Increased Platelet Thromboxane A₂/Prostaglandin H₂ Receptors in Patients With Acute Myocardial Infarction

Gerald W. Dorn II, MD, Noah Liel, MD, Joseph L. Trask, MD, Dale E. Mais, PhD, Michael E. Assey, MD, and Perry V. Halushka, MD, PhD

Platelets have been implicated in the formation of occlusive intracoronary thrombi leading to unstable angina pectoris and acute myocardial infarction. Evidence of platelet involvement in these syndromes includes increased thromboxane A₂ synthesis during ischemic events and enhanced in vitro sensitivity to agonists. To determine the density and affinity of platelet thromboxane A₂/prostaglandin H₂ (TXA₂/PGH₂) receptors in patients with acute myocardial infarction and unstable angina pectoris, the maximum number of binding sites (Bₘₐₓ) per platelet and the dissociation constant (Kₐ) of the TXA₂/PGH₂ receptor antagonist, [¹²⁵I]-PTA-OH, was determined at equilibrium in washed platelets. Patients with acute myocardial infarction had a significantly higher Bₘₐₓ (4,468±672 sites/platelet, n=9) compared with controls (2,206±203 sites/platelet, n=8). Restudied at a time when the patients' coronary artery disease was clinically stable, Bₘₐₓ values for the myocardial infarction group had returned to within normal limits. The dissociation constant for [¹²⁵I]-PTA-OH was not significantly different in the acute myocardial infarction patients compared with controls. In patients with acute myocardial infarction, the duration of chest pain was positively correlated (r=0.71, p<0.02) with the number of [¹²⁵I]-PTA-OH binding sites (Bₘₐₓ). In vitro platelet sensitivity to the TXA₂/PGH₂ mimetic, U46619, was assessed in aggregation studies. The maximal velocity of aggregation (slope) correlated with platelet TXA₂/PGH₂ receptor number (r=0.67, p<0.001) and was significantly higher (p<0.02) in the acute myocardial infarction patients compared with the other study groups. There was no significant difference in the aggregation EC₅₀ values for the thromboxane mimetic U46619 between unstable angina, acute myocardial infarction, and control groups. The data show that patients with acute myocardial infarction have increased numbers of platelet TXA₂/PGH₂ receptors and that the receptor number is greatest in patients with prolonged ischemic chest pain. The results suggest a possible therapeutic role for specific TXA₂/PGH₂ receptor antagonists in acute coronary ischemic syndromes. (Circulation 1990;81:212–218)

The presence of occlusive intraluminal coronary artery thrombi in acute myocardial infarction and unstable angina pectoris has been established by angiographic,¹−⁵ angioscopic,⁶ and pathologic⁷⁻⁸ studies. The involvement of platelets in the genesis of these coronary thrombi is suggested by studies demonstrating increased numbers of circulating platelet aggregates,⁹ increased levels of platelet factor 4 or β-thromboglobulin,¹⁰⁻¹² and increased production of thromboxane A₂¹³⁻¹⁵ during these events. Thromboxane A₂ is synthesized and released by platelets during platelet aggregation and thrombus formation.¹⁶ An important role for platelet aggregation or thromboxane A₂ production in the pathophysiology of acute coronary ischemic syndromes is supported by the observation that aspirin, an inhibitor of platelet aggregation and thromboxane A₂ synthesis, is beneficial in unstable angina pectoris and acute myocardial infarction.¹⁷⁻¹⁹

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TABLE 1. Clinical Characteristics of Subject Groups

