Platelet Activation During Coronary Angioplasty in Humans

Christine M. Gasperetti, MD; Steven L. Gonias, MD, PhD; Lawrence W. Gimple, MD; Eric R. Powers, MD

Background. Previous studies have indicated that balloon angioplasty is associated with local platelet activation. In addition, different contrast media have different effects on thrombus formation during angioplasty in humans. We hypothesized that coronary angioplasty in humans is associated with activation of platelets to specific platelet agonists and that this activation may be differently modified by different angiographic contrast agents.

Methods and Results. We studied 25 patients referred for angioplasty of the left anterior descending or circumflex coronary arteries. All patients were pretreated with aspirin and received heparin. Blood samples for assessment of platelet aggregation to serotonin, ADP, epinephrine, and collagen were obtained from the coronary sinus before any contrast injection, after initial diagnostic contrast injections, and after three balloon inflations. Patients were randomized to receive iopamidol, diatrizoate, or ioxaglate. Contrast alone was not associated with altered platelet aggregation. However, balloon angioplasty was consistently associated with increased platelet aggregation to serotonin but not to ADP, epinephrine, or collagen. These effects were similar with the three contrast agents studied except that the use of iopamidol was associated with increased platelet responsiveness to all concentrations of ADP after balloon dilation.

Conclusions. Coronary angioplasty in humans was associated with increased platelet aggregation in blood drawn from the coronary sinus. This effect was primarily seen when serotonin was used as an agonist. (Circulation. 1993;88:2728-2734.)

KEY WORDS • angioplasty • platelets • contrast media

Platelets play an important role in the response to balloon inflation during coronary angioplasty. Damage to the arterial wall may lead to platelet activation and thrombus formation.1-4 This response has been extensively described in animal models.1-6 Mural thrombosis after balloon angioplasty can result in acute vessel closure and has been implicated as a stimulus to restenosis.7-8 The importance of thrombosis during angioplasty in humans is less well understood.9-12 Angiographically apparent thrombus formation occurs in some patients after balloon angioplasty, and complications of thrombus formation can be reduced in some with the use of antiplatelet agents.13 It has been suggested that platelet activation may also play a role in restenosis after angioplasty in humans.14-16

Different contrast media have been found to have different effects on in vitro platelet function.17-23 Previous work has suggested that the use of different contrast media are associated with different rates of thrombus formation during angioplasty, suggesting that different effects of contrast agents on platelet function and thrombosis demonstrated in vitro may have important clinical implications.24,25 The purpose of this study was to examine whether diagnostic contrast injections followed by balloon dilation of the coronary artery results in platelet activation during coronary angioplasty in humans. We hypothesized that platelets obtained from the coronary sinus immediately after contrast injection and balloon inflation would show evidence of activation as demonstrated by increased aggregability to known platelet agonists. We also hypothesized that different contrast agents might differently modify this platelet activation.

Methods

Patient Population

The study population included 25 patients (19 men and 6 women; mean age, 59±12 years). Patients were selected if they were referred for coronary angioplasty of the left anterior descending artery, the left circumflex artery, or one of the major proximal branches of these vessels. Patients were excluded if they had a recent myocardial infarction or rest angina or any illnesses known to influence platelet function including chronic inflammatory disease, active bleeding, severe anemia, polycythemia, or chronic renal failure. Patients who required pretreatment with corticosteroids before receiving contrast media were excluded. Informed consent was obtained from all patients in accordance with the requirements of the Human Investigation Committee of the University of Virginia.

Study Protocol

All patients had been on chronic pretreatment with aspirin (at least 325 mg/d) before angioplasty. On arrival in the cardiac catheterization laboratory, venous
access and arterial femoral access were obtained. Ten thousand units of heparin was administered intravenously to all patients. A 7F National Institutes of Health (NIH) catheter was placed into the coronary sinus under fluoroscopic guidance, and correct placement was confirmed by measurement of the oxygen saturation of blood obtained through the catheter. At least 10 minutes separated heparin administration and initiation of platelet sampling. No contrast medium was given until baseline samples for platelet aggregation studies were obtained.

