Abciximab Attenuates Coronary Microvascular Endothelial Dysfunction After Coronary Stenting

Eve D. Aymong, MD; Michael J. Curtis, MD; Mostafa Youssef, MD; Michelle M. Graham, MD; Lana Shewchuk, BN; Wendy Leschuk; Todd J. Anderson, MD

Background—Platelet glycoprotein IIb/IIIa receptor blockade with abciximab decreases ischemic events after percutaneous coronary intervention (PCI); however, the mechanism of this benefit has not been fully elucidated. The present study was designed to assess endothelium-dependent vasomotion after coronary stenting and to determine if abciximab alters this response.

Methods and Results—The study group consisted of 48 patients (59±10 years of age) with discrete coronary stenoses who underwent stenting alone (n=28) or stenting plus abciximab (n=20). A control group consisted of 31 additional patients who had vasomotor testing on a non-PCI vessel. Coronary blood flow (CBF) was measured (0.014-inch Doppler wire) 30 minutes after uncomplicated PCI and in response to the intracoronary infusion of acetylcholine (Ach) (10^-7, 10^-6 mol/L Ach) and adenosine (24 µg). Ach-mediated increase in CBF was impaired after stent insertion when compared with the control group (41±52% versus 70±48%; P<0.05). The stenting plus abciximab group demonstrated a superior CBF response to Ach compared with the stenting alone group (83±93% versus 41±52%; P<0.05), with no difference between groups in the peak flow or percent change in flow to adenosine. By multivariate analysis, concomitant administration of abciximab was strongly predictive of the change in CBF to Ach (P<0.005).

Conclusions—Abciximab preserves the CBF response to Ach after coronary stenting. The preservation of microvascular endothelial function may help explain the beneficial clinical effect of this agent in patients undergoing PCI. (Circulation. 2002;105:2981-2985.)

Key Words: angioplasty ■ endothelium ■ nitric oxide ■ glycoproteins

The coronary endothelium modulates vascular function. Through nitric oxide (NO) and other paracrine factors, a healthy endothelium maintains vasodilatation and has anti-atherogenic properties. Endothelial dysfunction occurs in the presence of atherosclerosis and its risk factors, leading to impairment of endothelial-dependent vasodilatation and alterations in the normal interaction that occurs between the vascular wall, inflammatory cells, and platelets.

Percutaneous coronary intervention (PCI) with balloon angioplasty and adjuvant coronary stenting has become the treatment of choice for many presentations of coronary atherosclerosis. Although well tolerated, balloon inflation causes deep arterial injury, resulting in endothelial denudation, platelet and leukocyte activation, oxidative stress, and vasoconstrictor release. In a small subset of patients, this leads to adverse effects on the microvasculature, resulting in clinical events. Balloon angioplasty has been shown to cause immediate and prolonged endothelial dysfunction of conduit vessels. Abnormalities in endothelial-dependent vasodilatation have been found up to 6 months after the procedure in patients treated with coronary stents. However, the immediate effect of stenting on microvascular endothelial function has not been well studied.

The platelet glycoprotein IIb/IIIa receptor blocker abciximab reduces complications after routine coronary stenting. Initial rationale for use was its potent blockade of the \( \alpha_{\text{IIb}}\beta_3 \) integrin receptor on platelets. However, abciximab also blocks the \( \alpha_{\text{IIb}}\beta_3 \) vitronectin receptor as well as expression of Mac-1, both mediators of inflammatory reactions to arterial injury. By modulating inflammatory cell responses and their interactions with platelets and the endothelium, abciximab may influence microvascular endothelial responses.

The purpose of the present study was to evaluate microvascular coronary function after coronary stenting and to determine the effect of abciximab on endothelial function.

Methods

Patient Population

Patients undergoing nonemergent PCI with and without the concomitant use of abciximab were eligible for the study (n=48). The group included both patients with stable angina admitted for elective PCI and patients who had presented with an unstable coronary syndrome...
but had stabilized without recurrent symptoms for at least 48 hours before study. Exclusion criteria included previous coronary artery bypass grafting, congestive heart failure, myocardial infarction in the territory of the study artery, presence of thrombus, and inability to obtain informed consent from the patient.

In addition, a control group included 31 additional subjects who underwent endothelial function testing in a nonintervened atherosclerotic vessel (stenosis of <30%) at the time of PCI. The study protocol and inclusion and exclusion criteria were the same as the study population who underwent PCI. There was no significant difference in patient demographics, risk factors, or degree of atherosclerosis between the control group and the study cohort.

Only patients with a discrete (<20 mm) lesion involving a proximal site in any branch of the left coronary system were included. The distal vessel had to be free of angiographic coronary disease. The protocol was approved by the University of Calgary Investigational Review Board and Ethics Committee and conducted using rules of Good Clinical Practices in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients before the beginning of the procedure. Long-acting vasoactive medications, including calcium-channel blockers, β-blockers, ACE-inhibitors, and nitrates, were discontinued 18 hours before catheterization.

