Impaired Coronary Tissue Plasminogen Activator Release Is Associated With Coronary Atherosclerosis and Cigarette Smoking

Direct Link Between Endothelial Dysfunction and Atherothrombosis

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Background—The aim of the study was to establish the influence of proximal coronary artery atheroma and smoking habit on the stimulated release of tissue plasminogen activator (tPA) from the heart.

Methods and Results—After diagnostic coronary angiography in 25 patients, the left anterior descending coronary artery (LAD) was instrumented, and the proximal LAD plaque volume was determined by use of intravascular ultrasound (IVUS). Blood flow and fibrinolytic responses to selective LAD infusion of saline, substance P (10 to 40 pmol/min; endothelium-dependent), and sodium nitroprusside (5 to 20 μg/min; endothelium-independent) were measured by intracoronary IVUS and Doppler, combined with arterial and coronary sinus blood sampling. Mean plaque burden was 5.5 ± 0.8 mm³/mm vessel (range 0.6 to 13.7 mm³/mm vessel). LAD blood flow increased with both substance P and sodium nitroprusside (P < 0.001), although coronary sinus plasma tPA antigen and activity concentrations increased only during substance P infusion (P < 0.006 for both). There was a strong inverse correlation between the LAD plaque burden and release of active tPA (r = -0.61, P = 0.003). Cigarette smoking was associated with impaired coronary release of active tPA (current smokers, 31 ± 23 IU/min; ex-smokers, 50 ± 33 IU/min; nonsmokers 202 ± 73 IU/min; P < 0.05).

Conclusions—We found that both the coronary atheromatous plaque burden and smoking habit are associated with a reduced acute local fibrinolytic capacity of the heart. These important findings provide evidence of a direct link between endogenous fibrinolysis, endothelial dysfunction, and atherothrombosis in the coronary circulation and may explain the greater efficacy of thrombolytic therapy for myocardial infarction in cigarette smokers. (Circulation. 2001;103:1936-1941.)

Key Words: thrombolysis • endothelium • coronary disease • ultrasonics

The fibrinolytic factor tissue plasminogen activator (tPA) is a serine protease that regulates the degradation of intravascular fibrin and is released from the endothelium through the translocation of a dynamic intracellular storage pool. If endogenous fibrinolysis is to be effective, then the rapid mobilization of tPA from the endothelium is essential, because thrombus dissolution is much more effective if tPA is incorporated during, rather than after, thrombus formation. The efficacy of plasminogen activation and fibrin degradation is further determined by the relative balance between the acute local release of tPA and its subsequent inhibition through formation of complexes with the serpin, plasminogen activator inhibitor type 1 (PAI-1). This dynamic aspect of endothelial function and fibrinolytic balance may be directly relevant to the pathogenesis of atherothrombosis, but only recently have robust methods to determine acute tPA release been developed.

Small areas of denudation and thrombus deposition are a common finding on the surface of atheromatous plaques and are usually subclinical. In the presence of an imbalance in the fibrinolytic system, however, such microthrombi may propagate, ultimately leading to arterial occlusion. Indeed, in genetic murine models, tPA deficiency is associated with myocardial necrosis and the development of regional wall motion abnormalities. Recently, Rosenberg and Aird postulated that vascular bed–specific defects in hemostasis exist and that coronary thrombosis critically depends on the local fibrinolytic balance. To date, however, no clinical studies have directly assessed the acute local fibrinolytic capacity of...
the coronary vascular bed in patients with coronary artery disease.

Using forearm venous occlusion plethysmography and the endothelium-dependent agonist substance P, we recently characterized a new model of assessing the acute release of endogenous tPA in vivo in humans. This has allowed us to show that cigarette smoking is associated with an impairment of acute tPA release in the forearm circulation. We hypothesized that the acute local coronary release of tPA would be influenced by both the extent of coronary atheroma and smoking habit. Therefore, the aims of the present study were first, to apply this approach to the coronary circulation and thereby establish a method of assessing acute coronary tPA release; second, to determine the relationship between the extent of coronary artery atheroma, quantified by intravascular ultrasound (IVUS), and the acute fibrinolytic capacity of the coronary vascular bed; and third, to show whether cigarette smoking impairs coronary, as well as forearm, tPA release.

