Platelet Glycoprotein IIb/IIIa Receptor Inhibitor Preserves Coronary Flow Reserve During Progressive Coronary Arteriostenosis in Swine


Abstract—Thrombosis resulting from blood platelet aggregation via glycoprotein (GP) IIb/IIIa receptor activation triggers the local release of vasoactive substances. Therefore, inhibition of these receptors could affect coronary vasoactive function during thrombotic coronary arteriostenosis. Twenty pigs were instrumented with an aortic catheter and with hydraulic occluders and flow probes on both the left anterior descending (LAD) and the left circumflex (LCx) coronary arteries. One of these 2 coronary arteries was repeatedly injured by external clamping for 15-second periods at 30-minute intervals while the pigs were given either a GP IIb/IIIa receptor inhibitor (L-739,758) (n=5), heparin (n=5), aspirin (n=3), or saline (n=7). There were no baseline differences between the 4 groups in mean arterial pressure, resting coronary blood flow (CBF), or reactive hyperemic response (RHR), which was induced by brief coronary artery occlusion and expressed as flow debt repayment. After multiple injuries, resting CBF had decreased by 95±2% (ie, nearly complete coronary artery occlusion) at 15±4 minutes in the control group, whereas in the heparin-, aspirin-, and GP IIb/IIIa inhibitor–treated groups, resting CBF had decreased by only 21±7% at 18±3 minutes, 15±3% at 18±5 minutes, and 15±7% at 21±4 minutes, respectively, suggesting that heparin, aspirin, and the GP IIb/IIIa inhibitor each prevented injury-induced coronary artery occlusion. After the initial injury, the RHR was progressively reduced in the control and heparin- and aspirin-treated groups but not in the GP IIb/IIIa inhibitor–treated group. At a comparable level of resting CBF (=15% below baseline), the RHR was reduced more in the control (−56±9%), heparin-treated (−49±9%), and aspirin-treated (−61±12%) groups (P<0.05) than in the GP IIb/IIIa inhibitor–treated group (−26±6%). When the resting CBF had decreased by ≈35%, the RHR still was reduced significantly more (P<0.01) in the heparin-treated group (−64±9%) than in the GP IIb/IIIa inhibitor–treated group (−21±6%). In a separate group of control pigs (n=4) subjected to 2 injuries, coronary perfusion pressure distal to the injury site was reduced by 14±1 mm Hg from the arterial pressure, and the RHR was 20±6%. When the distal coronary perfusion pressure was reduced similarly (−14±1 mm Hg) in a separate group of GP IIb/IIIa inhibitor–treated pigs (n=4) by 2 injuries and the use of a hydraulic occluder, the RHR was 130±16% (P<0.01 versus control). Our data demonstrate for the first time that a platelet GP IIb/IIIa receptor inhibitor can preserve the distal coronary vasodilatory response during progressive coronary arteriostenosis. (Arterioscler Thromb Vasc Biol. 2000;20:2309-2315.)

Key Words: coronary reactive hyperemia • coronary reserve • heparin • aspirin • coronary injury • glycoprotein IIb/IIIa

Intense vasoconstriction is often clinically observed after percutaneous transluminal coronary balloon angioplasty (PTCA),1–3 and it occurs both at the site of balloon dilatation and distal to this site.1 It is possible that the potent vasoactive substances released during the intracoronary blood platelet adhesion and aggregation and resultant thrombosis that occur after PTCA are responsible for this vasoconstriction. Therefore, blockade of platelet aggregation may have beneficial effects on coronary vascular function. It is well known that thrombosis resulting from platelet aggregation is ultimately mediated by the activation of blood platelet glycoprotein (GP) IIb/IIIa receptors. Inhibition of these receptors with either the anti–GP IIb/IIIa antibody abciximab (ReoPro), the cyclic peptide GP IIb/IIIa antagonist eptifibatide (Integrilin), or the low-molecular-weight nonpeptide GP IIb/IIIa antagonist tirofiban (Aggrastat) has been shown to be effective in the treatment of acute coronary ischemic syndromes, such as unstable angina and PTCA.4–12 We hypothesized that in addition to an antithrombotic effect, inhibition of GP IIb/IIIa receptors may also affect coronary vascular dynamic function, particularly during progressive coronary arteriostenosis. To test our hypothesis, we first examined the effects of an analogue of tirofiban, L-739,758,13 on resting coronary blood flow (CBF) during progressive coronary arteriostenosis induced by repeated injury of either the left anterior descending (LAD) or the left circumflex (LCx) coronary artery in swine.

