Prevention of Reoccluding Platelet-Rich Thrombi in Canine Femoral Arteries With a Novel Peptide Antagonist of Platelet Glycoprotein IIb/IIIa Receptors

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The composition of an evolving arterial thrombus may be a determinant of how effectively pharmacologic agents prevent reocclusion after initially successful thrombolysis. In this study, reoccluding platelet- or fibrin-rich thrombi as delineated by scanning electron microscopy were produced selectively in the femoral arteries of dogs with the use of electrically induced vascular injury or implantation of copper wire, respectively. Initial thrombolysis after intravenous infusion of tissue-type plasminogen activator (1 mg/kg over 30 minutes) was less frequent in the preparation producing platelet-rich thrombi than in that producing fibrin-rich thrombi (lysis in 19 of 24 versus 18 of 18, p=0.06). In dogs with initial arterial recanalization, intravenous infusion of arginine-glycine-aspartate-O-methyltyrosine amide (RGDY), which competes with fibrinogen for binding to platelet glycoprotein IIb/IIIa receptors, prevented reocclusion caused by recurrence of platelet-rich thrombi in six of six dogs within 90 minutes; reocclusion occurred in five of seven saline-infused control dogs (p=0.02). RGDY was only partially effective in preventing reocclusion caused by recurrence of fibrin-rich thrombi (reocclusion in three of six versus five of six controls, p=0.54). Similar results were obtained with aspirin in both preparations. At least 98% of platelet aggregation induced ex vivo by collagen was inhibited by either RGDY or aspirin. In contrast with aspirin, however, platelet function returned to normal within 1 hour after discontinuation of RGDY. Thus, the relative proportions of platelets or fibrin incorporated into thrombi influence the efficacy of both tissue-type plasminogen activator for inducing thrombolysis and antiplatelet agents for preventing reocclusion. RGDY is a potent, short-acting inhibitor of platelet aggregation that effectively prevents reocclusion under conditions in which platelet deposition predominates. (Circulation 1989;80:1775–1782)

Reocclusion of coronary arteries recanalized with thrombolytic agents occurs in approximately 19% of patients during treatment for acute myocardial infarction. Although continuing platelet activation and fibrin accretion at a site of vascular injury are two mechanisms postulated to precipitate reocclusion, the role of each is not well defined. The composition of reoccluding thrombi may be similar to that observed after persistent arterial thrombosis, that is, there may be a platelet-rich mass overlying the damaged vessel wall contiguous with a meshwork of fibrin and blood cells.

Because the proportions of fibrin and platelets in reoccluding thrombi may vary, it is important to determine the efficacy of agents with the potential to prevent reocclusion under experimental conditions that influence the relative amounts of fibrin and platelets in thrombi. Accordingly, we modified two preparations that were partially characterized previously, one in which injury to the arterial endothelium was induced by anodal current resulting in a platelet-rich thrombus and a second one developed in our laboratory in which an intraluminal coil of copper wire was used to produce a relatively

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fibrin-rich thrombus.7 The goals of this study were to morphologically characterize the reoccluding thrombi produced by each preparation in the femoral arteries of dogs after initial pharmacologic thrombolysis and to determine whether inhibition of platelet function could prevent reocclusion in either or both preparations. Platelet function was inhibited with the use of arginine-glycine-aspartate-O-methyltyrosine amide (RGDY) (SC-46749, Monsanto/Searle), a novel peptide analog of the adhesive protein recognition sequence Arg-Gly-Asp that binds to platelet glycoprotein (GP) IIb/IIIa receptors, and with aspirin. These diverse agents were selected because they inhibit different pathways that may be involved in platelet activation in vivo.

