Smoking Is Associated With Epicardial Coronary Endothelial Dysfunction and Elevated White Blood Cell Count in Patients With Chest Pain and Early Coronary Artery Disease

Shahar Lavi, MD; Abhiram Prasad, MD; Eric H. Yang, MD; Verghese Mathew, MD; Robert D. Simari, MD; Charanjit S. Rihal, MD; Lilach O. Lerman, MD, PhD; Amir Lerman, MD

Background**—**Smoking is a major risk factor for cardiovascular events. One of the potential mechanisms may be related to both coronary endothelial dysfunction and increased inflammatory response. The present study was designed to test the hypothesis that smoking is associated with epicardial coronary endothelial dysfunction and inflammation.

Methods and Results**—**Coronary endothelial function in response to acetylcholine was assessed in 881 patients (115 current smokers and 766 nonsmokers, including 314 previous smokers). Smokers were significantly younger than nonsmokers (43±1 versus 51±1 years, $P<0.0001$), had more epicardial vasoconstriction in response to intracoronary acetylcholine (−19±2% versus −14±1% change in coronary artery diameter, $P=0.03$), and were more likely than nonsmokers to have epicardial endothelial dysfunction (46% versus 35%, $P=0.005$), but their microvascular endothelial function was intact. Smokers had higher white blood cell counts than nonsmokers (7.7 ± 0.2 versus $6.6\pm0.1\times10^9$/L, $P<0.0001$), higher myeloperoxidase (156±19 versus 89±8 ng/mL), higher lipoprotein-associated phospholipase A_2 (242±12 versus 215±5 ng/mL), and higher levels of intracellular adhesion molecule (283±14 versus 252±5 ng/mL). There were no differences in the levels of C-reactive protein, fibrinogen, or vascular cell adhesion molecule between the groups.

Conclusion**—**Young smokers are characterized by epicardial coronary endothelial dysfunction, preserved microvascular endothelial function, and increased levels of inflammatory biomarkers and oxidative stress. The present study provides further information regarding the potential mechanisms by which smoking contributes to cardiovascular events. **(*Circulation*. 2007;115:&NA;-.)**

Key Words: endothelium ■ smoking ■ inflammation

The endothelium, which separates the vascular smooth muscle cells from the blood, is a dynamic organ that has a vital role in the regulation of vascular tone, inflammation, and thrombogenesis.[1–3] Endothelial dysfunction is regarded as the early event in atherogenesis and is characterized by an imbalance between endothelium-dependent vasodilator and vasoconstrictor activity, as well as by altered antiinflammatory and anticoagulant properties of the endothelium.[2,3] Both peripheral[4] and coronary[5] endothelial dysfunction have been demonstrated in smokers and predict long-term cardiovascular events.[6,7]

Clinical Perspective p ■■■

The mechanism by which smoking may contribute to cardiovascular events before the development of significant coronary artery disease is not fully explored but may involve the induction of endothelial dysfunction.[4,5] Cigarette smoking is associated with oxidative stress,[8] a potential mediator of endothelial dysfunction,[9] and with increased blood thrombogenicity[10] and inflammatory response,[11] which are characteristics of endothelial dysfunction.

The role of inflammation in coronary artery disease continues to emerge,[12] and the increase in white blood cell (WBC) count in patients with heart disease may be considered a marker of systemic inflammation. An elevated WBC count has been associated with a greater risk of cardiovascular events,[13] and an increased WBC count was observed in smokers with progressive atherosclerosis.[14]

Although both smoking and inflammation may be associated with endothelial dysfunction, the association between total WBC count, smoking, and coronary endothelial dysfunction in patients without significant coronary atheroscle-

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From the Division of Cardiovascular Diseases (S.L., A.P., E.H.Y., V.M., R.D.S., C.S.R., A.L.) and Division of Nephrology and Hypertension (L.O.L.), Mayo College of Medicine, Rochester, Minn.