Methods

Patient Selection

Patients were excluded if they had significant left main stem disease or a minimal luminal diameter of <2 mm in the proximal left anterior descending coronary artery (LAD). Coronary risk factors were determined in all patients by standard clinical criteria. The study was undertaken with the approval of the local research ethics committee, in accordance with the Declaration of Helsinki, and with the written informed consent of each subject.

Study Protocol

All patients discontinued their medication on the study day, attended in the fasting state, and underwent diagnostic coronary angiography at 8 AM. The coronary sinus was cannulated from the femoral vein with a preformed specific 6F catheter (Torcon NB catheter, Cook) that was placed in the right femoral artery. Stable and selective cannulation of the coronary sinus was achieved in all 11 patients. Arterial samples were obtained through an 8F hemostatic sheath placed in the right femoral artery. The left coronary artery was cannulated with a 7F guiding catheter, and a 0.014-in 12.5-MHz Doppler wire (FloWire, Cardiometrics, Endosonics) was passed into the LAD. A 3.2F Ultracross 20-MHz IVUS imaging catheter (Scimed, Boston Scientific Corp) was advanced into the LAD over the Doppler wire. The IVUS examination of the proximal artery was performed at 0.5 mm/s with a motorized pullback device (Boston Scientific Corp). After the pullback examination, the IVUS imaging catheter was repositioned just distal to the ostium of the LAD. The Doppler guidewire was retracted to the tip of the imaging catheter and maintained in a stable position by the short monorail segment of the IVUS catheter.

Drug Administration

Pharmaceutical-grade substance P (Clinalfa AG), an endothelium-dependent vasodilator, and sodium nitroprusside (David Bull Laboratories), an endothelium-independent vasodilator, were administered after dissolution in saline. Five-minute infusions were administered at 1 mL/min via the IVUS catheter flush port. The agents were given in the following order: saline, substance P 10 pmol/mL, substance P 20 pmol/mL, substance P 40 pmol/mL, sodium nitroprusside 5 μg/mL, and sodium nitroprusside 20 μg/mL.

Measurement of Plaque Volume and Coronary Blood Flow

Computerized 3D reconstructions of the proximal LAD were performed offline by a single blinded operator using the TomTec computer system (Echoscan, TomTec Imaging Systems). The proximal atheromatous plaque volume was calculated with a well-validated edge-detection algorithm as previously described.

The LAD cross-sectional area was measured by computerized planimetry (Clearview, Boston Scientific Inc) of the vessel lumen at the onset of the QRS complex. Blood flow velocity was determined by use of average peak velocity of the Doppler signal (FloMap, Cardiometrics). Blood flow in the LAD was previously defined as half the product of the average peak velocity and the cross-sectional area and was determined from the mean of 5 measurements made in the final minute of each infusion period.

Blood Sampling and Plasma Assays

Ten milliliters of arterial and 10 mL of coronary sinus blood were obtained simultaneously at the end of each infusion period and collected into acidified buffered citrate (Biopool Stabilyte) and citrate (Monovette, Sarstedt) tubes, and platelet-free plasma was decanted and stored at −80°C before assay. Coronary sinus oxygen saturations were determined at the end of each infusion period with an automated oximeter (Oxicam 300, Watco Services). Plasma tPA