Initial baseline coronary sinus blood samples were obtained. Subsequent coronary sinus samples were drawn 1 minute after diagnostic contrast injections before balloon inflation and 1 minute after the third of three balloon inflations (with the balloon catheter withdrawn into the guiding catheter). Another group of patients were studied to confirm that platelet activation did not occur due to factors unrelated to contrast administration or balloon dilation or the sampling technique. These patients were also receiving aspirin chronically. Serial blood samples were drawn at time intervals similar to those used in the study group but before contrast medium was given or percutaneous transluminal coronary angioplasty performed. This group of patients served as a control group.

In five additional patients, the possibility that platelets were activated during transit through a long catheter was evaluated. Ten minutes after systemic heparinization in patients being treated chronically with aspirin, blood samples were simultaneously obtained through a 7F NIH catheter placed in the inferior vena cava and from puncture of an antecubital vein with a 21-gauge needle.

**Contrast Media**

Upon enrollment, study patients were randomized to receive one of three contrast media: a nonionic low-osmolarity agent (iopamidol-370, Isovue; n=7); an ionic hyperosmolar agent (diatrizoate, Renografin-76; n=9); or an ionic low-osmolarity agent (ioxaglate, Hexabrix;
n=9). Operators and laboratory staff were blinded to the type of contrast medium used.

**Platelet Aggregation Studies**

Blood samples were drawn into sodium citrate dextrose (9:1 vol:%) using plastic syringes. The initial 3 mL of blood drawn from the catheter was discarded. Platelet-rich plasma and platelet-poor plasma were prepared by standard methods.26 Platelet count was measured in triplicate by thrombocytometer or Coulter counter. These counts were averaged and diluted performed to 200 μL/mL using platelet-poor plasma. Platelet aggregation was performed by Born’s method using a turbimetric device (Payton Associates, Scabrou, Ontario, Canada).27 Aggregation studies were begun within 1 hour after initial samples were obtained and completed within 2 hours of sampling. Samples were run consecutively in the order in which they were obtained. Each test was terminated upon maximal response within 3 minutes. The order and concentrations in which agonists were prepared for all samples were: 10, 1, 0.5, and 0.25 μmol/L ADP; 13 μmol/L serotonin; 5 μmol/L epinephrine, and 0.1 μmol/L collagen.

**Analysis of Platelet Aggregation**

Platelet aggregation curves were analyzed for maximum percent response (maximum percent reduction in absorbance compared with platelet-poor plasma) within 3 minutes of exposure to the various agonists and for maximum slope of the response (given in the figures and tables as percent reduction in absorbance per minute). This analysis was performed with the observer blinded to patient identity and to the type of contrast medium used.

**Angiographic Analysis**

Visual analysis for the presence of thrombus and/or coronary dissection was performed by two observers blinded to patient identity and to the type of contrast medium used. Criteria for the presence of thrombus were (1) intraluminal filling defect, (2) total occlusion with convex, irregular, hazy margins, or (3) distal embolization. Dissection was determined to be present if contrast medium was identified outside the lumen of the artery. Quantitative analysis was performed in identical projections before and after angioplasty. Stenosis severity is reported as percent diameter reduction of the coronary lesion compared with the diameter of a normal adjacent arterial segment.

**Statistical Analysis**

Mean data are presented as mean±SEM.28 Results were analyzed by one-way ANOVA. For dichotomous variables, χ² analysis was used unless the expected value for a cell was less than 5, in which case Fisher’s exact test was used. A two-tailed Student’s t test was used for continuous variables. A P value of <.05 was considered significant.