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Correspondence to Amir Lerman, MD, Division of Cardiovascular Diseases, Mayo Clinic, Mary Brigh 4-523, First St SW, Rochester, MN 55905. E-mail Lerman.Amir@mayo.edu

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rosis is not fully clarified. Furthermore, the differential effect of smoking on macrovascular and microvascular endothelial function is unknown.

The purpose of the present study was to test the hypothesis that smoking is associated with coronary endothelial dysfunction and increased systemic inflammatory response. To address our hypothesis, we assessed coronary endothelial function in response to intracoronary administration of the endothelium-dependent vasodilator acetylcholine, systemic inflammation, and cardiovascular risk factors in smoking and nonsmoking patients without significant coronary artery disease.

Methods

Patient Population

The study was approved by the Mayo Clinic Institutional Review Board, and informed consent was obtained from all participants. The study group consisted of 881 consecutive patients who were referred for evaluation of chest pain and who did not have significant coronary artery disease (>30%) on diagnostic coronary angiography. Some of the patients had been described in previous publications.[7,15–17] Angiography was performed after an overnight fast, and all vasoactive medications affecting cardiovascular hemodynamics were discontinued for at least 48 hours before the study.

Study Protocol

After diagnostic angiography and exclusion of patients with significant coronary artery disease, a 6F or 7F guiding catheter was placed into the left main coronary artery. Coronary vasoreactivity was assessed as described previously.[16,17] In brief, 5000 U of heparin was given intravenously, and a Doppler guidewire (FloWire, Volcano Corp, Rancho Cordova, Calif) was positioned within a coronary infusion catheter (Ultrafuse, SciMed Life Systems, Minneapolis, Minn) in the midportion of the left anterior descending coronary artery. Velocity signals were obtained instantaneously from the Doppler wire by an online fast Fourier transform, and average peak velocity was determined. This method was validated previously,[16,17] and analysis of data from our laboratory demonstrates that the variation in repeated measurements is 8±3%.

Intracoronary bolus injections of incremental doses (18 to 60 μg) of adenosine were administered until maximal hyperemia was achieved or the largest dose was given to evaluate endothelium-independent microvascular coronary flow reserve. Coronary flow reserve was calculated by dividing the average peak velocity after adenosine injection by the average peak velocity at baseline.

Subsequently, to assess endothelium-dependent vasoreactivity, the endothelium-dependent vasodilator acetylcholine was selectively infused at increasing concentrations (10^{-6}, 10^{-5}, and 10^{-4} mol/L) for 3 minutes at each concentration into the left anterior descending coronary artery to obtain effective coronary concentrations of 10^{-8}, 10^{-7}, and 10^{-6} mol/L, respectively. Coronary artery diameter (CAD) and average peak velocity were measured, and coronary blood flow (CBF) was calculated after each infusion of acetylcholine. Finally, endothelium-independent epicardial coronary artery function was determined by the change in CAD in response to intracoronary nitroglycerin bolus (100 μg; Abbott Laboratories, Abbott Park, Ill).

CAD was measured offline by an independent investigator in the mid left anterior descending artery in the segment 5 mm distal to the tip of the Doppler wire and in the distal left anterior descending artery with a quantitative coronary angiography program (Medis Corp, Leiden, the Netherlands) as described previously.[18] CBF was calculated from the Doppler-derived time velocity integral and vessel diameter as $\pi\times(\text{CAD}/2)^2\times(\text{average peak velocity}/2)$.[17] Endothelium-dependent coronary flow response was calculated as the percent change in CBF in response to acetylcholine. According to our previous studies, we defined coronary epicardial endothelial dysfunction as a decrease in diameter >20% in response to the maximum dose of acetylcholine. Microvascular endothelial dysfunction was defined as ≤50% increase in CBF in response to the maximal dose of acetylcholine compared with baseline CBF.[16,17] In patients who did not receive the full dose of acetylcholine or adenosine, the highest dose was used for analysis.