<table>
<thead>
<tr>
<th>Dx</th>
<th>n</th>
<th>Age (yr)</th>
<th>M/F</th>
<th>Cigarette smoking</th>
<th>Chest pain duration (hr)</th>
<th>CPK</th>
<th>Heparin</th>
<th>NTG</th>
<th>β-Blockers</th>
<th>Calcium channel blockers</th>
<th>Lidocaine</th>
</tr>
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<tbody>
<tr>
<td>MI</td>
<td>9</td>
<td>60±5</td>
<td>8/1</td>
<td>5/9</td>
<td>14±3</td>
<td>1,883±506*</td>
<td>2/9</td>
<td>9/9</td>
<td>4/9</td>
<td>5/9</td>
<td>2/9</td>
</tr>
<tr>
<td>UA</td>
<td>5</td>
<td>60±6</td>
<td>5/0</td>
<td>4/5</td>
<td>9±3</td>
<td>124±41</td>
<td>1/5</td>
<td>4/5</td>
<td>2/5</td>
<td>3/5</td>
<td>0/5</td>
</tr>
<tr>
<td>INL</td>
<td>4</td>
<td>52±8</td>
<td>2/2</td>
<td>1/4</td>
<td>7±1</td>
<td>75±17</td>
<td>0/4</td>
<td>3/4</td>
<td>1/4</td>
<td>2/4</td>
<td>0/4</td>
</tr>
<tr>
<td>NNL</td>
<td>8</td>
<td>33±2</td>
<td>8/0</td>
<td>6/8</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

Dx, diagnostic group; M/F, ratio of male to female subjects; CPK, peak creatine phosphokinase; NTG, nitroglycerin; β-blockers, beta adrenergic receptor antagonists; MI, myocardial infarction; UA, unstable angina; INL, intensive care unit noncoronary chest pain; NNL, normal controls.

*p<0.01 compared with UA and INL.

Enhanced platelet sensitivity to a variety of aggregatory stimuli,20–22 including stable thromboxane A₂ mimetics,23,24 has been reported in patients with coronary artery disease. However, the mechanism responsible for this phenomenon in unstable coronary artery syndromes is unknown. Thromboxane A₂ and its precursor, prostaglandin H₂, induce platelet aggregation through interaction with specific membrane receptors.16 If the affinity or number of platelet thromboxane A₂ receptors were increased in patients with unstable coronary artery disease, it might result in increased platelet sensitivity to thromboxane A₂ and predispose to enhanced platelet activation.25,26 [125I]-PTA-OH is a specific thromboxane A₂/prostaglandin H₂ (TXA₂/PGH₂) receptor antagonist that has previously been used in radioligand binding studies to characterize human platelet TXA₂/PGH₂ receptors.25,26 To test for a possible TXA₂/PGH₂ receptor abnormality in patients with unstable coronary artery disease, we employed radioligand binding studies with [125I]-PTA-OH to assess the number and affinity of platelet receptors in subjects with acute and convalescent myocardial infarction, unstable angina pectoris, nonischemic chest pain, and normal controls.

Methods

From January to December, 1987, patients admitted to cardiac or medical care units (Medical University, Charleston Memorial, or Veterans Administration Hospitals in Charleston, South Carolina) were entered into the study if they presented with presumed cardiac rest pain of greater than 30 minutes duration. Patients were excluded if they had taken aspirin or other nonsteroidal anti-inflammatory drugs up to 2 weeks before hospital admission, if they had diabetes mellitus, if the hospital admission was greater than 24 hours after the most recent episode of pain, or if they received thrombolytic therapy or underwent cardiac catheterization before the study. Blood for the receptor binding and platelet aggregation studies (40–60 ml) was drawn from an antecubital vein via a 19-gauge needle into a syringe containing indomethacin (10 μM) and EDTA (5 mM). Blood was usually drawn between 8 and 10 AM in order to avoid any diurnal influences.27 All initial studies were performed within 24 hours of hospital admission and within 48 hours of the most recent episode of chest pain. A normal control subject and a patient were studied at the same time. The study protocol was approved by the Medical University of South Carolina Institutional Review Board for Human Research, and all patients gave written, informed consent before the study.