**Results**

**Clinical and Angiographic Characteristics**

Clinical and angiographic characteristics are shown in Table 1. Twenty-four of 25 patients presented with a crescendo pattern of angina. All patients were chronically receiving aspirin. There was no angiographic evidence of intracoronary thrombus before or after angioplasty in any patient. There were no differences between patient groups receiving different contrast agents with regard to stenosis severity before or after angioplasty.

### Table 3. Aggregation Responses to Serotonin

<table>
<thead>
<tr>
<th></th>
<th>Combined (n=25)</th>
<th>Iopamidol (n=7)</th>
<th>Diatrizoate (n=9)</th>
<th>Ioxaglate (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Slope</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>36±4</td>
<td>12±2</td>
<td>48±18</td>
<td>16±4</td>
</tr>
<tr>
<td>After contrast</td>
<td>35±4</td>
<td>12±2</td>
<td>44±17</td>
<td>16±4</td>
</tr>
<tr>
<td>After inflation</td>
<td>49±5†</td>
<td>15±2*</td>
<td>63±24*</td>
<td>18±3*</td>
</tr>
<tr>
<td><strong>Height</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>31±10</td>
<td>12±3</td>
<td>40±13</td>
<td>12±2</td>
</tr>
<tr>
<td>After contrast</td>
<td>32±10</td>
<td>9±2</td>
<td>26±8</td>
<td>10±2</td>
</tr>
<tr>
<td>After inflation</td>
<td>48±16*</td>
<td>14±3*</td>
<td>40±14*</td>
<td>13±2*</td>
</tr>
</tbody>
</table>

Slope indicates maximum percent reduction in absorbance per minute and height, maximum percent reduction in absorbance within 3 minutes.

*Significant change (P<.05) compared with baseline; †significant change (P<.001) compared with baseline.
**Control Patients**

Aggregation responses in the control group are given in Table 2. No significant changes in platelet aggregation to any agonist developed over time in the absence of contrast injection or balloon inflation.

**Serotonin**

Responsiveness to serotonin was not affected by initial diagnostic contrast injections (Fig 1 and Table 3). However, balloon inflation resulted in significant increases in both the slope and the height of the aggregation responses to serotonin. This increase in platelet responsiveness to serotonin occurred after balloon inflation in each of the three individual contrast groups (Table 3).

**Table 4. Aggregation Responses to ADP**

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Combined (n=25)</th>
<th>Iopamidol (n=7)</th>
<th>Diatrizoate (n=9)</th>
<th>Ioxaglate (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>Height</td>
<td>Slope</td>
<td>Height</td>
</tr>
<tr>
<td>0.25 μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>28±4</td>
<td>12±2</td>
<td>30±12</td>
<td>14±4</td>
</tr>
<tr>
<td>After contrast</td>
<td>31±5</td>
<td>12±2</td>
<td>44±18</td>
<td>14±5</td>
</tr>
<tr>
<td>After inflation</td>
<td>34±4</td>
<td>13±2</td>
<td>42±16*</td>
<td>15±4</td>
</tr>
<tr>
<td>0.50 μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>44±5</td>
<td>16±2</td>
<td>44±9</td>
<td>21±5</td>
</tr>
<tr>
<td>After contrast</td>
<td>45±5</td>
<td>15±2</td>
<td>54±12</td>
<td>18±5</td>
</tr>
<tr>
<td>After inflation</td>
<td>47±5</td>
<td>18±2</td>
<td>60±10*</td>
<td>18±4</td>
</tr>
<tr>
<td>1.0 μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>51±4</td>
<td>24±2</td>
<td>57±7</td>
<td>26±3</td>
</tr>
<tr>
<td>After contrast</td>
<td>50±4</td>
<td>23±2</td>
<td>64±10</td>
<td>25±4</td>
</tr>
<tr>
<td>After inflation</td>
<td>62±4*</td>
<td>23±2</td>
<td>77±8*</td>
<td>27±3</td>
</tr>
<tr>
<td>10.0 μmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>62±3</td>
<td>47±2</td>
<td>60±5</td>
<td>50±3</td>
</tr>
<tr>
<td>After contrast</td>
<td>60±3</td>
<td>44±2</td>
<td>66±10</td>
<td>46±3</td>
</tr>
<tr>
<td>After inflation</td>
<td>68±4*</td>
<td>46±2</td>
<td>81±8*</td>
<td>49±4</td>
</tr>
</tbody>
</table>

Slope indicates maximum percent reduction in absorbance per minute and height, maximum percent reduction in absorbance within 3 minutes.

