using \[^{13}N\]ammonia and dynamic PET imaging. The Siemens/CTI ECAT EXACT HR positron emission tomograph, which acquires 47 transaxial frames of 10 seconds, 2 frames of 30 seconds, and 1 frame of 900 seconds. The cold pressor test was performed 45 minutes later as follows: The patient’s left hand was immersed in ice water for 45 seconds before a second dose of \[^{13}N\]ammonia (15 to 20 mCi) was injected. The same image acquisition sequence used for the baseline study was started at the time of the tracer injection. The cold pressor test was maintained for another minute to permit trapping of \[^{13}N\]ammonia in the myocardium. Finally, for determining the coronary vasodilator capacity, 0.56 mg/kg dipyridamole IV was infused over 4 minutes. \[^{13}N\]ammonia (15 to 20 mCi) was injected 4 minutes after the end of the dipyridamole infusion, and serial images were recorded in the same sequence.

Heart rate, arterial blood pressure, and 12-lead ECG were recorded continuously throughout the study. Heart rate and the arterial blood pressure obtained during the first 2 minutes of each dynamic image acquisition sequence were averaged and used to calculate the rate-pressure product as an index of cardiac work.

**Semiaquantitative Analysis**

The transaxially acquired image sets were reoriented into 12 short-axis images of the left ventricle (progressing from the apex to the base), which were assembled into polar maps of the relative distribution of myocardial blood flow. The entire left ventricular myocardium and the territories of the 3 major coronary arteries (left anterior descending, left circumflex, and right coronary arteries) were analyzed in each participant at rest and during dipyridamole hyperemia.

Normal myocardial perfusion was defined as an \[^{13}N\]ammonia uptake within 2 SD of the normal mean for both rest and dipyridamole images. To rule out blood flow defects and thus significant coronary artery disease in the study participants, the polar maps were compared with a database of 20 normal individuals previously established at our institution.

**Quantification of Myocardial Blood Flow**

Regional myocardial blood flow was quantified in the 3 vascular territories (left anterior descending, left circumflex, and right coronary arteries) as described previously. Then, 70° to 90° sectorial regions of interest were placed in the 3 major coronary vascular territories on a basal, midventricular, and apical cross-sectional image. A small (25-mm²) region of interest was centered in the left ventricular blood pool to derive the arterial input function. The regions of interest were copied to the first 120 seconds of the dynamic imaging sequence to obtain blood pool and myocardial time-activity curves.

A single time-activity curve was obtained for each vascular territory by averaging the time activity data from the 3 short-axis planes. Because myocardial blood flow did not differ between vascular territories, a single measurement of myocardial blood flow was obtained by averaging the territorial time activity data.

Partial volume effects were corrected by use of a recovery coefficient that assumes a uniform left ventricular wall thickness of 1 cm. Both the blood pool and myocardial time-activity curves were corrected for physical decay and were fitted to a previously validated two-compartment tracer kinetic model that corrects for spillover of activity from the blood pool into the left ventricular myocardium.

**Serum Lipid Measurements**

Total serum cholesterol and HDL cholesterol were measured with enzymatic methods. LDL cholesterol was calculated mathematically. Total cholesterol levels <200 mg/dL were considered normal; cholesterol levels between 200 and 239 mg/dL were defined as borderline; and levels ≥240 mg/dL were considered elevated. HDL cholesterol ≥40 mg/dL was defined as normal. LDL cholesterol values ≤130 mg/dL were considered normal; values between 130 and 159 mg/dL were considered borderline; and levels ≥160 mg/dL were considered elevated.

**Statistical Analysis**

Descriptive statistics are expressed as mean±SD. Hemodynamic measurements and myocardial blood flow at rest, during cold pressor test, and during dipyridamole-induced hyperemia were compared by use of one-way ANOVA. Comparisons between groups were made by use of the unpaired t-test. The difference in the relative proportion of women between smokers and nonsmokers was tested by Fisher’s exact test.