**Methods**

**Animal Preparations**

Procedures involving animals were conducted according to the guiding principles of the American Physiological Society and were approved by the Committee on the Humane Care of Laboratory Animals at Washington University. Forty-two mongrel dogs weighing 4–9 kg were anesthetized with intravenous sodium pentobarbital (30 mg/kg), intubated, and ventilated with oxygen-enriched room air. Polyethylene catheters were placed in both external jugular veins for infusion of agents and withdrawal of blood samples. In some dogs, a catheter was placed in a common carotid artery for measurement of blood pressure. Patency of the catheters was maintained without heparin by frequent arterial flushes or continuous venous infusion of 0.9% NaCl. Esophageal body temperature was maintained near 37°C with the use of a heating pad and a heat lamp. Venous pH was maintained within the physiologic range by adjustment of ventilation. The left femoral artery of each dog was exposed distal to the saphenous branch, and side branches were ligated. A Doppler flow probe was placed proximal to the intended site of thrombosis.

**Induction of Thrombosis**

Thrombosis was induced either by applying anodal current to a transmural electrode resulting in vascular injury or by implanting a coil of copper wire distal to the Doppler probe. The electrode method was modified from the technique of Romson et al.8 Briefly, the electrode consisted of the tip (4–5 mm) of a 23-gauge needle crimped on the bared end of 30-gauge Teflon-insulated silver wire (A-M Systems, Everett, Washington). To minimize leakage of current to the perivascular tissue, a polyethylene tubing sleeve was positioned over the needle-wire tubing connection. The needle was inserted obliquely approximately 3 mm into the arterial lumen and stabilized by sutures through the tissue on either side of the vessel. Thrombosis was initiated by connecting the electrode in series with the positive terminal of a 9-V battery, an ammeter, and a 50-kΩ potentiometer. A ground wire was sutured to the subcutaneous tissue to complete the circuit. Current (300 μA) was applied through the electrode until a cyclic pattern of partial occlusion and spontaneous recanalization was evident from the Doppler flow tracing analogous to that described by Folts et al,8 who showed in their preparation that the pattern was caused by intermittent accumulation and abrupt dislodgement of platelet thrombi.

The copper wire method was adapted from a technique developed previously in our laboratory7 and involved wrapping copper wire (0.5-mm diameter) in a loose spiral around a 20-gauge needle. The needle was removed and, at one end, the wire was bent parallel with the long axis of the coil and filed to a point to more easily penetrate the vessel. The wire was pushed through the vessel wall and rotated until approximately three complete turns of the coil were present in the lumen.

**Experimental Protocol**

Thirty minutes after the occurrence of complete thrombosis verified by zero-flow velocity, human recombinant tissue-type plasminogen activator (t-PA) (Activase, Genentech, South San Francisco, California) was infused intravenously at a dose of 1 mg/kg (1.2×10⁶ IU/mg) over 30 minutes with 10% of the total dose infused as a bolus during the first 2 minutes. This regimen resulted in a peak t-PA–antigen level in plasma averaging 2,250 ng/ml (n=29) and only a modest, 11% decrease in plasma fibrinogen (n=31) compared with baseline values. Successful recanalization was defined as a return of average flow velocity to at least 50% of the baseline value.

As an adjunct to thrombolysis, dogs with vascular injury–induced or copper wire–induced thrombosis were randomly selected before the study to receive either normal saline (infused intravenously as a control), RGDY, or aspirin. RGDY was infused intravenously at a rate of 4 mg/kg/min, a dosage that totally inhibits platelet aggregation ex vivo in dogs,9 beginning at the end of the infusion of t-PA and continuing for 90 minutes. A water-soluble form of aspirin, lysine-acetylsalicylic acid (Lorox Pharmaceuticals, Skokie, Illinois), was injected intravenously (30 mg/kg acetylsalicylate) over a 2-minute interval beginning 5 minutes before the end of the infusion of t-PA. Average flow velocity was monitored continuously, and the occurrence of cyclic partial occlusions or complete reocclusion (defined as zero-flow velocity persisting for at least 1 minute) was noted for 90 minutes after the end of the infusion of t-PA.