*Significant change (P<.05) compared with baseline.

**ADP**

Initial contrast injections had no effect on platelet responsiveness to any concentration of ADP. Balloon angioplasty, however, resulted in significant increases in the slopes of the aggregation responses to 10 μmol/L and 1 μmol/L ADP when all patients were combined (Fig 2 and Table 4). This overall effect seen for all patients primarily was due to an augmentation in the responses from those patients receiving iopamidol, with little augmentation seen in the other contrast groups. In the iopamidol group, the slopes of the responses to each concentration of ADP tested (0.25, 0.5, 1.0, and 10 μmol/L) were significantly augmented after balloon angioplasty.

**Collagen and Epinephrine**

Neither initial contrast injections nor balloon inflation affected the responses to either collagen or epi-
TABLE 5. Aggregation Responses to Epinephrine

<table>
<thead>
<tr>
<th></th>
<th>Combined (n=25)</th>
<th>Iopamidol (n=7)</th>
<th>Diatrizoate (n=9)</th>
<th>Ioxaglate (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope Height</td>
<td>Slope Height</td>
<td>Slope Height</td>
<td>Slope Height</td>
</tr>
<tr>
<td>Baseline</td>
<td>42±4 29±2</td>
<td>48±18 31±2</td>
<td>40±14 27±4</td>
<td>38±12 25±2</td>
</tr>
<tr>
<td>After contrast</td>
<td>45±5 27±2</td>
<td>48±18 29±3</td>
<td>50±15 27±3</td>
<td>36±12 24±3</td>
</tr>
<tr>
<td>After inflation</td>
<td>42±4 26±2</td>
<td>51±20 30±2</td>
<td>45±16 25±5</td>
<td>32±10 24±3</td>
</tr>
</tbody>
</table>

Slope indicates maximum percent reduction in absorbance per minute and height, maximum percent reduction in absorbance within 3 minutes.

nephrine (Fig 3 and Tables 5 and 6). Responses were similar in each of the contrast groups.

Sampling Through a Long Catheter

There were no significant differences in platelet responses between samples obtained through a long catheter and samples obtained via antecubital puncture (Table 7).

Discussion

In the present study, we examined changes in the aggregation responsiveness of platelets obtained from the coronary sinus in patients undergoing coronary balloon angioplasty. The data demonstrate that diagnostic contrast injections before balloon inflation had no significant effect on responsiveness of platelets obtained from the coronary circulation. However, balloon dilation of the coronary artery resulted in significant platelet activation. This activation was manifested by an increased responsiveness to serotonin. Aggregation responses after balloon dilation were, in general, similar in the three different contrast agent groups, although the slopes of the aggregation responses to all concentrations of ADP after balloon inflation were accentuated in patients receiving iopamidol. Thus, balloon dilation and arterial injury may be more important than the specific contrast agent used in inducing platelet activation during coronary angioplasty.

Platelet Activation During Angioplasty

The findings of the present study demonstrate platelet activation in response to balloon inflation during coronary angioplasty in humans. Previous work has demonstrated platelet activation after balloon angioplasty in animal models.1-6 Furthermore, studies in animal models have suggested that platelet activation plays an important role in thrombus formation and restenosis after angioplasty.7,8 The importance of platelet activation during angioplasty in humans has been suggested by the observation that antiplatelet therapy with aspirin prevents ischemic complications during balloon angioplasty.9 The present study demonstrates that coronary angioplasty in humans is associated with measurable platelet activation.