Blood samples were obtained with subjects in the fasting state before the coronary angiogram for measurement of the following inflammatory biomarkers: WBC count, soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular cell adhesion molecule-1 (sVCAM-1), C-reactive protein, and fibrinogen; as well as for measurement of the following oxidative stress markers: lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$) and myeloperoxidase. Total WBC count and differential leukocyte count were assessed by standard Coulter counter techniques (Coulter LH 700, Beckman Coulter Corp, Miami, Fla). The intra-assay coefficients of variation for WBC, neutrophil, lymphocyte, and monocyte counts were 1.4%, 0.7%, 2.2%, and 5.5%, respectively.

Lp-PLA$_2$ mass was measured as described previously with an ELISA (PLAC test, diaDexus, Inc, San Francisco, Calif).[19] This assay consists of 2 high-affinity monoclonal antibodies to Lp-PLA$_2$. The range of detection was 50 to 1000 ng/mL, and the interassay coefficients of variation were 7.8% at 276 ng/mL, 6.1% at 257 ng/mL, and 13.5% at 105 ng/mL.

Serum C-reactive protein concentrations were measured with a high-sensitivity radioimmunoassay kit (Kamiya Biomedical, Seattle, Wash). Plasma myeloperoxidase was measured by a 2-site "sandwich" ELISA (Immunodiagnostik, Bensheim, Germany).[20] sICAM-1 and sVCAM-1 concentrations were measured with a sandwich enzyme–linked immunoassay technique with a commercially available kit (R&D Systems Inc, Minneapolis, Minn).[21] The interassay coefficients of variations for both assays were 10%.

Data Analysis

Continuous variables are presented as mean±SEM and dichotomous variables as numbers and percentages. The baseline characteristics of groups were compared by use of 1-way ANOVA for continuous variables and by the Pearson χ^2 statistic for categorical variables. Single-predictor and multivariable linear regression models were used to calculate the effect of smoking on endothelial dysfunction. WBC count and other variables found to show marginal association with endothelial dysfunction in the single-predictor analysis ($P<0.20$) were used in the multivariable model. Adjustments were made for the following baseline clinical characteristics: age, gender, history of hypertension, hyperlipidemia, diabetes mellitus, body mass index, WBC count, statin use, and hemoglobin level. Three-group comparisons were performed simultaneously. The level selected for statistical significance was set at probability value <0.05.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

All patients were referred to the cardiac catheterization laboratory for evaluation of coronary artery disease by their attending cardiologists. Patients were divided according to their smoking status as current smokers (within the last month, n=115) or nonsmokers (n=766). Nonsmokers included both previous smokers (n=314) and never-smokers (n=452). The clinical characteristics of the patients are outlined in Table 1. Smokers were younger than nonsmokers, were more likely to be male, and had lower body mass index values. The prevalence of other risk factors (hypertension, hyperlipidemia, and diabetes mellitus) was similar in smokers and nonsmokers, although high-density lipoprotein levels were lower in smokers, as described previously,[22] and the use of statins was lower in smokers than in previous smokers and never-smokers (17%, 36%, and 25%, respectively; $P<0.001$). There was no difference in the use of any of the other cardiovascular medications (Data Supplement Table I). The

TABLE 1. Baseline Characteristics of the Patient Cohort

	Smokers (n=115)	Previous Smokers (n=314)	Never-Smokers (n=452)
Age, y	43±1	52±0.6	50±0.6*†
Male gender	66 (57)	124 (39)	144 (32)*†
Hypertension	41 (36)	127 (40)	179 (40)
Hyperlipidemia	49 (43)	175 (56)	214 (47)†
Diabetes mellitus	6 (5)	31 (10)	36 (8)
Body mass index, kg/m^2	27.4±0.5	28.4±0.3	28.9±0.3*†
Cholesterol, mmol/L	4.8±0.1	5±0.06	5±0.05
LDL, mmol/L	2.87±0.08	2.9±0.14	2.9±0.14
HDL, mmol/L	1.16±0.05	1.34±0.02	1.37±0.02*†
Triglyceride, mmol/L	1.68±0.09	1.66±0.05	1.58±0.04
Glycosylated hemoglobin, %	5.5±0.1	5.6±0.1	5.5±0.1
Hemoglobin, g/dL	13.7±0.1	13.4±0.08	13.4±0.07*