Received January 12, 2000; revision accepted June 13, 2000.
From the Department of Pharmacology, Merck Research Laboratories, West Point, Pa.
Correspondence to You-Tang Shen, MD, Department of Pharmacology, Merck Research Laboratories, WP46-200, West Point, PA 19486. E-mail youtang.shen@merck.com
© 2000 American Heart Association, Inc.
Arterioscler Thromb Vasc Biol. is available at http://www.atvbaha.org

2309
We then studied whether GP IIb/IIIa receptor inhibition alters coronary flow reserve by measuring the coronary reactive hyperemic response to a brief, complete coronary artery occlusion before and after each injury. The effects of the GP IIb/IIIa receptor inhibitor were compared with those of heparin and aspirin not only on the basis of the number of injuries necessary to cause stenosis but also at comparably reduced levels of resting CBF to determine whether a possible difference in the degree of stenosis could account for the observed differential effects. Finally, we measured coronary reactive hyperemic responses in additional control and GP IIb/IIIa receptor inhibitor–treated pigs at comparably reduced levels of coronary perfusion pressure to address whether GP IIb/IIIa receptor inhibition preserves coronary flow reserve during injury-induced coronary arteriostenosis by an effect on the coronary vasculature or simply by preventing thrombotic stenosis at the site of coronary artery injury.

Methods

Animal Model

A porcine model was used in this study because the porcine coronary arterial anatomy, including the relative lack of preexisting collateral channels and anastomoses,14,15 and coronary metabolism are similar to those of the human.19 The experiments were short-term to avoid any influence from coronary artery collateral development during chronic coronary arteriostenosis.16 All of the animals used in this study were maintained in accordance with the guidelines of the Guide for the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources of the National Research Council (1996), and the studies were approved by the Merck Research Laboratories Institutional Animal Care and Use Committee. The pigs were housed individually under conventional conditions, fed commercial pig ration, and allowed access to water ad libitum before surgery.

Twenty-eight Yorkshire farm pigs 4 to 6 months old and weighing 31 ± 3 kg were sedated with a mixture of ketamine (12 mg/kg IM) and xylazine (8 mg/kg IM). After tracheal intubation, general anesthesia was maintained with isoflurane (1.0 to 3.0 vol% in O2). A left thoracotomy was performed at the fourth intercostal space. A catheter. LAD and LCx blood flows were measured with a volume flow probe (Transonic Systems) were also placed around the LCx and LAD coronary arteries proximal to the occluders to continuously measure CBF. In the remaining 8 pigs, only the LAD was instrumented with a volume flow probe and hydraulic occluders, 2 in the treated group and 1 in the control group. The additional occluder in the treated group was used to produce partial stenosis. In addition, a catheter made of polyethylene tubing (PE-280) was implanted in one of the distal branches of the LAD to measure the coronary perfusion pressure distal to the injury site.

Experimental Protocol

A schematic of the experimental protocol used in the first set of experiments is shown in Figure 1. Briefly, experiments were initiated when both the systemic hemodynamics and the CBF were stable, which occurred 30 to 60 minutes after the animals were instrumented. The pigs were infused intravenously and continuously at the same flow rate (5 mL/min) with 0.9% saline (NaCl in H2O) (n = 7), L-739,758 (an analogue of the GP IIb/IIIa receptor inhibitor tirofiban) at a dose of 100 μg · kg−1 · h−1 (n = 5), heparin at a dose of 1 U · kg−1 · min−1 after a bolus dose of 350 U/kg (n = 5), or aspirin at a dose of 10 mg/kg (n = 3). The GP IIb/IIIa inhibitor was prepared as a 5-mg/mL solution in 100 mmol/L NaOH, then diluted to 0.1 mg/mL in 0.9% saline buffered with 10 mmol/L Na2HPO4. Activated clotting time was measured periodically throughout the heparin experiments and was always 15 minutes greater than the pretreatment level. Baseline measurements of mean arterial pressure, resting phasic and resting mean CBF, heart rate, and reactive hyperemic response, which was induced by coronary artery occlusion for 15 seconds, were made 30 minutes after the administration of the saline, GP IIb/IIIa inhibitor, heparin, or aspirin was begun. Then, either the LCx or the LAD was clamped with a hemostat at a site proximal to the flow probe for 15-second periods at ~30-minute intervals until resting CBF had fallen to almost zero or until the artery had been clamped a minimum of 6 times. The unclamped artery served as a control.