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
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<tbody>
<tr>
<td>No.</td>
</tr>
<tr>
<td>Sex, male</td>
</tr>
<tr>
<td>Age, y</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
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<tr>
<td>Risk factors, n</td>
</tr>
<tr>
<td>Current/ex-smoker</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Hyperlipidemia</td>
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<tr>
<td>Family history</td>
</tr>
<tr>
<td>Serum lipid profile, mg/dL</td>
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<tr>
<td>Total cholesterol</td>
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<tr>
<td>LDL cholesterol</td>
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<tr>
<td>HDL cholesterol</td>
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<tr>
<td>Total/HDL cholesterol ratio</td>
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<tr>
<td>Triglycerides</td>
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<td>Medical therapy, n</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>β-Adrenergic blockade</td>
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<tr>
<td>Lipid-lowering therapy</td>
</tr>
<tr>
<td>Calcium antagonism</td>
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<tr>
<td>Long-acting nitrate</td>
</tr>
<tr>
<td>ACE inhibition</td>
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<tr>
<td>Diuretics</td>
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<tr>
<td>Previous myocardial infarction, n</td>
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<tr>
<td>Noninvasive testing, n</td>
</tr>
<tr>
<td>Low risk</td>
</tr>
<tr>
<td>High risk</td>
</tr>
<tr>
<td>Not performed</td>
</tr>
<tr>
<td>Angiographic data, n</td>
</tr>
<tr>
<td>Good left ventricular function</td>
</tr>
<tr>
<td>Normal/mild disease</td>
</tr>
<tr>
<td>Single-vessel disease</td>
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<tr>
<td>2-Vessel disease</td>
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<td>3-Vessel disease</td>
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</table>
and PAI-1 antigen and activity concentrations were determined with ELISAs and a photometric method as previously described.2,6

Data Analysis and Statistics
Coronary tPA release was defined as the product of the LAD plasma flow and the plasma arterial and coronary sinus concentration differences. To compare vasomotor and fibrinolytic responses with proximal atheromatous plaque volume, the area under the curve (AUC) was calculated for each response: coronary blood flow, plasma arterial and coronary sinus tPA concentration differences, and estimated net tPA release.

Data were examined by ANOVA with repeated measures, Student’s t test, and univariate and multivariate regression analysis with StatView v5.0.1 (SAS Institute Inc). Where ANOVA demonstrated significant differences in responses, post hoc comparisons were made by use of the Fisher protected least significant difference test (StatView v5.0.1). Multivariate regression analysis was performed only on those factors that were shown to have a significant association by univariate analysis. All results are expressed as mean±SEM. Statistical significance was taken at the 5% level.

Results
Baseline patient characteristics are shown in Table 1. In keeping with the anticipated profile of patients undergoing coronary angiography, the study population was predominantly male and middle-aged and had a combination of risk factors. Throughout the study, there were no significant changes in heart rate, mean arterial pressure, or hematocrit (0.40±0.01).

Plaque Volume and Blood Flow Responses
The proximal 29±1 mm of the LAD was reconstructed and found to contain 160±24 mm³ of atheromatous plaque: a plaque burden of 5.5±0.8 mm³/mm vessel (range, 0.6 to 13.7 mm³/mm vessel). There was a significant linear correlation between the plaque burden and the serum total cholesterol:HDL cholesterol ratio (r=0.55, P=0.004).

LAD blood flow increased with both substance P and sodium nitroprusside infusion (P<0.001, ANOVA; see Table 2). There was a significant linear correlation between the percentage increase in coronary sinus oxygen saturations and LAD flow (r=0.46, P<0.001). There was no correlation, however, between the plaque burden and the AUC for the coronary blood flow responses to substance P or sodium nitroprusside infusion. In contrast, there was an association between the number of risk factors for atherosclerosis and the coronary blood flow responses to substance P (Figure 1: r=−0.42, P<0.05).

Plasma Fibrinolytic Parameters
There was a significant increase in plasma tPA antigen and activity concentrations from the coronary sinus during substance P infusion (Table 2: ANOVA, P<0.001 and P<0.006, respectively) but not during sodium nitroprusside infusion. There was a significant inverse correlation between the plaque burden and the AUC for active tPA release (Figure 2: r=−0.61, P=0.003) and a trend for the AUC for tPA antigen release (r=−0.34, P=0.15). There was also an inverse linear correlation between the basal coronary sinus plasma tPA antigen concentration and the AUC for active tPA release (r=−0.58, P<0.005).