Role of Serotonin

In the present study, the activation of platelets that occurred as a result of balloon angioplasty was detected when serotonin was used as the aggregation agonist. Previous studies have suggested that platelet responses to serotonin may play an important role in the cyclic changes noted in stenotic coronary arteries in animals.29,30 In animal models, serotonin antagonists prevent cyclic flow reductions in stenotic arteries, as do thromboxane receptor antagonists.29 Because these two antagonists administered together are more effective than either alone, platelet activation in stenotic coronary vessels may be mediated by both thromboxane and serotonin. The hyperresponsiveness to serotonin induced by balloon angioplasty demonstrated in our study together with the previously reported importance of serotonin-mediated effects on platelets in experimental situations29,31 suggest the possibility that increased serotonin responsiveness may be an important mediator of platelet deposition during human angioplasty. This suggests the potential value of studies examining serotonin blockers during and after angioplasty in humans.

Effects on Contrast Media

In vitro studies have demonstrated that contrast media have important effects on platelet function and thrombosis and that these effects differ between different contrast agents.7-14 We have demonstrated previously that the use of a low-osmolality nonionic contrast agent was associated with increased thrombus formation during coronary angioplasty in humans.24 This observation suggested the hypothesis that contrast agents might influence the effect of balloon dilation on platelet activation and that different agents might have different effects. The results of our study did not, however, confirm an important effect of contrast agents on platelet aggregation in this setting. The only significant effect of contrast was an augmentation of the slope of the aggregation responses after balloon inflation to

TABLE 6. Aggregation Responses to Collagen

<table>
<thead>
<tr>
<th></th>
<th>Combined (n=25)</th>
<th>Iopamidol (n=7)</th>
<th>Diatrizoate (n=9)</th>
<th>Ioxaglate (n=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope Height</td>
<td>Slope Height</td>
<td>Slope Height</td>
<td>Slope Height</td>
</tr>
<tr>
<td>Baseline</td>
<td>36±4 26±2</td>
<td>38±14 28±3</td>
<td>43±14 28±4</td>
<td>27±8 21±4</td>
</tr>
<tr>
<td>After contrast</td>
<td>36±4 24±2</td>
<td>36±14 26±4</td>
<td>40±13 28±3</td>
<td>33±11 20±3</td>
</tr>
<tr>
<td>After inflation</td>
<td>32±3 23±2</td>
<td>31±12 26±3</td>
<td>38±12 25±3</td>
<td>27±9 18±3</td>
</tr>
</tbody>
</table>

Slope indicates maximum percent reduction in absorbance per minute and height, maximum percent reduction in absorbance within 3 minutes.
all concentrations of ADP in the group receiving iodipidol. Thus, differing effects of different contrast agents on thrombus formation during coronary angioplasty may not be primarily mediated through contrast effects on platelet function but may be due to other thrombotic effects.17,31-33

Study Limitations

There are a number of potential limitations of our study. All patients received aspirin and an intravenous bolus of heparin before angioplasty. Both of these agents are known to affect platelet aggregation, particularly in response to epinephrine and collagen.35,36 Different results might have been obtained had these drugs not been administered. However, human coronary angioplasty is routinely performed after aspirin pretreatment and heparin administration. Furthermore, despite these treatments, thrombus during angioplasty procedures and late restenosis continue to be important clinical problems. In addition, all of our studies were internally controlled since precontrast, preangioplasty blood samples were obtained in all patients.

Diagnostic doses of contrast agent were used. The doses used were not strictly controlled but were enough to allow for optimal visualization of the vessels before and during the angioplasty procedure. We chose to perform the study so that our results would be relevant to clinical angioplasty procedures as routinely performed. Studies giving larger doses of contrast might reveal different results but might not be relevant to clinical angioplasty.