Discriminant and logistic regression analyses were performed to assess relationships between cigarette smoking and myocardial blood flow at rest, resting blood flow normalized to the rate-pressure product, myocardial blood flow during cold pressor, cold pressor blood flow normalized to the rate-pressure product, and myocardial blood flow during dipyridamole-induced hyperemia. This analysis revealed that the normalized myocardial blood flow response to cold was the only variable that discriminated between smokers and nonsmokers. Therefore, a stepwise and all-possible-subset multiple regression was used to evaluate the relationship between normalized blood flow response during cold (the dependent variable) and independent variables such as age, sex, total cholesterol, HDL or LDL/LDL, years of smoking, or pack-years in all 33 participants. Of note, when HDL was included as a variable in a subset, the LDL/HDL ratio was not present and vice versa. Also, when pack-years was present in a subset, years of smoking was not included and vice versa. Thus, our mathematical model accounted for the possibility of covariance of these factors. From these subsets, the one with the independent variables that yielded the highest multiple R was selected for the multiple regression equation. Values of P<0.05 were considered significant.

**Results**

**Hemodynamic Findings**

Heart rate and blood pressure at baseline, during cold pressor testing, and during dipyridamole-induced hyperemia are listed in Table 1. At baseline, systolic, diastolic, and mean arterial blood pressures were higher in smokers than in nonsmokers (P<0.02). However, the rate-pressure product was similar for both groups. Smokers and nonsmokers responded to cold with significant increases in systolic and mean arterial blood pressure and rate-pressure product, whereas heart rate increased only in smokers. Heart rate and rate-pressure product increased to similar degrees during dipyridamole-induced hyperemia in the 2 groups.

**Semiaquantitative Analysis of PET Images**

Visual inspection and polar map analysis of the myocardial \[^{13}N\]ammonia distribution at rest and during dipyridamole hyperemia revealed homogeneous tracer uptake in smokers and nonsmokers. No perfusion defects were identified. The absence of other risk factors (except for smoking in the smoking group), together with the normal \[^{13}N\]ammonia...
stress and rest perfusion images, indicated a low likelihood for coronary artery disease in all participants. Myocardial Blood Flow and Coronary Vasomotion

Myocardial blood flow at baseline did not differ between the 2 groups (0.68 ± 0.14 versus 0.68 ± 0.13 mL · g⁻¹ · min⁻¹, P = NS). However, myocardial blood flow increased during cold pressor testing only in nonsmokers (0.91 ± 0.18 mL · g⁻¹ · min⁻¹, P < 0.05) but not in smokers (0.78 ± 0.14 mL · g⁻¹ · min⁻¹, P = NS; Table 2). Thus, myocardial blood flow during cold pressor testing was about 16% lower in smokers than in nonsmokers (P < 0.05).

The magnitude of the blood flow response to cold varied between participants (from a 20% decrease to a 103% increase). Resting myocardial blood flow is correlated linearly to the rate-pressure product as an index of cardiac work. Cold-induced increases in rate-pressure product also remained significantly correlated to changes in blood flow in nonsmokers (y = 15.54 + 0.53x; r = 0.63; P < 0.008). To account for interindividual differences in the flow response to cold, myocardial blood flow was therefore normalized to the rate-pressure product at rest and during cold pressor testing in both groups. Normalized myocardial blood flow was derived from the ratio of blood flow (milliliters per gram per minute) to the rate-pressure product (beats per minute times millimeters of mercury) times 10⁰⁰₀₀. Despite similar rate-pressure products at rest and during cold in smokers and nonsmokers, normalized myocardial blood flow declined in smokers but remained unchanged in nonsmokers (0.86 ± 0.10 versus 0.72 ± 0.11, P = 0.0006, and 0.99 ± 0.25 versus 0.96 ± 0.27, P = NS; the Figure).