Current smokers had a higher basal plasma tPA antigen concentration despite similar plasma PAI-1 concentrations.
TABLE 2. Hemodynamics, Coronary Blood Flow, and tPA and PAI-1 Concentrations During Substance P and Sodium Nitroprusside Infusion

<table>
<thead>
<tr>
<th></th>
<th>Substance P, pmol/min</th>
<th>Sodium Nitroprusside, μg/min</th>
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<tbody>
<tr>
<td></td>
<td>Saline</td>
<td>10</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td>65±2</td>
<td>64±3</td>
</tr>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>98±3</td>
<td>99±3</td>
</tr>
<tr>
<td>Coronary sinus oxygen saturation, %</td>
<td>44±2</td>
<td>48±2</td>
</tr>
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IVUS and Doppler

<table>
<thead>
<tr>
<th></th>
<th>Luminal cross-sectional area, mm²</th>
<th>Average peak velocity, cm/s</th>
<th>Absolute coronary blood flow, mL/min</th>
<th>Change in coronary blood flow, %</th>
<th>Plasma tPA antigen, ng/mL</th>
<th>Plasma tPA activity, IU/mL</th>
<th>Plasma PAI-1 antigen, ng/mL</th>
<th>Plasma PAI-1 activity, AU/mL</th>
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<tbody>
<tr>
<td></td>
<td>15.7±1.0</td>
<td>21.4±1.6</td>
<td>103±12</td>
<td>0</td>
<td>7.9±0.5</td>
<td>0.3±0.2</td>
<td>0.5±0.1</td>
<td>70±7</td>
</tr>
<tr>
<td></td>
<td>16.4±1.0</td>
<td>27.3±2.2†</td>
<td>138±18</td>
<td>36±6‡</td>
<td>8.8±0.7†</td>
<td>0.8±0.3</td>
<td>1.1±0.3‡</td>
<td>70±7</td>
</tr>
<tr>
<td></td>
<td>16.5±1.0†</td>
<td>27.5±2.4†</td>
<td>140±19</td>
<td>37±7†</td>
<td>9.1±0.7‡</td>
<td>0.7±0.3</td>
<td>0.5±0.1</td>
<td>70±7</td>
</tr>
<tr>
<td></td>
<td>16.9±1.0‡</td>
<td>28.0±2.3‡</td>
<td>143±18‡</td>
<td>46±10‡</td>
<td>8.1±1.0</td>
<td>0.6±0.2</td>
<td>1.0±0.3*</td>
<td>68±11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
<td>109±18</td>
<td>8.1±1.0</td>
<td>0.7±0.2†</td>
<td>0.7±0.2</td>
<td>0.5±0.1</td>
<td>67±12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
<td>131±20‡</td>
<td>8.1±1.0</td>
<td>0.7±0.2‡</td>
<td>0.7±0.2</td>
<td>0.5±0.1</td>
<td>67±12</td>
</tr>
<tr>
<td></td>
<td></td>
<td>§</td>
<td>140±24‡</td>
<td>0.0±0.2</td>
<td>0.7±0.2</td>
<td>0.7±0.2</td>
<td>0.5±0.1</td>
<td>0±1</td>
</tr>
</tbody>
</table>

AU indicates arbitrary units. n=14 for sodium nitroprusside responses; n=22 for fibrinolytic parameters (except PAI-1 activity; n=13).

*p<0.05; †p<0.01; ‡p<0.001, Fisher’s protected least significant difference test (vs baseline).

§P<0.007; †p=0.05, ANOVA with repeated measures.

and coronary arterial plaque burden (Table 3). Current and ex-smokers released significantly less active tPA than non-smokers (Figure 3; ANOVA, P<0.05). Hypercholesterolemia, hypertension, diabetes mellitus, and a family history of premature coronary artery disease did not appear to influence active tPA release, although some of the subgroup sample sizes were small.