In a separate set of experiments, the reactive hyperemic response was measured in an additional 8 pigs, 4 control and 4 GP IIb/IIIa inhibitor–treated, in which the LADs were clamped twice for 15-second periods 15 minutes apart. In the GP IIb/IIIa inhibitor–treated group, a hydraulic occluder placed around the LAD was used to partially occlude the vessel so that the coronary perfusion pressure distal to the site of injury could be reduced by a similar degree to that resulting from the 2 injuries alone in the control group. Saline or L-739,758 was infused into the control or the treated pigs, respectively, at the same rates as those used in the first set of experiments.

Data Analysis

Hemodynamic recordings were made with a data tape recorder and a multiple-channel oscillograph. Arterial pressure was measured with a strain-gauge manometer connected to a fluid-filled aortic catheter. LAD and LCx blood flows were measured with a volume flowmeter (Transonic Systems). A cardiotachometer, triggered by the phasic arterial pressure signal, provided instantaneous and continuous measurements of heart rate. Coronary vascular resistance was calculated as the quotient of mean arterial pressure and mean CBF. Total CBF during reactive hyperemia was measured with a planimeter to integrate the area of the mean CBF recording. Blood flow debt, reactive hyperemic flow, and blood flow debt repayment were calculated as described previously.17,18 The equations used were as follows:

Blood flow debt (mL) = control blood flow rate (mL/s) × duration of occlusion (seconds).

Reactive hyperemic flow (mL) = total blood flow during reactive hyperemia (mL) - [control blood flow rate (mL/s) × duration of reactive hyperemia (seconds)].
Effects of the IIb/IIIa Inhibitor, Heparin, and Aspirin During Coronary Artery Injury