Patient Groups

On the basis of clinical presentation, serial electrocardiographic and enzymatic tests (CPK-MB), and cardiac catheterization data, patients were retrospectively assigned to diagnostic subgroups by one of the authors who was blinded to the receptor and aggregation assay results. Acute myocardial infarction (nine patients) was defined as an increase in total plasma CPK greater than twice normal with an MB fraction of 5% or greater in patients with objective evidence of coronary atherosclerosis by cardiac catheterization or unequivocal electrocardiographic changes. In the acute myocardial infarction patients, the infarction was located by electrocardiographic or angiographic means as five anterior, two inferior, and two non–Q wave infarctions. Unstable angina pectoris (five patients) was defined as chest pain at rest for greater than 30 minutes with a crescendo angina pattern in the absence of an increase in plasma CPK levels and with objective evidence of coronary atherosclerosis. Intensive care unit (ICU) controls (four patients) were patients admitted to an ICU with chest pain thought to be of cardiac origin but who were subsequently found by coronary arteriography to have noncardiac chest pain with normal coronary arteries. The normal control group (eight subjects) consisted of nonhospitalized subjects without a history of cardiac disease. The myocardial infarction patients and normal control subjects were restudied after a convalescent period of at least 4 months at a time when there had been no angina for at least 1 week. Of the eight myocardial infarction patients who were restudied, three had undergone coronary artery bypass surgery, and one had received a cardiac transplantation.

Clinical characteristics of the four patient groups are shown in Table 1. The ages of the acute myocardial infarction, unstable angina, and ICU control patients were not significantly different from each
other. Duration of chest pain was not significantly different in the acute myocardial infarction patients compared with the unstable angina or ICU control patients. The proportion of the patients who were smoking cigarettes was similar in the acute myocardial infarction and unstable angina groups. Patient medications are shown by class of drug. No patients had taken aspirin or other nonsteroidal anti-inflammatory drugs for at least 2 weeks before the initial study. However, all myocardial infarction patients were taking aspirin at the time of the convalescent study.

Radioligand Binding Assays and Platelet Aggregation Studies

Washed platelets were prepared by differential centrifugation and resuspended in assay buffer (50 mM Tris-HCl, 100 mM NaCl, 5 mM dextrose, 10 μM indomethacin, pH 7.4) to 5×10⁶ platelets/ml. The methods to assess binding of [¹²⁵I]-PTA-OH to washed platelets have been described previously.²⁶ Briefly, washed platelets (5×10⁹), various concentrations of [¹²⁷I]-PTA-OH (0.5–1,000 nM), and approximately 0.2 nM (~10⁵ cpm) [¹²⁵I]-PTA-OH (200 μl total volume) were incubated at 37°C for 30 minutes. Bound ligand was separated from free by vacuum filtration using Whatman GF/C glass fiber filters. Nonspecific binding was defined as that binding remaining in the presence of 1 μM [¹²⁷I]-PTA-OH. Specific binding was typically 55–65% of total binding.

For platelet aggregation studies, platelets were diluted in assay buffer to 2.5×10⁸ platelets/ml, and CaCl₂ was added to a final concentration of 250 μM. Platelet aggregation was carried out in a Chronolog Model 300 aggregometer (Havertown, Pennsylvania) as previously described.²⁸ Washed platelets were incubated with various concentrations of the thromboxane A₂ mimetic U46619²⁹ in silanized glass cuvettes at 37°C, and the aggregation response (maximal light transmission) was observed for 2 minutes. Concentration-response curves were constructed and the EC₅₀ values determined. The EC₅₀ was defined as the concentration required to produce 50% of the maximum aggregation response 1 minute after the addition of U46619. Maximal velocity of aggregation (V₅₀) was determined as the initial slope of the aggregation response to 2.5 or 5 μM U46619.

Statistical Analysis

The equilibrium binding data were analyzed using LIGAND, a nonlinear curve-fitting program from which the dissociation constant (Kₒ) and maximum number of binding sites per platelet (Bₘₐₓ) were determined. Differences between Kₒ, Bₘₐₓ, EC₅₀, and aggregation V₅₀ for the study groups were compared using one-way analysis of variance (ANOVA) and Newman-Keuls test. For comparison of thromboxane A₂ receptor density to chest pain duration and aggregation V₅₀, a regression analysis was performed, and Pearson’s correlation coefficient was determined. All values are expressed as mean±SEM.