Values are expressed as mean±SEM or n (%). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

*$P<0.05$, smokers vs nonsmokers; †$P<0.05$ between all groups.

average degree of stenosis in the left anterior descending artery was 5±0.5% in all groups, and no association was found between the degree of stenosis and endothelial dysfunction.

All 3 tests of vascular function (acetylcholine, adenosine, and nitroglycerin) were performed in all patients. Coronary hemodynamic data are presented in Table 2. Blood pressure was lower in smokers, as was reported previously.[22] Coronary flow reserve in response to adenosine was similar in smokers and nonsmokers and was higher in men than in women (3.2±0.1 versus 2.7±0.1, respectively; $P<0.0001$), as shown previously.[23] Intracoronary adenosine did not cause significant hemodynamic effects. Smokers and nonsmokers had similar increases in CAD in response to intracoronary nitroglycerin (11.1±2% versus 12.6±1%, $P=0.5$.)

The decrease in CAD in response to acetylcholine was more pronounced in smokers than in nonsmokers (previous smokers and never-smokers), and more smokers were classified as having epicardial endothelial dysfunction (46% versus 34% and 35%, $P=0.03$). In contrast, smokers were less likely to have microvascular endothelial dysfunction (Figure 1). Smokers had a greater decrease in CAD and increase in CBF after administration of acetylcholine than previous smokers and never-smokers. The dose-response curve of CAD and CBF to acetylcholine is shown in Figure 2. The results of the single-predictor and multivariable models are shown in Table II in the Data Supplement. After adjustment for other important variables (age, diabetes mellitus, hypertension, body mass index, gender, hemoglobin level, WBC count, high-density lipoprotein levels, and statin use), smoking (current smoking versus currently not smoking) remained an important and significant predictor of coronary epicardial endothelial dysfunction as determined by the decrease in CAD in response to acetylcholine ($P=0.02$), whereas the effect of smoking on CBF response was nonsignificant ($P=0.3$). We did not find a direct correlation between the degree of endothelial dysfunction and smoking duration in either the current smokers or the previous-smoker groups; however, current smokers who smoked for >30 years had a greater decrease in CAD in response to acetylcholine (25±3%) and were more likely to have endothelial dysfunction (61%; P=NS). The previous-smoker group was further divided into 3 groups according to the duration of smoking abstinence: <1 year, 1 to 10 years, or >10 years. There was a graded relationship between the duration of smoking abstinence and the degree of decrease in CAD in response to acetylcholine (−22±3%, −13±1%, and −12±2%, respectively; $P=0.04$). Sixty percent of the patients with less than 1 year of abstinence from smoking had macro-

TABLE 2. Hemodynamic Data

	Smokers (n=115)	Previous Smokers (n=314)	Never-Smokers (n=452)
Mean blood pressure, mm Hg	95±1.4	99±1	100±1*†
Heart rate, bpm	70±1.2	72±0.5	71±0.5
CFR to adenosine	2.84±0.07	2.68±0.04	2.82±0.03†
Baseline CAD, mm	2.3±0.05	2.2±0.03	2.2±0.03
Baseline CBF, mL/min	59±3	54±2	51±1*†
Δ% CAD to acetylcholine	−19±2	−14.6±1	−13.2±1*
Δ% CBF to acetylcholine	81±10	66±6	50±5*†

Values are expressed as mean±SEM. CFR indicates coronary flow reserve.

*$P<0.05$, smokers vs nonsmokers; †$P<0.05$ between all groups.