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Injury-1</th>
<th>Injury-2</th>
<th>Injury-3</th>
<th>Injury-4</th>
<th>Injury-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean arterial pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>84±3.8</td>
<td>−3±6</td>
<td>−1±5</td>
<td>+1±4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IIb/IIIa inhibitor</td>
<td>88±8.5</td>
<td>−3±2</td>
<td>−2±2</td>
<td>−6±3</td>
<td>−9±3</td>
<td>−7±2</td>
</tr>
<tr>
<td>Heparin</td>
<td>83±5.6</td>
<td>+2±3</td>
<td>+2±4</td>
<td>−1±3</td>
<td>−6±2</td>
<td>−14±4</td>
</tr>
<tr>
<td>Aspirin</td>
<td>85±6.6</td>
<td>−2±3</td>
<td>−9±4</td>
<td>−9±3</td>
<td>−9±4</td>
<td>...</td>
</tr>
<tr>
<td>Heart rate, bpm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>110±6.3</td>
<td>−1±1</td>
<td>−4±3</td>
<td>−3±4</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IIb/IIIa inhibitor</td>
<td>103±3.9</td>
<td>−2±2</td>
<td>−4±2</td>
<td>−5±2</td>
<td>−5±1</td>
<td>−7±1*</td>
</tr>
<tr>
<td>Heparin</td>
<td>105±8.6</td>
<td>−2±3</td>
<td>+1±4</td>
<td>+6±3</td>
<td>+7±3</td>
<td>+7±5</td>
</tr>
<tr>
<td>Aspirin</td>
<td>95±2.0</td>
<td>0±1</td>
<td>−1±3</td>
<td>−2±4</td>
<td>+5±3</td>
<td>...</td>
</tr>
<tr>
<td>Resting CBF, mL/min</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>18±2.1</td>
<td>+4±5</td>
<td>+5±6</td>
<td>−12±13</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IIb/IIIa inhibitor</td>
<td>19±5.0</td>
<td>+4±8</td>
<td>+3±11</td>
<td>+1±8</td>
<td>−7±11</td>
<td>−16±6</td>
</tr>
<tr>
<td>Heparin</td>
<td>17±1.1</td>
<td>+6±6</td>
<td>0±8</td>
<td>+1±4</td>
<td>−4±4</td>
<td>−17±8</td>
</tr>
<tr>
<td>Aspirin</td>
<td>18±2.6</td>
<td>−3±3</td>
<td>−3±3</td>
<td>−5±3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Coronary vascular resistance, mm Hg · mL⁻¹ · min⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.2±0.4</td>
<td>−3±6</td>
<td>−5±6</td>
<td>+21±18</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IIb/IIIa inhibitor</td>
<td>5.5±1.2</td>
<td>−3±9</td>
<td>−1±11</td>
<td>−6±6</td>
<td>+3±10</td>
<td>+16±7</td>
</tr>
<tr>
<td>Heparin</td>
<td>4.9±0.4</td>
<td>−3±4</td>
<td>+5±10</td>
<td>−1±5</td>
<td>−2±6</td>
<td>+7±11</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4.9±0.3</td>
<td>+1±3</td>
<td>−6±3</td>
<td>−5±2</td>
<td>+3±4</td>
<td>...</td>
</tr>
<tr>
<td>CBF deficit, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>4.6±0.5</td>
<td>+6±5</td>
<td>+5±6</td>
<td>−9±6</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IIb/IIIa inhibitor</td>
<td>4.4±0.9</td>
<td>+6±4</td>
<td>+5±8</td>
<td>+3±4</td>
<td>−6±8</td>
<td>−13±3*</td>
</tr>
<tr>
<td>Heparin</td>
<td>4.6±0.2</td>
<td>+2±8</td>
<td>−5±9</td>
<td>+4±8</td>
<td>−9±11</td>
<td>−16±8</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4.4±0.7</td>
<td>+3±6</td>
<td>−2±2</td>
<td>−5±3</td>
<td>−13±9</td>
<td>...</td>
</tr>
<tr>
<td>Repayment of CBF deficit, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>532±103</td>
<td>−32±13</td>
<td>−57±3*</td>
<td>−65±2*</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>IIb/IIIa inhibitor</td>
<td>540±76</td>
<td>−11±12</td>
<td>−13±8</td>
<td>−4±10</td>
<td>−15±4</td>
<td>−26±3*</td>
</tr>
<tr>
<td>Heparin</td>
<td>585±79</td>
<td>−24±10</td>
<td>−18±12</td>
<td>−52±12†</td>
<td>−66±4†</td>
<td>−62±9†</td>
</tr>
<tr>
<td>Aspirin</td>
<td>474±58</td>
<td>−20±9</td>
<td>−53±19</td>
<td>−54±16†</td>
<td>−60±4†</td>
<td>...</td>
</tr>
</tbody>
</table>

IIb/IIIa inhibitor was L-739,758.

*P<0.01, significant difference from baseline.
†P<0.01, significant difference between the heparin, aspirin, and IIb/IIIa inhibitor groups.

Blood flow debt repayment (%)=|reactive hyperemic flow (mL)/blood flow debt (mL)|×100.

The coronary reactive hyperemic response was not examined in 2 of the 7 control animals in the first set of experiments because the first one was not instrumented with hydraulic occluders and there were technical problems with another one. The data from the GP IIb/IIIa receptor antagonist (L-739,758), heparin, aspirin, and control groups were compared by 1-way ANOVA with the Student-Newman-Keuls test. The probability values were corrected with the Bonferroni procedure. All values are expressed as the mean±SEM. Statistical significance was accepted at the P<0.05 level.

Results

There was no significant difference in mean arterial pressure, heart rate, or resting CBF at baseline (ie, immediately before coronary artery injury) between the control, GP IIb/IIIa inhibitor, heparin, and aspirin groups (Table). The changes in resting CBF after mechanically induced coronary artery injury are shown in Figure 2. In the control pigs, resting CBF had fallen to nearly zero after 3 injuries, whereas in the pigs treated with the GP IIb/IIIa inhibitor and heparin, resting CBF was reduced by only 16±6% and 17±8% after 5 injuries, respectively.