Results

[¹²⁵I]-PTA-OH Binding to Washed Human Platelets

Patients with acute myocardial infarction had a significantly (p=0.006, one-way ANOVA) greater number of [¹²⁵I]-PTA-OH binding sites (4,468±672 sites per platelet) compared with the normal controls (2,206±203 sites per platelet), as shown in Figure 1 and Table 2. A representative Scatchard plot for a myocardial infarction patient and a control subject is

![Graph showing binding data](image)

**Figure 1.** [¹²⁵I]-PTA-OH Bₘₐₓ values in the study groups. Each data point is from a single subject. AMI, acute myocardial infarction; CMI, convalescent myocardial infarction; UA, unstable angina; INL, intensive care unit noncoronary chest pain controls; NNL, normal controls; RNNL, repeat study of normal controls. The AMI group had a significantly greater Bₘₐₓ compared with the other groups (p=0.006) and with their convalescent study (p<0.001).

### Table 2. Platelet Thromboxane A₂ Receptor Characteristics in Four Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Platelet count (×10⁹/μl)</th>
<th>Bₘₐₓ (sites/platelet)</th>
<th>Kₒ (nM)</th>
<th>EC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls (n=8)</td>
<td>NM</td>
<td>2,206±203</td>
<td>28±4</td>
<td>77±7 (8/8)</td>
</tr>
<tr>
<td>Intensive care unit controls (n=4)</td>
<td>251±11</td>
<td>2,579±121</td>
<td>33±13</td>
<td>81±15 (4/4)</td>
</tr>
<tr>
<td>Myocardial infarction (n=9)</td>
<td>238±25</td>
<td>4,468±672*</td>
<td>48±10</td>
<td>71±5 (6/9)</td>
</tr>
<tr>
<td>Unstable angina (n=5)</td>
<td>248±38</td>
<td>2,661±377</td>
<td>25±3</td>
<td>91±19 (4/5)</td>
</tr>
</tbody>
</table>

NM, not measured.

Data are expressed as mean±SEM. For aggregation studies, technical problems prevented obtaining results on all patients so number of patient results is shown in parentheses after EC₅₀ value.

*Significantly different from controls (p<0.001).
shown in Figure 2. The $K_d$ for $[^{125}\text{I}]-\text{PTA-OH}$ binding to the platelets of the acute myocardial infarction patients was 48±10 nM, which did not differ significantly from the normal control subjects (28±4 nM). There were no differences in platelet count between the study groups (Table 2).

In patients with unstable angina pectoris, the $B_{\text{max}}$ was 2,661±377 sites per platelet (Figure 1), and the $K_d$ was 25±3 nM. There was no significant difference in $K_d$ or $B_{\text{max}}$ values between the unstable angina pectoris patients and normal controls, indicating a similar affinity and density of receptors between groups.

Patients admitted to the ICU with suspected ischemic chest pain but who were subsequently found to have noncardiac pain and normal coronary arteries had a $B_{\text{max}}$ and $K_d$ for $[^{125}\text{I}]-\text{PTA-OH}$ binding sites similar to those of normal controls (Figure 1, Table 2).

The duration of chest pain for the 24 hours preceding the study in the acute myocardial infarction patients ranged from 1 to 24 hours. The density of $[^{125}\text{I}]-\text{PTA-OH}$ binding sites positively correlated ($r=0.71$, $p<0.02$) with chest pain duration (Figure 3). Thus, myocardial infarction patients with the most prolonged chest pain tended to have higher numbers of binding sites. There was no significant correlation between chest pain duration and $K_d$ nor between severity of coronary artery stenosis, presence of intraluminal thrombus by coronary arteriography, number of diseased coronary arteries, or peak CPK and either $K_d$ or $B_{\text{max}}$.