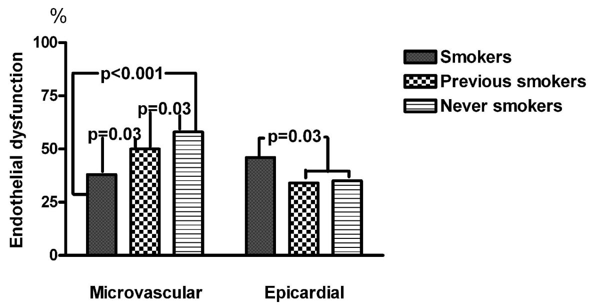

Figure 1. Epicardial and microvascular endothelial dysfunction according to smoking status.

vascular endothelial dysfunction compared with 35% of patients who had not smoked for 1 to 10 years and 23% of the group who had not smoked for >10 years ($P<0.01$).

Both total WBC count and absolute leukocyte subtype (neutrophils, lymphocytes, and monocytes) counts were higher in smokers than in nonsmokers (Table 3), with no difference between men and women. There was no significant difference in the distribution of leukocyte subtypes, as reflected by the similar neutrophil/lymphocyte ratio. The relationship between WBC counts and smoking status is shown in Figure 3. Smokers had higher levels of sICAM-1, myeloperoxidase, and Lp-PLA$_2$ than nonsmokers (Table 3). These associations were unaffected by adjustment for statin therapy. Lp-PLA$_2$ levels were also significantly correlated with macrovascular endothelial function ($r=-0.32$, $P<0.0001$). There were no differences between smokers and nonsmokers in the levels of C-reactive protein, fibrinogen, or sVCAM-1.

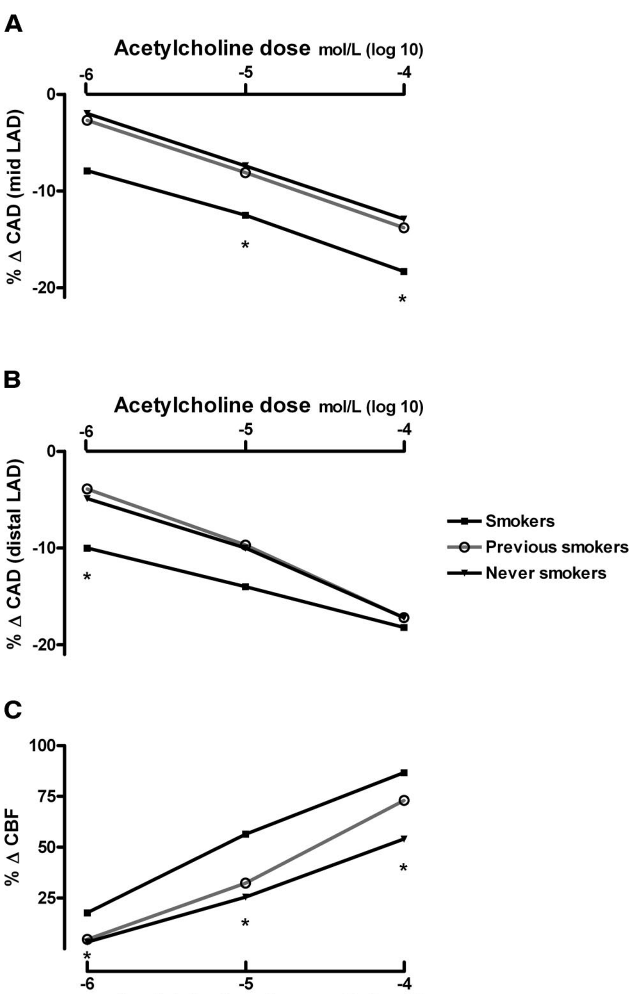

Figure 2. Dose-response curves to intracoronary acetylcholine according to smoking status. A, Percent change in CAD in mid left anterior descending artery (LAD). B, Percent change in CAD in distal LAD. C, Percent change in CBF in LAD. *$P<0.05$.