Because the number of injuries that were necessary to affect resting CBF varied within the groups as well as between the groups (ie, 2.4±0.4, 4.6±0.4, and 3.0±0.4 injuries for the control, GP IIb/IIIa inhibitor, and heparin groups, respectively), the plot of the time course of the change in resting CBF for these groups begins after the injury that resulted in a prolonged reduction in resting CBF (Figure 3). The resting CBF fell by 93±2% at 14±2.7 minutes in the control group, whereas in the GP IIb/IIIa inhibitor group, the decrease in resting CBF was delayed and then CBF was maintained between 70% and 80% of the baseline, ie, preinjury level, despite additional injuries performed at 30-minute intervals. The time course of the reduction in resting CBF in the heparin group was similar to that in the GP IIb/IIIa inhibitor group, indicating that the GP IIb/IIIa inhibitor and heparin each prevented the proximal thrombotic coronary occlusion that occurred after multiple mechanically induced
injuries in the control group. Also shown in Figure 3 are the changes in resting CBF in the uninjured vessels, i.e., the contralateral coronary arteries, for each of the groups. The resting CBF in the uninjured arteries was unchanged in the GP IIb/IIIa inhibitor and heparin groups. In the control group, however, the resting CBF through the uninjured artery was reduced by ~15% when the resting CBF through the injured artery was reduced by ~95% from the baseline level. This decrease in blood flow in the uninjured artery was most likely due to a decrease in left ventricular pump function and consequently coronary perfusion pressure because of the marked and rapid reduction in blood flow in the injured artery.

The baseline and percent change from baseline values for coronary vascular resistance, blood flow deficit, and repayment of CBF deficit after injury in the control (n=7), GP IIb/IIIa inhibitor–treated (n=5), heparin-treated (n=5), and aspirin-treated (n=3) pigs. The data are expressed as percent change from the baseline values obtained before the first injury. The GP IIb/IIIa inhibitor and heparin each prevented the proximal thrombotic coronary occlusions that occurred in the control pigs in response to mechanically induced coronary artery injury.

Figure 2. Resting CBF after repeated coronary artery injuries in control (n=7), GP IIb/IIIa inhibitor–treated (n=5), heparin-treated (n=5), and aspirin-treated (n=3) pigs. After an average of 4 injuries, the resting CBF in the control pigs was almost zero, whereas the resting CBF fell by ~20% after an average of 5 injuries or by 40% after 3 injuries in the GP IIb/IIIa inhibitor and heparin groups or aspirin group, respectively.

Figure 3. Time course of the change in resting CBF in the injured and uninjured arteries in the control (n=5), GP IIb/IIIa inhibitor–treated (n=5), and heparin-treated (n=5) pigs. The data are expressed as percent change from the baseline values obtained before the first injury. The GP IIb/IIIa inhibitor and heparin each prevented the proximal thrombotic coronary occlusions that occurred in the control pigs in response to mechanically induced coronary artery injury.

Figure 4. Effects of coronary artery injuries on the repayment of flow deficit in control (n=5), GP IIb/IIIa inhibitor–treated (n=5), heparin-treated (n=5), and aspirin-treated (n=3) pigs. The data are expressed as percent change from the baseline values. Note that the repayment of flow deficit after injury was reduced less in the GP IIb/IIIa inhibitor group than in the control, heparin, and aspirin groups.
acute proximal coronary thrombosis induced by repeated tirofiban, heparin, and aspirin each effectively prevented an analogue (L-739,758) of the GP IIb/IIIa receptor inhibitor. The major finding of the present study was that although an extent of coronary arteriostenosis, the data from the different groups also were compared at similarly reduced levels of resting CBF. Figure 5 shows the relationship between the repayment of CBF deficit and resting CBF for the 3 groups. At a comparable level of resting CBF (∼15% below baseline), the repayment of flow deficit was reduced more (P<0.05) in the control (−56±9%), heparin (−49±9%), and aspirin (−61±12%) groups than in the GP IIb/IIIa inhibitor group (−26±6%). When the resting CBF had decreased by ∼35%, the repayment of CBF deficit was reduced significantly (P<0.01) more in the heparin group (−64±9%) than in the GP IIb/IIIa inhibitor group (−21±6%).