Study Protocol

Coronary stenting was performed by standard procedure. Abciximab (Reopro, Eli Lilly) was given at the beginning of the PCI procedure (0.25 mg/kg bolus followed by 10 µg/min infusion). Intracoronary nitroglycerin 200 µg was given as required during the procedure and then after stent implantation in all subjects. All medications were infused through a single lumen infusion catheter (Ultraflute X, Scimed) positioned distal to the stented site. A 0.014-inch wire with a Doppler crystal at its tip (Endosonics Inc) was positioned distal to the infusion catheter in a straight segment of the study artery.

The infusion protocol consisted of the following interventions: (1) dextrose 5% for 2 minutes; (2) dextrose 5% for 15 minutes to achieve a stable baseline, with nitroglycerin (200 µg) given 2 minutes before the end of the infusion to reduce the conduit vessel vasoconstriction seen after PCI; (3) serial infusions of acetylcholine (Ach) at estimated intracoronary concentrations of 10⁻⁷ and 10⁻⁸ mol/L (Miochol, Ciba Vision) for 3 minutes each to assess endothelium-dependent vasodilation; or (4) nitroglycerin 200 µg followed by a bolus of 24 µg of adenosine. At the end of each infusion, quantitative coronary angiography was performed. Throughout the study and at the end of each intervention, the coronary velocity, heart rate, blood pressure, ECG, and clinical status were recorded.

Quantitative Coronary Angiography and Coronary Blood Flow

The details of our methods have been previously published.17 An automated edge-detection program was used to measure the diameter of the vessel (CMS software, Medis Corp). A 5-mm segment of vessel that encompassed a region 5 mm distal to the Doppler tip and a 10-mm segment of the distal vessel were analyzed. The coronary flow was calculated as the following: 

\[ CBF = \frac{D^2 \times \text{APV}}{4} \times \text{D} \times \text{t} \]

where CBF is flow (mL/min), D is vessel diameter (mm) by automated edge-detection program, APV is peak average velocity (cm/s), and 0.6 is the conversion factor. The technician performing the analysis was blinded to the use of abciximab.

Statistical Analysis

The study population was prospectively divided into 2 groups according to whether abciximab was used in addition to coronary stent implantation. The primary end point of the study was the percent change in CBF to the maximum Ach response after stenting alone compared with patients receiving abciximab. In addition, to study the effect of stenting on endothelial function, we compared responses in the stenting alone group with the control group who did not undergo PCI. Statistical analysis was performed with SAS (Statistical Analysis Systems, SAS Institute Inc) statistical software.

Results

Patient Characteristics

The study group consisted of 48 patients undergoing non-emergent PCI, 41 men and 7 women (mean age, 59 ± 10 years). Twenty-eight patients underwent stenting alone, and 20 had a stent deployed with adjuvant abciximab. Baseline characteristics of the 2 groups are presented in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stent Alone (n=28)</th>
<th>Stent + Abciximab (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>58±10</td>
<td>59±10</td>
<td>0.68</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>25 (89)</td>
<td>16 (80)</td>
<td>0.43</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>16 (57)</td>
<td>4 (20)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>10 (36)</td>
<td>5 (25)</td>
<td>0.43</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>1 (4)</td>
<td>4 (20)</td>
<td>0.15</td>
</tr>
<tr>
<td>Family history, n (%)</td>
<td>11 (39)</td>
<td>3 (15)</td>
<td>0.11</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.07±1.14</td>
<td>4.98±0.85</td>
<td>0.76</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.93±0.89</td>
<td>2.94±0.80</td>
<td>0.98</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>0.96±0.22</td>
<td>1.16±0.28</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>2.33±1.24</td>
<td>2.02±0.95</td>
<td>0.96</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28±5</td>
<td>27±4</td>
<td>0.54</td>
</tr>
<tr>
<td>Unstable angina, n (%)</td>
<td>15 (54)</td>
<td>16 (80)</td>
<td>0.06</td>
</tr>
<tr>
<td>Previous MI, n (%)</td>
<td>7 (25)</td>
<td>5 (25)</td>
<td>0.99</td>
</tr>
<tr>
<td>Previous PCI, n (%)</td>
<td>4 (14)</td>
<td>4 (20)</td>
<td>0.70</td>
</tr>
<tr>
<td>Stenosis before stenting, %</td>
<td>68±12</td>
<td>74±13</td>
<td>0.11</td>
</tr>
<tr>
<td>Stenosis after stenting, %</td>
<td>3±8</td>
<td>1±8</td>
<td>0.56</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; BMI, body mass index; and MI, myocardial infarction.