Discussion

The present study demonstrates that young smokers without evidence of significant coronary artery disease are characterized by epicardial coronary endothelial dysfunction and preserved microvascular endothelial function. Furthermore, smokers have increased levels of several inflammatory biomarkers, which may be related to their endothelial dysfunction. The study provides an additional potential mechanism for the contribution of smoking to cardiovascular events and progression of atherosclerosis in humans.

There are large amounts of data that support the association between smoking and cardiovascular morbidity, including increased risk of myocardial infarction and sudden cardiac death, but the precise mechanism by which smoking contributes to these events is not established.[24] Smoking may be associated with decreased nitric oxide biosynthesis,[25] and it is hypothesized that endothelial dysfunction plays a major role in cardiovascular events in smokers.[26]

Previously, Zeiher et al[5] demonstrated that flow-mediated dilatation of coronary arteries in response to papaverine was blunted in patients with coronary atherosclerosis who smoke. The present study extends this observation by using a specific endothelium-dependent vasodilator, acetylcholine, for assessment of endothelial function in young patients with early coronary atherosclerosis. Moreover, the present study examined the effect of smoking on both epicardial and coronary microcirculation.

The present study reports for the first time the differential effect of smoking on the epicardial and coronary microcirculation. We found a lower CBF response to acetylcholine in nonsmokers than in smokers, which reflects abnormal coronary microcirculation endothelial function, possibly owing to their older age and higher body mass index. It is possible that this finding is attributed to selection bias. The patients in the study were referred because of chest pain, and some had either microvascular or epicardial endothelial dysfunction. Although the normal microcirculatory endothelial function in smokers may be due to selection bias, it is clear that whereas smoking causes macrovascular endothelial dysfunction, it does not cause microvascular endothelial dysfunction. The lower prevalence of use of statins in the smokers' group may be due to their younger age and lack of need for treatment with statins in this group. Statins can improve endothelial function; however, their effect is more significant on microvascular than on macrovascular endothelial function.[20] Thus, the higher prevalence of statin use in the nonsmokers' group may have resulted in underestimation of the strength of the present results with regard to the preservation of microvascular endothelial function in smokers. Moreover, in

TABLE 3. Inflammatory and Oxidative Stress Biomarkers in Smokers and Nonsmokers

	Smokers (n=115)	Previous Smokers (n=314)	Never-Smokers (n=452)
WBC, $\times 10^9$/L	7.7±0.2	6.7±0.1	6.6±0.1*†
Neutrophils, $\times 10^9$/L	4.4±0.2	3.9±0.1t	4±0.1*†
Monocytes, $\times 10^9$/L	0.6±0.01	0.5±0.01	0.5±0.01*†
Lymphocytes, $\times 10^9$/L	2.2±0.1	1.9±0.04	1.9±0.03*†
Neutrophils/lymphocytes	2.2±0.2	2.4±0.1	2.4±0.1
hs-CRP, mg/L	0.91±0.3	1.2±0.2	0.9±0.2
Fibrinogen, μmol/L	8.04±0.34	8.08±0.2	7.94±0.17
sICAM-1, ng/mL	283±14	270±8	239±7*†
sVCAM-1, ng/mL	606±38	613±23	590±20
Lp-PLA_2, ng/mL	242±7	224±4	209±3*†
Myeloperoxidase, ng/mL	156±20	103±12	78±10*†

Values are expressed as mean±SEM. hs-CRP indicates high-sensitivity C-reactive protein.
*$P<0.05$, smokers vs nonsmokers; †$P<0.05$ between all groups.

multivariable analysis after adjustment for statin therapy, smoking remained an independent predictor of endothelial dysfunction.