To determine the site of the beneficial effect of the GP IIb/IIIa inhibitor on coronary flow reserve, the reactive hyperemic response was measured in control and GP IIb/IIIa inhibitor–treated pigs subjected to coronary artery injury while coronary perfusion pressure was measured simultaneously distal to the injury site. The repayment of CBF deficit was inversely correlated with the reduction in the distal coronary perfusion pressure in both groups (Figure 6). When the distal coronary perfusion pressure was reduced by similar amounts, however, the repayment of CBF deficit in the control group was significantly attenuated (P<0.01) compared with that observed in the GP IIb/IIIa inhibitor–treated group. For example, when the distal coronary perfusion pressure fell by 14±1 and 20±1 mm Hg, the repayments of CBF deficit in the control group were 20±6% and 12±7%, respectively, whereas in the GP IIb/IIIa inhibitor–treated group they were 130±16% and 65±14%, respectively, which were significantly different (P<0.01) from the control values in both cases.

Discussion
The major finding of the present study was that although an analogue (L-739,758) of the GP IIb/IIIa receptor inhibitor tirofiban, heparin, and aspirin each effectively prevented acute proximal coronary thrombosis induced by repeated injury of coronary arteries in swine, the reactive hyperemic response after injury was clearly preserved by the GP IIb/IIIa receptor inhibitor but not by heparin or aspirin. This suggests that in addition to or because of its antithrombotic effect, the GP IIb/IIIa receptor inhibitor was able to maintain the distal coronary artery vasodilatory response. To the best of our knowledge, this is the first study of the effect of a GP IIb/IIIa receptor inhibitor on coronary flow reserve during progressive coronary arteriostenosis.

After 2 coronary artery injuries in the control pigs, resting CBF was unchanged, whereas the reactive hyperemic response was markedly reduced, indicating that these injuries were sufficient to cause stenosis. When the coronary arteries in the control pigs were subjected to further injury, the resting CBF fell steeply to almost zero, indicating nearly complete occlusion of the coronary artery. In contrast, the resting CBF was only slightly changed in the GP IIb/IIIa inhibitor–treated, heparin-treated, and aspirin-treated pigs. Thus, it appears that the GP IIb/IIIa inhibitor, heparin, and aspirin each delayed the onset of stenosis and prevented the complete coronary artery occlusion that had occurred in the control pigs as a result of repeated coronary artery injury. After 3 coronary artery injuries, however, the reactive hyperemic response was reduced more in the heparin-treated and aspirin-treated groups than in the GP IIb/IIIa inhibitor–treated group, suggesting that the coronary vasodilatory response was preserved by inhibiting the GP IIb/IIIa receptor.

One of our concerns in the present study was that the greater reactive hyperemic response observed in the GP IIb/IIIa inhibitor–treated group compared with that observed in the heparin- and aspirin-treated groups after the same number of injuries could have been attributable partly to a difference in the degree of stenosis because of a variable degree of mechanically induced injury or because of differences in the antithrombotic efficacy of heparin, aspirin, and...
the GP IIb/IIIa inhibitor, as evidenced by the fact that the number of injuries necessary to reduce the resting CBF was different for these groups. In an attempt to account for these factors, the reactive hyperemic responses of the groups were compared at similarly reduced levels of resting CBF, when the degrees of stenosis should have been similar. When resting CBF was reduced ≈15% or 35%, the reactive hyperemic responses in the pigs treated with the GP IIb/IIIa inhibitor were still greater than those in the pigs treated with either heparin or aspirin, suggesting that GP IIb/IIIa receptor inhibitors are more efficacious in preserving coronary flow reserve during progressive coronary arteriosclerosis, possibly because of their greater ability to inhibit platelet function.