Eight of the nine acute myocardial infarction patients and all normal control subjects were restudied at a time when the patients were stable, either while taking medication or after surgery. The normal control subjects were restudied in parallel under identical conditions. All of the myocardial infarction patients were taking aspirin at the time of the convalescent study, which was performed from 5 to 15 months after the initial study (mean 9.6±1.2 months). At restudy, the $[^{125}\text{I}]-\text{PTA-OH}$ $B_{\text{max}}$ (myocardial infarction 1,501±182, normal 1,557±160 sites/platelet; $p=\text{NS}$) and $K_d$ values (myocardial infarction 15.5±1, normal 14.9±1.6 nM; $p=\text{NS}$) of the myocardial infarction patients were identical to normal controls (Figure 1).

**Platelet Aggregation**

The aggregation response of washed platelets stimulated with the stable thromboxane A$_2$ mimetic U46619 was evaluated in parallel with radioligand binding studies in the acute and convalescent groups.

The initial slope of the aggregation curve was determined as a measure of maximal aggregation velocity for the highest concentration of U46619 (2.5 or 5 μM). For all of the initial study subjects,
aggregation $V_{\text{max}}$ significantly correlated with platelet TXA$_2$/PGH$_2$ receptor number (Figure 4). Aggregation $V_{\text{max}}$ was significantly increased in the myocardial infarction patients ($p=0.02$, one-way ANOVA) relative to the other study groups (Figure 4). There were no significant differences in the maximal aggregation or the EC$_{50}$ values of U46619-induced platelet aggregation between the groups. The EC$_{50}$ values were as follows: acute myocardial infarction (97±26 nM), convalescent myocardial infarction (80±7 nM), unstable angina pectoris (120±33 nM), ICU noncardiac chest pain (81±15 nM), normal controls (67±6 nM), and repeat normal controls (99±8 nM).

Discussion

The present study provides evidence of increased numbers of $[^{125}\text{I}]-$PTA-OH binding sites, thought to represent the TXA$_2$/PGH$_2$ receptor on washed platelets of patients with acute myocardial infarction. These patients also exhibited an associated increase in the maximal velocity of U46619-induced platelet aggregation, which correlated with platelet TXA$_2$/PGH$_2$ receptor number. In addition, platelet TXA$_2$/PGH$_2$ receptor number correlated with the duration of chest pain in acute myocardial infarction and unstable angina pectoris patients.

The mechanism responsible for the apparently increased receptor density in these patients is unknown. It does not appear that all patients with coronary artery disease have platelets with increased numbers of TXA$_2$/PGH$_2$ receptors chronically because 1) patients with unstable angina and some of the patients with acute myocardial infarction had normal receptor number, and 2) at the time of restudy when they were clinically stable, the acute myocardial infarction patients' platelet receptor numbers were not different from those of the controls.

It has previously been shown that the life span of platelets is decreased in patients with atherosclerotic disease and acute myocardial infarction and that this results in a greater proportion of younger, larger, and more active platelets in the circulation. Prolonged chest pain or postinfarction angina indicates ongoing myocardial ischemia, possibly from phasic thrombotic coronary artery occlusions with continued platelet activation and consumption. In the present study, platelet count did not differ significantly among the study groups, but platelet volume was not measured. Therefore, the presence of larger, younger platelets is a possible explanation for our findings of increased receptor numbers in acute myocardial infarction patients and of the correlation between TXA$_2$/PGH$_2$ receptor density and chest pain duration.

Another possible explanation for increased platelet TXA$_2$/PGH$_2$ receptors is stimulation by other aggregating agents. This type of phenomenon has been observed with platelet fibrinogen receptors, which are acutely increased in number after exposure to agonists such as arachidonic acid. The possibility of a similar increase in TXA$_2$/PGH$_2$ receptors after platelet stimulation has not been systematically examined. However, it should be noted that ADP and norepinephrine have previously been shown not to affect $[^{125}\text{I}]-$PTA-OH binding to washed canine platelets.

The present study is the first to demonstrate a disease-related change in platelet TXA$_2$/PGH$_2$ receptors. However, other platelet receptors undergo regulation in coronary artery disease. Jaschonek et al showed a decrease in platelet prostacyclin receptor density and resistance to the antiaggregatory effects of prostacyclin in patients with acute myocardial infarction but not stable angina. Others have suggested an increase in the affinity for density of platelet $\alpha$-adrenergic receptors in patients with unstable angina pectoris. Therefore, in unstable coronary artery syndromes, platelet hypersensitivity to thromboxane A$_2$ and epinephrine and resistance to prostacyclin may be related to receptor changes.