Our studies may underestimate the extent to which platelets are activated during angioplasty. Our method assumes that platelets obtained from the coronary sinus reflect platelet events occurring at the site of coronary angioplasty. This assumption may or may not be correct. Activated platelets may have been deposited on the injured coronary arterial surface. Because of this adherence, activated platelets may have been underrepresented in coronary venous blood. In addition, blood sampling proximal to the site of angioplasty as well as in the coronary sinus might have indicated deposition of activated platelets on the coronary arterial surface. Thus, platelet activation during contrast injections and balloon inflations may have been more intense than we were able to observe, and different effects of the different contrast agents might have been more apparent had platelet function been tested at the site of balloon angioplasty. Coronary sinus rather than peripheral blood sampling was performed so that sampling would be as close to the site of balloon angioplasty as possible.

Data from control patients demonstrated that responses to serotonin tended to decrease with sequential sampling in the absence of contrast injection or balloon angioplasty. One possible explanation for this observation is that initial catheter placement may have resulted in augmented responses to serotonin in the first samples obtained. Whatever the mechanism, the decreasing responses to serotonin in sequential samples in the control patients suggest that effects of serotonin responsiveness after angioplasty may have been underestimated.

Studying a larger number of patients might have identified further statistically significant differences between the effects of the different contrast agents. However, the data obtained indicate that even if additional significant differences were found, they probably would be quantitatively small and, therefore, of uncertain significance.

Coronary sinus sampling was not performed during contrast injections. Rather, sampling was performed after contrast had time to clear from the coronary circulation so that persistent rather than transient effects of contrast injection on platelet activation would be observed. Contrast media have been shown to have effects on platelets that are concentration dependent.17 In this study we chose to examine the more persistent effects of contrast rather than effects of transient high concentrations.

Previous studies have identified the activation of platelets with release of β-thromboglobulin and platelet factor IV during withdrawal of blood through long catheters in patients not receiving heparin.37 In the present study, no significant platelet activation by withdrawal of blood through a long catheter was seen in patients chronically treated with aspirin and pretreated with heparin.

Our results might have been affected by changes in platelet activation that were related to the duration of the procedure, the sampling technique, or the duration between sampling and measurement. However, all of these variables were kept constant between patients. In addition, control patients were studied with a protocol identical to that used for patients studied during angioplasty.

### Table 7. Aggregation Responses in Samples From Long Catheters (n=5)

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Long Catheter</th>
<th></th>
<th>Antecubital Needle</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Slope</td>
<td>Height</td>
<td>Slope</td>
<td>Height</td>
</tr>
<tr>
<td>Serotonin, 13 μmol/L</td>
<td>35±8</td>
<td>9±2</td>
<td>30±9</td>
<td>7±2</td>
</tr>
<tr>
<td>ADP, μmol/L</td>
<td>18±8</td>
<td>8±2</td>
<td>17±7</td>
<td>7±2</td>
</tr>
<tr>
<td>0.25</td>
<td>31±9</td>
<td>10±2</td>
<td>31±9</td>
<td>13±4</td>
</tr>
<tr>
<td>0.5</td>
<td>54±10</td>
<td>25±6</td>
<td>44±10</td>
<td>21±4</td>
</tr>
<tr>
<td>1.0</td>
<td>74±9</td>
<td>48±6</td>
<td>72±6</td>
<td>51±7</td>
</tr>
<tr>
<td>10.0</td>
<td>36±3</td>
<td>33±3</td>
<td>36±2</td>
<td>30±2</td>
</tr>
<tr>
<td>Collagen, 0.1 μmol/L</td>
<td>28±9</td>
<td>24±9</td>
<td>19±8</td>
<td>19±7</td>
</tr>
</tbody>
</table>

Slope indicates maximum percent reduction in absorbance per minute and height, maximum percent reduction in absorbance within 3 minutes.
plasty except for the absence of contrast injections or balloon inflations. The absence of progressive platelet activation with time in the control patients confirms that increases in platelet aggregation after balloon inflation were due to balloon angioplasty.

Acknowledgments
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References
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