Data are expressed as mean±SD for continuous variables and number and percent for categorical variables. A 2-sided P value of 0.05 or less was considered statistically significant.

Linear regression analysis was used with percent change in CBF to Ach as the dependent variable. All baseline characteristics were included in a univariate analysis to identify significant predictors. These included body mass index, previous PCI or myocardial infarction, traditional coronary atherosclerotic risk factors, as well as treatment group. In addition, multivariate models were created as follows. A stepwise selection procedure including all baseline characteristics was used first; candidate variables were added to the model if they met the criteria of a significance of < 0.15 designated for entry into the model. A model was also created that included treatment group (abciximab or not) and variables that were statistically different at baseline.

There were significantly more smokers (P=0.02) and lower high-density lipoprotein (HDL) cholesterol levels (P=0.01) in the stenting alone group compared with the stenting plus abciximab group, respectively. However, unstable angina tended to be more common in the group that received abciximab (80% versus 54%, P=0.06). There was no difference in the morphology of the lesion or the final angiographic result.

The decision to use abciximab was left up to the primary operator. Patients included elective outpatients as well as nonurgent inpatients who had been admitted with unstable angina and stabilized on medical therapy. Given the hetero-
Stenting Outcomes

All patients underwent successful stent implantation without complications. The pre-stent minimal lumen diameter was 0.90±0.42 mm (71±13% stenosis). Excellent angiographic results were obtained with a post-stent residual stenosis of 2±8%, with a mean total inflation time of 140±148 seconds. Left ventricular function was preserved (ejection fraction, 70±9%).

Stimulated Endothelium-Dependent Vasomotion

Baseline CBF was similar in atherosclerotic control subjects who did not undergo coronary stenting and patients with a stent implanted (29±15 versus 33±30 mL/min, P=0.57). However, the change in CBF after Ach infusion was significantly greater in control subjects (70±48%) compared with the stented group (41±52%, P<0.05) (Figure 1).

Physiological data for the stenting alone and stenting plus abciximab groups are presented in Table 2. Baseline CBF was not different between treatment groups at the beginning of the study protocol and after 15 minutes of 5% dextrose infusion. There was a small decrease in CBF (5±19%) after the 15-minute control period (P=0.04), which was similar for the 2 groups.

The change in CBF after Ach infusion was 41±52% in patients treated with stenting alone compared with 83±93% in patients who also received abciximab (P=0.05) (Figures 2 and 3). There was no difference between groups in the change in coronary diameter as measured by percent change in proximal and distal vessel diameter. Vasoconstriction still occurred in both groups despite the use of intracoronary nitroglycerin.

Adenosine-Mediated Vasomotion

The increase in CBF after the bolus of 24 μg of adenosine was similar in patients receiving stent alone compared with stent plus abciximab (percent increase in CBF to adenosine, 168±105% versus 203±127%, P=0.30). Peak adenosine flow was also not different between PCI groups (Figure 3). Despite this, coronary flow velocity reserve was higher in the group treated with abciximab compared with the group treated with stenting alone (3.6±1.0 versus 2.8±1.0, P=0.01). This may have been the result of lower baseline velocities in the abciximab group immediately before the adenosine bolus. The reason for the lower pre-adenosine velocity in the abciximab group was not clear but may relate to the relatively small number of patients studied.

Predictors of Ach-Mediated Increases in Coronary Blood Flow

All baseline characteristics were considered in a univariate analysis of the mean percent change in CBF to Ach. These included traditional coronary risk factors, age, sex, body mass index, unstable angina, previous PCI, and previous myocardial infarction as well as treatment group according to use of abciximab. The only statistically significant univariate predictor of the percent change in blood flow to Ach was the treatment group (P=0.05). Unstable angina, HDL cholesterol, and cigarette smoking were not significant in the univariate analysis.

Potential confounding by differences in the baseline characteristics of the treatment groups was explored with the use of multivariate linear regression. Stepwise regression identified abciximab use and cigarette smoking as the only signif-

![Figure 1](http://circ.ahajournals.org/) 

**Figure 1.** Ach-mediated change in CBF is attenuated after stenting (black) compared with atherosclerosis control subjects (white). *P<0.05.

![Figure 2](http://circ.ahajournals.org/) 

**Figure 2.** Ach dose response and CBF after stenting (●) compared with stenting and abciximab (●). *P<0.05 for the trend.
Atherosclerosis impairs coronary endothelial-dependent vasomotion of both conduit and resistance vessels in part because of attenuated NO activity. Attenuation of Ach-mediated increases in CBF with preadministration of both conduit and resistance vessels is in part because of attenuated NO activity. In the present study, we extend these observations to the immediate post-PCI condition. Because of the ubiquitous need to use nitroglycerin during PCI for the prevention of distal vessel vasospasm, our conclusions are confined to the microcirculation. The abnormal microvascular endothelial response that we observed after stenting may be explained by several pathophysiological mechanisms. These include chronic downregulation of endothelial NO synthase in a vessel exposed to low shear stress distal to a stenosis and release of the vasoconstrictors serotonin and endothelin-1. In addition, a dysfunctional interaction between the endothelium, platelets, and leukocytes results in a proinflammatory state with free radical production and microvascular plugging.