A potential mechanism by which smoking may contribute to endothelial dysfunction may be via oxidative stress. Cigarette smoke contains free radicals, which may lead to the formation of oxidative stress,[27] and indeed, increased levels of isoprostanes, a marker of in vivo oxidative stress, were observed in smokers.[8,11] In the present study, we found that smokers had significantly higher levels of myeloperoxidase than nonsmokers. Myeloperoxidase functions as a catalyzer in consumption of nitric oxide,[28] and it may serve as a potential link between smoking, oxidative stress, inflammation, and endothelial dysfunction. Serum myeloperoxidase levels have been shown to be correlated with peripheral endothelial dysfunction,[29] but in the present study, we did not find such a correlation with coronary endothelial function. The lack of direct correlation may be due to the fact that the activity of this enzyme is localized to the vascular wall[30]; however, this is speculative. Smokers have reduced ascorbate levels, and treatment with antioxidants improves the impairment of endothelial function in smokers.[31,32] Despite the positive effects of vitamin C on endothelial function in smokers shortly after its administration, this improvement does not last in the long term, possibly owing to the reduction in bioactivity of vitamin C that occurs with prolonged therapy.[31]

We have shown that dietary reversal of hypercholesterolemia in pigs normalized superoxide dismutase activity and

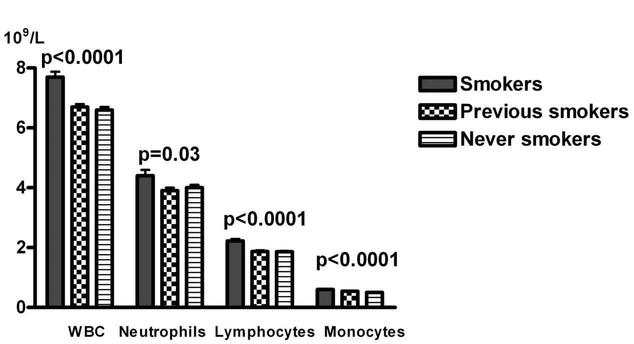

Figure 3. WBC and differential counts according to smoking status.

the impairment of epicardial endothelial function, with no effect on microvascular function.[33] In patients with coronary artery disease and abnormal brachial flow-mediated dilation, vitamin C produced a marked improvement in endothelium-dependent flow-mediated dilation, with no effect on hyperemic flow.[34] Therefore, both smoking and oxidative stress may have differential effects on epicardial vessels and small vessels. Furthermore, the CAD response to acetylcholine was similar in the previous-smoker and never-smoker groups, possibly owing to a decrease in oxidative stress, because it has been reported that isoprostanes decrease significantly after a 2-week period of abstinence from smoking.[8]

Although the mechanism of the differential effect of smoking on endothelial function is not fully understood, these findings may have important clinical implications. The development of dysfunctional endothelium at the level of the epicardial vessels may lead to thrombus formation[35] and plaque erosion, which have been implicated in the acute coronary syndromes and in sudden death in young smokers.[36,37] The relevant preservation of the microcirculation endothelium-dependent coronary flow reserve in smokers may explain in part the better prognosis of smokers after myocardial infarction compared with nonsmokers.

In the present study, smokers were significantly younger than nonsmokers and had a lower body mass index. Although other risk factors such as diabetes mellitus, hypercholesterolemia, and hypertension were similar in smokers and nonsmokers, their potential increased prevalence in smokers is obscured by their younger age in the present study.

Smokers were more likely to have macrovascular coronary endothelial dysfunction, and the response to acetylcholine in previous smokers was similar to that of the never-smokers' group. It has been shown that myocardial flow reserve is significantly reduced immediately after smoking but is not affected by long-term smoking.[38] Indeed, in the present study, smokers and nonsmokers had similar coronary flow reserve in response to adenosine, and this supports the assumption that the observed hemodynamic differences between the groups are not related to acute effects of smoking.