To determine the site of this effect of the GP IIb/IIIa receptor inhibitor, the reactive hyperemic response was measured while the coronary perfusion pressure distal to the injury site was also measured in 2 additional groups of control and GP IIb/IIIa inhibitor–treated pigs. After 2 injuries in the GP IIb/IIIa inhibitor–treated pigs, a hydraulic occluder was used to reduce the coronary perfusion pressure by amounts similar to those resulting from injury alone in the control pigs. As expected, the coronary flow reserve was negatively correlated with the reduction in distal coronary perfusion pressure. When the distal coronary perfusion pressure was reduced by >20 mm Hg, the reactive hyperemic response was basically exhausted in both groups. When the coronary perfusion pressure was reduced by lesser but comparable amounts, however, the reactive hyperemic responses in the GP IIb/IIIa inhibitor–treated pigs were significantly greater than those in the control pigs, indicating that the effect of the GP IIb/IIIa receptor inhibitor was in the coronary vasculature distal to the injury site. Although the precise area within the distal vasculature is unknown, it is likely that this effect was occurring at vessels located in the epicardial and midmyocardial layers rather than in the endomyocardial layer. It has been shown previously that when the resting CBF was reduced by 40%, the epicardial blood flow was unchanged, whereas the endocardial blood flow fell by ≈70%, suggesting that coronary vasodilatory reserve was reduced considerably in the endocardial region but not in the epicardial region. Thus, it is conceivable that the reactive hyperemic response observed in the present study would not have occurred in the subendocardial microcirculation.

Coronary driving pressure and resting coronary vasomotor tone are known to affect the coronary reactive hyperemic response. The peak CBF rate after a brief occlusion has been shown to depend on the arterial pressure. Although our data show that after 5 injuries, mean arterial pressure had decreased slightly more in the heparin-treated group than in the GP IIb/IIIa inhibitor–treated group, it was ≈70 mm Hg, which should have been sufficient to not affect the coronary driving pressure and, consequently, the reactive hyperemic response. Furthermore, mean arterial pressure was reduced comparably in the heparin- and GP IIb/IIIa inhibitor–treated groups after 4 coronary artery injuries. Therefore, a difference in the coronary driving pressure is unlikely to have accounted for the observed difference in the reactive hyperemic response between the 2 groups. It has also been shown that the coronary reactive hyperemic response is inversely related to the degree of coronary vasodilation. In our study, neither the baseline levels of coronary resistance nor the coronary resistance after repeated injuries were different among the GP IIb/IIIa inhibitor, heparin, and aspirin groups, suggesting that the difference in the reactive hyperemic response between the groups cannot be attributed to a difference in the resting coronary vasomotor tone.

Many local metabolically linked substances have been proposed to be responsible for the modulation of coronary reactive hyperemia, including bradykinin, histamine, potassium, prostaglandin, serotonin, and endothelium-derived relaxing factor, with adenosine being the most likely substance. It is possible that the platelet GP IIb/IIIa receptors indirectly affect either a metabolic mediator or the release of a vasoconstrictive substance via their role in platelet aggregation and thrombus formation, because it has been shown that both activated platelets and thrombus formation control several vasoactive mediators. Thus, inhibition of the platelet GP IIb/IIIa receptor may prevent the release of some vasoconstrictive substances and, as a result, help to maintain the coronary reactive hyperemic response. It is unlikely that simply reducing thrombus formation accounts for these results, because heparin had similar effects on resting coronary flow but did not maintain coronary flow reserve.

In summary, heparin, aspirin, and the GP IIb/IIIa receptor inhibitor each prevented the reduction in resting CBF induced by coronary artery injury. At similarly reduced levels of CBF, however, only the GP IIb/IIIa receptor inhibitor preserved the coronary vasodilatory response to a brief coronary artery occlusion. In addition, this response was maintained in the GP IIb/IIIa receptor inhibitor group better than in the control group when coronary arterial perfusion pressure distal to the injury site was reduced by similar amounts. These results suggest that the beneficial effects of a GP IIb/IIIa receptor inhibitor on myocardial infarction and unstable angina may result from its enhanced ability to inhibit blood platelet function and are manifested in the distal coronary vasculature. Further investigation is necessary, however, to determine whether the effect of GP IIb/IIIa receptor inhibition observed in the present study using healthy animals would be altered in an arteriosclerotic model.

References


Platelet Glycoprotein IIb/IIIa Receptor Inhibitor Preserves Coronary Flow Reserve During Progressive Coronary Arteriostenosis in Swine

Arterioscler Thromb Vasc Biol. 2000;20:2309-2315
doi: 10.1161/01.ATV.20.10.2309
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2000 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/20/10/2309

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/