Attenuation of Ach-mediated increases in CBF with preserved responses to adenosine would imply a defect at the level of the endothelium. However, this does not clarify whether the diminished Ach response is attributable to abnormalities in stimulated NO production, decreased endothelium-derived hyperpolarizing factor or prostacyclin production, enhanced vasoconstrictors such as serotonin, thromboxane, and endothelin-1, or a combination of these mechanisms.

Abciximab and Vasomotor Responses
Abciximab is now commonly used in coronary stenting and has been shown to reduce morbidity and mortality rates in a wide range of patients. This monoclonal antibody blocks the glycoprotein IIb/IIIa receptor, the final common pathway for platelet aggregation and adhesion. The increase in CBF to Ach in patients with abciximab coadministration implies a favorable effect of the drug on microvascular physiology. Although it is likely that a rheological effect (attributable to decreased microvascular plugging) is present, the similar responses to adenosine would make this unlikely as the sole mechanism of action.

The antiplatelet effect of the agent would be expected to decrease platelet-leukocyte aggregates from forming in the resistance vessels. A previous study demonstrated a beneficial effect of abciximab on peak coronary velocity to adenosine in patients immediately after PCI for acute myocardial infarction. Abciximab may have specific benefits because of inhibition of leukocyte adhesion through the integrins Mac-1 and the αβv vitronectin receptor. A recent study demonstrated activation of CD11b on neutrophils with concomitant platelet aggregation in patients immediately after PCI. This response was favorably modulated with abciximab. Attenuation of oxidative stress through antiinflammatory mechanisms would improve Ach-mediated increases in CBF by enhancing NO bioactivity. We propose that a favorable effect on endothelial function is in part responsible for the beneficial effect of this agent after uncomplicated stent implantation. Coronary endothelial dysfunction is not only associated with ischemia but recently has been shown to be predictive of adverse cardiovascular events in patients with mild atherosclerosis. The relationship between endothelial function and its treatment on outcomes after PCI has not been assessed.

Discussion
The present study has demonstrated that after uncomplicated coronary stenting, Ach-mediated increases in CBF are blunted and that this abnormality can be attenuated by the administration of the platelet glycoprotein IIb/IIIa receptor blocker abciximab. This preservation of microvascular endothelial function may represent a mechanism whereby abciximab decreases complications after PCI.

Vasomotor Responses After PCI
The role of the endothelium in vascular disease has been well documented. Atherosclerosis impairs coronary endothelium-dependent vasomotion of both conduit and resistance vessels in part because of attenuated NO activity. In the present study, we extend these observations to the immediate post-PCI condition. Because of the ubiquitous need to use nitroglycerin during PCI for the prevention of distal vessel vasospasm, our conclusions are confined to the microcirculation. The abnormal microvascular endothelial response that we observed after stenting may be explained by several pathophysiological mechanisms. These include chronic downregulation of endothelial NO synthase in a vessel exposed to low shear stress distal to a stenosis and release of the vasoconstrictors serotonin and endothelin-1. In addition, a dysfunctional interaction between the endothelium, platelets, and leukocytes results in a proinflammatory state with free radical production and microvascular plugging.

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Limitations
The use of abciximab was not randomized because of the heterogeneous nature of the indications for intervention. Patients who received abciximab were more likely to have had unstable angina as a clinical precursor to their procedure. However, all analyses of Doppler and angiographic data were performed by an observer who was blinded to abciximab use. In addition, the effect of abciximab was consistent and strengthened after adjustment for possible confounding generated by baseline imbalances. The Ach responses were not different between patients undergoing elective procedures and those with stabilized acute coronary syndromes.

Although these novel observations are intriguing, mechanisms cannot be clearly ascertained. The diminished Ach responses can be assumed to be attributable to attenuation of stimulated NO bioactivity. Additional studies are required to help clarify these mechanisms. The measured end points were restricted to microvascular responses because of the need to use nitroglycerin to prevent spontaneous coronary vasoconstriction after PCI. This approach has been effectively used in previous studies of resistance vessel function, because nitroglycerin has only a transient effect of CBF. Finally, Ach-mediated vasomotor changes are only one measure of the very complex biological processes that encompass endothelial function.
Conclusions
The platelet glycoprotein IIb/IIIa receptor blocker abciximab preserves the CBF response to Ach observed after coronary stenting compared with control patients who did not receive abciximab. The preservation of microvascular endothelial function may in part explain the beneficial clinical effect of this agent in patients undergoing PCI.

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References
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