Table 2. Absolute Myocardial Blood Flow Measurements

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<th>Participant</th>
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<th>CPT</th>
<th>DIP</th>
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Mean 0.68 0.78§ 1.92‡ 0.68 0.91§† 2.04‡ 0.13 0.14 0.38 0.14 0.18 0.47

Abbreviations as in Table 1. Values are in mL · g⁻¹ · min⁻¹.

*P < 0.05 CPT vs rest; †P < 0.05 smokers vs nonsmokers; ‡P < 0.003 CPT vs DIP; and §P < 0.0002 DIP vs rest.
Hyperemic Blood Flow and Flow Reserve
The hyperemic blood flow response to dipyridamole infusion (1.92 ± 0.38 versus 2.04 ± 0.47 mL·g⁻¹·min⁻¹, P=NS; Table 2) was similar in smokers and nonsmokers. Myocardial flow reserve defined as the ratio of hyperemic to resting blood flow (2.88 ± 0.61 versus 3.06 ± 0.58, P=NS) did not differ between the 2 groups. Because dipyridamole uncouples flow from cardiac work, the hyperemic flows were not corrected for rate-pressure product.

Coronary Vascular Resistance
An index of coronary vascular resistance was calculated as the ratio of mean arterial blood pressure (millimeters of mercury) to myocardial blood flow (milliliters per gram per minute). At rest, this index did not differ between smokers and nonsmokers. The coronary vascular resistance remained unchanged during cold in smokers and nonsmokers (141 ± 23 versus 147 ± 23 and 128 ± 26 versus 115 ± 27 mm Hg · mL · g⁻¹ · min⁻¹, P=NS, respectively). However, the coronary vascular resistance during cold was higher in smokers than in nonsmokers, (147 ± 23 versus 115 ± 27 mm Hg · mL · g⁻¹ · min⁻¹, P=0.009).

To relate the hyperemic blood flow to one of its major determinants (the coronary driving pressure), the minimal coronary vascular resistance was calculated. The minimal coronary resistance during dipyridamole infusion did not differ between the 2 groups (52 ± 12 versus 46 ± 12 mm Hg · mL · g⁻¹ · min⁻¹, P=0.2).

Serum Lipid Measurements
None of the participants enrolled in the nonsmoking group had elevated total cholesterol levels (12 were considered to have normal and 5 to have borderline measurements), 4 had HDL <35 mg/dL, 3 had borderline LDL values, and 2 had elevated LDL measurements. In the smoking group, 11 had normal total cholesterol levels, 3 had borderline levels, and 2 had elevated levels. Eight smokers had HDL values <35 mg/dL, 1 had borderline LDL levels, and 3 had elevated LDL values.

The average levels of total and LDL cholesterol did not differ between smokers and nonsmokers (187 ± 40 versus 188 ± 35 and 120 ± 36 versus 117 ± 33 mg/dL, P=NS, respec-

tively). HDL tended to be lower in smokers (36 ± 10 versus 44 ± 14 mg/dL, P=0.07), whereas the HDL/LDL ratio did not differ between the 2 groups (0.34 ± 0.15 versus 0.41 ± 0.21, P=NS).

Discriminant and Multivariate Analyses
The discriminant analysis revealed that the normalized blood flow response to cold was the variable with the strongest relationship to cigarette smoking (discriminant equation: Z equals 5.839 times normalized blood flow response to cold minus 4.953; P<0.001). Therefore, to determine the relationship between the normalized blood flow response to cold and independent variables such as age, sex, total cholesterol, HDL or HDL/LDL ratio, years of smoking, or pack-years, a stepwise multiple regression analysis was performed. This analysis included all 33 participants and revealed a negative correlation between the normalized blood flow during cold and years of smoking (normalized blood flow during cold equals 0.7386 minus 0.00792 times years of smoking; P<0.001). In addition, it uncovered a positive correlation between normalized blood flow during cold and the HDL/LDL ratio (normalized blood flow during cold equals 0.7386 plus 0.5285 times HDL/LDL; multiple R=0.65; P<0.001).