There were no significant changes in plasma PAI-1 antigen and activity concentrations throughout the study (Table 2). Basal coronary sinus plasma PAI-1 antigen concentrations correlated positively with plaque burden (r=0.47, P<0.03) and negatively with release of active tPA (r=−0.44, P=0.04).

Multivariate regression analysis identified plaque burden and basal coronary sinus tPA antigen concentrations as the independent variables that were significantly associated with release of active tPA (P≤0.02 for both).

Discussion

For the first time, we have shown a direct relationship between both the coronary atheromatous plaque burden and smoking habit and the acute stimulated fibrinolytic capacity of the heart. These important findings suggest that both atherosclerosis and smoking habit adversely influence the local fibrinolytic balance in the coronary circulation and provide a direct link between endothelial dysfunction, atherothrombosis, and myocardial infarction.

This is the first clinical study to attempt to directly assess the acute release of tPA in the coronary circulation and to have found it to be sensitive to the presence of atheroma: a rapid decline in release of active tPA associated with an increasing plaque burden. The reduction in acute fibrinolytic capacity appears to reflect both an impairment of acute tPA release and an elevation of plasma PAI-1 concentrations. The mechanisms underlying this relationship remain to be established but are likely to involve chronic endothelial cell injury and possibly an impairment of the L-arginine–nitric oxide pathway. In addition, this association may reflect a chronic stimulation and upregulation of basal tPA release caused by arterial denudation and atheroma. The subsequent depletion of endothelial cell tPA stores, the associated increases in PAI-1 concentrations, and the overall reduction of the acute dynamic fibrinolytic response would potentially limit the capacity of the vasculature to lyse intraluminal thrombus. This is consistent with the epidemiological observations of a positive correlation between plasma tPA and PAI-1 antigen...
concentrations and future coronary events, as well as our findings of an inverse correlation of active tPA release with basal coronary sinus tPA and PAI-1 antigen concentrations.

Questions of cause and effect cannot be resolved by the present study. Indeed, our observations are consistent with a reduced fibrinolytic activity causing enhanced atherogenesis. Detailed postmortem studies have shown that plaque growth is induced by episodic subclinical plaque disruption and thrombus formation. The prolonged presence of residual thrombus over a disrupted or eroded plaque will provoke smooth muscle migration and the production of new connective tissue, leading to plaque expansion. This is consistent with the enhanced macrovascular fibrin deposition and atherogenesis seen in genetic murine models of tPA and plasminogen deficiency. It is likely, however, that both processes, impaired fibrinolysis and atherogenesis, cooperate and interact to damage vascular function and structure.

Consistent with our previous work in the peripheral circulation, we have observed an elevated basal plasma tPA and interact to damage vascular function and structure. 

Consistent with our previous work in the peripheral circulation, we have observed an elevated basal plasma tPA antigen concentration and an impaired coronary release of active tPA in cigarette smokers. These observations suggest that impaired endogenous fibrinolysis may contribute to the increased risk of coronary thrombosis seen in smokers through propagation of thrombus that would otherwise undergo lysis and remain subclinical. Although cigarette smokers have a higher overall mortality from myocardial infarction than nonsmokers, the in-hospital mortality has consistently been shown to be lower. This so-called “smokers’ paradox” can be explained by the observation that the infarct-related artery is more than twice as likely to become patent in current smokers than in nonsmokers after thrombolytic therapy for acute myocardial infarction. Indeed, it has been provocatively suggested that thrombolytic therapy should be given only to smokers and that such alternative strategies as primary angioplasty be used in nonsmokers. Our findings may account for these observations, because it might be anticipated that patients with impaired coronary endothelial cell tPA release would benefit most from thrombolytic therapy.