Several studies have demonstrated increased in vitro platelet aggregation to various stimuli, including thromboxane A$_2$ mimetics, in patients with stable and unstable coronary artery disease. Unlike prior studies, the present study was performed in washed platelets rather than platelet-rich plasma, which in acutely ill patients may contain substances such as epinephrine that are known to act synergistically with TXA$_2$/PGH$_2$ mimetics to induce platelet aggregation. We found that the myocardial infarction patients had a significantly increased maximal velocity of U46619-induced aggregation relative to the other study groups but that there was no difference in the EC$_{50}$ for U46619-induced aggregation. These changes in platelet function would be
anticipated from the binding results of increased [\(^{125}\)I]-PTA-OH \(B_{\text{max}}\) without a change in \(K_d\) in the myocardial infarction patients. Because the affinity for [\(^{125}\)I]-PTA-OH did not change, it is reasonable to assume that the affinity of TXA\(_2\)/PGH\(_2\) agonist binding would also not change. Thus, the EC\(_{50}\) value for U46619 would not be expected to change. In contrast, the initial maximal velocities for U46619-induced aggregations were increased, as would be expected with increased numbers of receptors. In fact, there was a positive correlation between the [\(^{125}\)I]-PTA-OH \(B_{\text{max}}\) values and U46619-induced maximal initial aggregation velocities in all of the study subjects (Figure 4).

In order to reduce confounding factors, our protocol excluded certain patients. Diabetic patients, like those with coronary artery disease, have increased platelet turnover, increased platelet sensitivity to various aggregating agents, and increased platelet thromboxane A\(_2\) production and so were excluded.\(^{42,43}\) Thrombokinase has been shown to activate platelets and increase thromboxane A\(_2\) synthesis\(^ {44}\) so patients who had received thrombolytic therapy were not studied. Finally, aspirin or other nonsteroidal anti-inflammatory drugs, which inhibit platelet thromboxane A\(_2\) synthesis, could theoretically upregulate TXA\(_2\)/PGH\(_2\) receptor numbers by lowering tonic levels of thromboxane A\(_2\). Therefore, patients who had taken these agents before admission were also excluded. At the time of the convalescent restudy, all myocardial infarction patients were taking aspirin. It might be anticipated that this would lead to an increase in receptor number, but instead, the myocardial infarction subjects had a decrease in number to normal values. Thus, it appears that the reversion to normal platelet TXA\(_2\)/PGH\(_2\) receptor numbers is due to stabilization of coronary disease rather than to aspirin therapy.

**Study Limitations**

There are at least two limitations to this study. The first is the potential of medications to influence the results. It was not ethical to withhold medications from acute myocardial infarction or unstable angina patients. In this regard the four patients admitted to the ICU with chest pain who subsequently had normal coronary arteriograms served as an important control group since they were treated with the same types of medications as the acute myocardial infarction and unstable angina patients. The \(K_d\) and \(B_{\text{max}}\) values for this group were not significantly different from those of the control subjects who took no medications. Therefore, the observed differences in \(B_{\text{max}}\) do not appear to be secondary to medications. A second limitation is the relatively small number of subjects in the patient groups. However, since the \(B_{\text{max}}\) values in the acute myocardial infarction group for six of the nine patients were greater than those of any of the subjects in the other study groups, it is anticipated that these differences would still be seen with a larger number of study subjects.

The significance of the increased number of platelet TXA\(_2\)/PGH\(_2\) receptors and the associated changes in platelet function in patients with acute myocardial infarction is unclear. However, given the constellation of platelet activation and increased thromboxane A\(_2\) synthesis in the setting of ischemic coronary artery syndromes, these observations are worthy of further investigation. They also raise the possibility that TXA\(_2\)/PGH\(_2\) receptor antagonists may be beneficial in acute ischemic coronary artery syndromes.

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