The strongest predictor for the normalized blood flow response to cold was the years of smoking (F value, 11.37), followed by the HDL/LDL ratio (F value, 7.40).

None of the other variables such as age (F value, 0.35; P=0.63), sex (F value, 0.95; P=0.60), total cholesterol (F value, 4.05; P=0.46), HDL (F value, 4.30; P=0.78), and pack-years (F value, 8.46; P=0.67) was predictive of the normalized myocardial blood flow response to cold.

Discussion
The current study demonstrates that the myocardial blood flow response to cold is impaired in “healthy” long-term smokers and that the degree of this impairment correlates best with the number of years of smoking. Interestingly, low HDL/LDL ratios were also independently correlated with an abnormal blood flow response to cold. These findings imply that long-term smoking and mild alterations in serum lipid
levels affect coronary vasomotion in otherwise apparently healthy individuals.

**Effects of Smoking on Endothelium-Dependent Coronary Vasomotion**

Abnormalities in coronary vasomotion in response to coronary risk factors such as smoking, hypertension, hyperlipidemia, diabetes mellitus, and age are thought to precede coronary atherosclerosis. A significant correlation between the coronary vasomotor response to intracoronary acetylcholine and that to cold pressor testing has been demonstrated in patients with mild atherosclerosis. Therefore, cold pressor testing has been proposed as a noninvasive tool to probe endothelium-dependent coronary vasomotion.

Cold pressor testing evokes a mixed nervous response via stimulation of coronary vasoconstrictor adrenergic $\alpha_1$ and $\alpha_2$, myocardial $\beta_1$ (indirect vasodilation), coronary $\beta_2$ (direct vasodilation), and endothelial adrenergic $\alpha_2$-receptors (indirect coronary vasodilation). In individuals with preserved endothelial function, the smooth muscle cell $\alpha_2$-receptor-mediated vasoconstriction is presumably opposed by endothelial $\alpha_2$-receptor-mediated release of nitric oxide, causing smooth muscle relaxation. Together with stimulation of coronary and myocardial $\beta_2$-receptors, the net result is an increase in coronary blood flow. This complex balance between vasoconstrictor and vasodilator effects appears to be altered in endothelial dysfunction, in which coronary vasomotion in otherwise apparently healthy individuals. Furthermore, cardiovascular conditioning lowers the resting heart rate-pressure product in smokers and nonsmokers. Thus, the abnormal coronary vasomotion in response to cold observed in long-term smokers is unlikely to be attributable to differences in lifestyles between the 2 study groups.

Estrogen also might affect coronary vasomotor function and thus flow responses to cold pressor testing. However, the current study population consisted of 16 smokers (13 men and 3 women) and 17 nonsmokers (10 men and 7 women). The relative proportion of women was similar for the 2 groups ($P=0.26$). In the smoking group, 2 women were postmenopausal and 1 woman was premenopausal. In the nonsmoking group, 4 women were postmenopausal and 3 were premenopausal. Of note, none of the women enrolled was under estrogen-replacement therapy or contraceptive medication. Thus, only 4 of 33 participants might have exhibited some effect of estrogen on myocardial blood flow. In addition, the multivariate analysis failed to identify an effect of sex on the myocardial blood flow response to cold.

In the absence of any significant intergroup differences and together with previous observations (as described above), the abnormal blood flow response to cold in the long-term smokers observed in the current study most likely resulted from coronary endothelial dysfunction.

**Effect of Serum Cholesterol on the Myocardial Blood Flow Response to Cold**

The HDL/LDL ratio was the only other risk factor for coronary artery disease that independently predicted the normalized blood flow response to cold. In particular, the normalized flow response to cold was impaired in the presence of low HDL/LDL ratios. A close correlation between abnormal serum lipid levels and endothelial dysfunction has been demonstrated in animal experiments and clinical studies. Decreased activity of endothelial derived nitric oxide, excessive free radical production, or increased oxidation of LDL might explain the endothelial dysfunction in hypercholesterolemic patients. Our study supports the concept that even mild alterations in serum cholesterol profiles induce coronary endothelial dysfunction independent of other risk factors for coronary artery disease such as age, male sex, or cigarette smoking.