Quantitative coronary angiography has suggested that there is a direct association between coronary atherosclerosis and endothelium-dependent vasodilation. Quantitative coronary angiography, however, has several inherent limitations and inaccuracies that occur because it can assess only the arterial lumen and is unable to take account of “Glagovian” arterial remodeling. In contrast, IVUS provides a more accurate assessment of intracoronary plaque volume that has been extensively validated. Using this methodology, we did not find an association between the atherosclerotic plaque burden and the magnitude of the substance P–induced vasodilation. This is, in part, likely to reflect the independent influence of atherosclerotic risk factors on endothelium-dependent vasomotion and is borne out by the correlation of the vasodilation to substance P with the prevalence of these risk factors.

Study Limitations

This study was conducted in the necessary clinical setting of patients with a combination of risk factors and concomitant therapies undergoing diagnostic coronary angiography. The modest sample size means that this study lacks sufficient power to address the influence of all the individual variables associated with coronary artery disease. In particular, because the number of patients with diabetes mellitus or normocholesterolemia was small, our study may have failed to detect potential associations between these factors. Moreover, it is difficult to assess the effect of hypercholesterolemia and hypertension given the high incidence of treatment with

### TABLE 3. Influence of Smoking Status on Plaque Burden and Basal Plasma tPA and PAI-1 Concentrations

<table>
<thead>
<tr>
<th></th>
<th>Current Smokers (n=6)</th>
<th>Ex-Smokers (n=9)</th>
<th>Nonsmokers (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plaque burden, mm³/mm³</td>
<td>5.2±1.1</td>
<td>6.5±1.2</td>
<td>4.5±1.6</td>
</tr>
<tr>
<td>Plasma tPA antigen, ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary sinus concentration</td>
<td>9.4±1.3†</td>
<td>8.2±0.4</td>
<td>6.3±0.7*</td>
</tr>
<tr>
<td>Arterial concentration</td>
<td>9.0±1.4†</td>
<td>7.8±0.3</td>
<td>6.3±0.8*</td>
</tr>
<tr>
<td>Plasma PAI-1 antigen, ng/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary sinus concentration</td>
<td>0.3±0.1</td>
<td>0.6±0.2</td>
<td>0.6±0.2‡</td>
</tr>
<tr>
<td>Arterial concentration</td>
<td>0.3±0.0</td>
<td>0.5±0.1</td>
<td>0.5±0.2‡</td>
</tr>
<tr>
<td>Plasma PAI-1 activity, IU/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary sinus concentration</td>
<td>88±15</td>
<td>67±9</td>
<td>59±14</td>
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<tr>
<td>Arterial concentration</td>
<td>84±15</td>
<td>70±11</td>
<td>60±15</td>
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<tr>
<td>Plasma PAI-1 activity, AU/mL</td>
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<td></td>
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<tr>
<td>Coronary sinus concentration</td>
<td>14±6</td>
<td>25±5</td>
<td>24±8</td>
</tr>
<tr>
<td>Arterial concentration</td>
<td>12±5</td>
<td>26±4</td>
<td>23±8</td>
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</table>

AU indicates arbitrary units.

*P<0.04, †P=0.06, ANOVA with repeated measures.
†P=0.01, Fisher’s protected least significant difference test (nonsmokers vs current smokers).
lipid-lowering and antihypertensive therapy. Given the concordance between our previous findings in the forearm circulation of smokers, however, the influence of such risk factors as diabetes mellitus and hypercholesterolemia may be more readily assessed in the peripheral circulation.

In conclusion, we have demonstrated, for the first time, a direct association between the coronary atheromatous plaque burden and smoking habit with the acute local fibrinolytic capacity of the coronary circulation. These important findings may provide the main link between endothelial dysfunction and atherothrombosis, as well as an explanation for the smokers’ paradox. Interventions aimed at the enhancement of the local coronary fibrinolytic capacity could potentially be of major clinical importance.

Acknowledgments
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References
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