There is a growing body of evidence to suggest that systemic inflammation plays a role in the progression and complications of coronary atherosclerosis. Inflammatory response is most widely measured by total and differential WBC counts,[39] and previous studies have demonstrated increased WBC counts in smokers[40] that decrease rapidly after smoking cessation.[41]

High WBC counts were found to be a marker of future all-cause[42] and cardiac[43] mortality, especially in acute coronary syndrome.[44] Data from several prospective cohort studies suggest that an elevated WBC count in patients without evidence of heart disease is associated with an increased risk of future cardiac events.[43,45] Thus, an elevated WBC count may not be just a marker of increased risk but may also play a role in the pathophysiology of atherosclerosis and cardiac events; however, cigarette smoking partially explained the increase in WBC count, and endothelial function was not assessed in these previous studies. We found that smokers not only had significantly increased absolute WBC counts, but they also had increased levels of neutrophils, lymphocytes, and monocytes compared with nonsmokers. Furthermore, the previous-smoker and never-smoker groups had similar WBC counts. In addition, we measured other systemic inflammatory biomarkers and found that smokers had higher levels of Lp-PLA$_2$, myeloperoxidase, and sICAM-1 than nonsmokers but similar levels of C-reactive protein, sVCAM-1, and fibrinogen. Thus, it appears that smoking may have a differential effect on inflammatory pathways that play a role in endothelial dysfunction.

We have recently shown that Lp-PLA$_2$ levels, a parameter of low-density lipoprotein oxidation, are correlated with endothelial dysfunction.[15] In the present study, we did not find a direct correlation between the degree of endothelial dysfunction and other inflammatory biomarkers, but we found that Lp-PLA$_2$ levels were elevated in smokers and significantly correlated with endothelial function. Lp-PLA$_2$, an enzyme secreted by macrophages and lymphocytes, hydrolyzes the *sn*-2 fatty acids of oxidized phospholipids to yield oxidized fatty acid and lysophosphatidylcholine, potentially proinflammatory particles that may affect endothelial function.[15,46] It is possible that Lp-PLA$_2$ plays a role in the effect of smoking on endothelial function and serves as a mechanistic link between inflammation and endothelial dysfunction.

Limitations and Clinical Implications

Patients in the present study were referred for coronary angiography and coronary endothelial function assessment because of chest pain. This group is a selected population that represents patients with chest pain without significant coronary artery disease but may not represent all patients with early atherosclerosis. The measurement of CBF in 1 vessel does not necessarily reflect the microcirculation in other vessels; however, we used this method mainly to explore the changes in flow and not to obtain absolute values.

Cigarette smoke contains multiple toxic particles, and it is not feasible to deduce a single specific mechanism in the pathogenesis of atherosclerosis in smokers. Although we did not find a linear correlation between WBC counts and the degree of endothelial dysfunction in the present study, inflammation may still play a role in the pathogenesis, progression, and complications of coronary endothelial dysfunction in smokers. The effect of smoking on endothelial dysfunction is probably multifactorial, and thus, some influence on endothelial function via oxidative stress and inflammatory pathways, possibly via Lp-PLA$_2$, may exist.

Both inflammation and endothelial dysfunction are implicated in the pathogenesis of ischemic heart disease, and their corresponding values in previous smokers were comparable to those of never-smokers. This provides further support that smoking cessation should be strongly recommended.

In summary, the present study demonstrates that young smokers who were referred to the cardiac catheterization laboratory and were found to have nonsignificant coronary atherosclerosis are characterized by epicardial endothelial dysfunction, preserved microvascular endothelial function, and increased levels of several inflammatory biomarkers. The present study highlights the potential mechanism by which smoking contributes to cardiovascular events and the importance of smoking cessation.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Smoking is considered a major risk factor for cardiovascular events, but its mechanisms are not fully understood. We hypothesized that smoking is associated with both epicardial coronary endothelial dysfunction and inflammation before the development of significant coronary artery disease. We assessed white blood cell count and other inflammatory biomarkers, as well as microvascular and macrovascular endothelial function, using acetylcholine infusion and quantitative coronary angiography in smokers and nonsmokers. Smokers had a higher white blood cell count and more epicardial vasoconstriction in response to intracoronary acetylcholine than nonsmokers but had preserved microvascular endothelial function. These results provide further insights into the pathophysiology of coronary events in smokers.