**Effects of Smoking on Endothelium-Independent Coronary Vasomotion**

Dipyridamole induces coronary vasodilation by increases in the interstitial concentration of adenosine, a potent endothelial coronary vasodilator. This mechanism is generally considered endothelium independent. The myocardial blood flow
flow response to dipyridamole was preserved in healthy adult long-term smokers in the present study. This is consistent with a previous report from our laboratory that demonstrated a normal hyperemic response to dipyridamole in healthy young volunteers with relatively short histories of smoking. Thus, endothelium-independent coronary vasodilator capacity is preserved in long-term smokers.

Study Limitations
First, the blood flow measurements in long-term smokers could have been affected by short-term nicotine effects. Nicotine evokes the release of catecholamines with subsequent adrenergically mediated increases in cardiac work and coronary blood flow. However, the smokers abstained from smoking for at least 4 hours before the PET study. This time interval is sufficient to reduce serum nicotine levels to nearly unmeasurable levels. Moreover, we ascertained that the smokers had indeed refrained from smoking by randomly measuring serum nicotine levels in 7 of the 16 smokers before the PET study. Five had unmeasurable levels, and 2 had levels of 10 and 15 ng/mL. These levels are substantially lower than those reported by Benowitz et al., who described that peak nicotine concentrations while smoking the usual brand of cigarette ranged from 18.4 to 55.1 ng/mL. In addition, Czernin et al. previously demonstrated that short-term smoking increases the baseline myocardial blood flow and attenuates the hyperemic response to dipyridamole. Yet in the current study, both resting and hyperemic blood flows did not differ between long-term smokers and nonsmokers. Both observations confirm that smokers in fact refrained from smoking for some time before the PET study and argue against an explanation for the abnormal blood flow response to cold in the present study.

Second, the uptake of $^{13}$N-ammonia during the cold pressor test was homogeneous in smokers and nonsmokers by visual analysis. Polar maps of the relative $^{13}$N-ammonia tracer distribution were generated for the myocardial blood flow study during cold pressor testing. However, because no normal database for the relative $^{13}$N-ammonia distribution during cold pressor testing was available, these polar maps were normalized to the peak 5% of activity within each map as described previously. This analysis revealed homogeneous tracer distribution throughout all 3 vascular territories during cold in both groups. Thus, smokers did not exhibit a greater degree of heterogeneity in relative myocardial perfusion than nonsmokers. Absolute flow values during cold pressor testing were similar in the 3 vascular territories in smokers and nonsmokers.

Third, flow-limiting coronary artery disease might have affected the blood flow response to cold in long-term smokers. Coronary artery disease could have been ruled out with certainty only through coronary arteriography, which seemed unjustified in these asymptomatic individuals. However, dipyridamole stress testing did not reveal any perfusion defects, a finding that argues against flow-limiting coronary artery disease in both the smokers and nonsmokers enrolled in the present study.

Finally, the correction for partial volume effects, which assumes a uniform myocardial wall thickness of 1 cm, might have introduced a systematic error in the blood flow measurements. On the basis of phantom studies, partial volume effects were corrected for by use of a recovery coefficient of 0.73. Assuming that wall thickness remained constant between studies, a systematic error in correcting for partial volume would have equally affected all 3 blood flow measurements.

Conclusions
Smoking and, to a lesser degree, reduced HDL/LDL ratios predict abnormalities in the myocardial blood flow response to cold, suggesting a defect located at the level of the coronary endothelium. The severity of endothelial dysfunction is associated with the total duration of smoking. The abnormalities in coronary function as detected by quantitative PET imaging might represent an early stage of coronary artery disease in long-term smokers.

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References


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