To determine the composition of recurrent thrombi induced by electrical vascular injury and the intraluminal copper wire, arteries that reocluded during the 90-minute observation period were ligated proximal and distal to the thrombus. The isolated arterial segment was excised and fixed for scanning electron microscopy by immersion in 1% parafo-
maldehyde and 2% glutaraldehyde in 80 mM cacodylate buffer, pH 7.4, containing 2 mM CaCl₂.

Platelet Aggregometry

Blood samples for platelet aggregation studies were collected before the administration of antiplatelet agents (or saline) and 45–90 minutes after the infusion of t-PA had been stopped. An additional sample was collected 30–60 minutes after the end of the infusion of RGDY. Blood was withdrawn from the jugular vein into a plastic syringe containing one part 3.8% trisodium citrate to nine parts blood. Platelet-rich plasma (PRP) was obtained by centrifugation of the citrated blood at 70g for 10 minutes at room temperature. After removal of the PRP, the remaining sample was centrifuged at 1,500g for 10 minutes to obtain platelet-poor plasma (PPP). Platelet counts in PRP were determined by hemocytometry and adjusted to a final concentration of 2.25×10⁵/μl with autologous PPP. Aggregation was measured turbidimetrically with an aggregometer (Payton Associates, Buffalo, New York). A 450-μl aliquot of the count-adjusted PRP was warmed to 37°C in a silanized cuvette and stirred continuously at 900 rpm. After equilibration for 1 minute, bovine tendon collagen (Helena Laboratories, Beaumont, Texas) was added and aggregation was recorded as an increase in light transmission with reference to that of PPP representing 100% transmission. The minimal (threshold) concentration of collagen resulting in an irreversible increase in light transmission of greater than 50% was determined with final collagen concentrations of 0.7, 1.4, 2.8, 5.6, 11.1, and 22.2 μg/ml. With the use of the same threshold concentration of collagen determined at baseline, percent inhibition of platelet aggregation associated with infusion of saline or antiplatelet agents was calculated as the difference in values for maximal light transmission in samples acquired before and during infusions. Blood samples obtained during infusion of RGDY were collected in freshly prepared citrated tubes containing 100 μM (final concentration) of the aminopeptidase inhibitor bestatin (Sigma Chemical, St. Louis, Missouri) to prevent degradation of RGDY during the platelet aggregation studies. Bestatin had no effect on the aggregation response to collagen per se.

Microscopy

After fixation, arterial segments from four dogs with vascular injury–induced reoccluding thrombi and four dogs with copper wire–induced reoccluding thrombi were prepared for scanning electron microscopy. The vessel was bisected longitudinally to expose the thrombus in situ surrounding the copper wire or needle. The tissue was rinsed in 80 mM cacodylate buffer (pH 7.4), postfixed for 1 hour in 1% osmium tetroxide in cacodylate buffer, dehydrated in a series of increasing concentrations of ethanol, and critical-point dried with Peldri II (Ted Pella, Redding, California) overnight at 23°C in a fume hood. Specimens were sputter-coated with chrome followed by gold-palladium (60:40) and examined with a JEOL 840 scanning electron microscope. Central, proximal, and distal regions of each thrombus were assigned a score for their relative composition of platelets and fibrin between 1 (0% platelets, 100% fibrin) and 5 (100% platelets, 0% fibrin).

Statistical Analysis

Fisher’s exact test was used for the comparison of the incidence of recanalization and reocclusion between groups. Analysis of variance was used to assess differences in physiologic variables between groups. Student’s t test was used to assess differences in histologic scores between preparations. A Wilcoxon signed-rank test was used to analyze differences in the frequency of partial occlusions because of the large number of zero values. A p value less than or equal to 0.05 was considered significant.

Results

Thrombolysis and Rethrombosis After Vascular Injury–Induced Thrombosis

Among the 24 dogs in which stable thrombotic occlusion was induced, five (20.8%) failed to exhibit recanalization after infusion of t-PA (Table 1). Among the remaining 19 dogs in which recanalization was successful, the time of onset of occlusion, time of onset of recanalization, and extent of recanalization assessed with the Doppler probe did not differ significantly in the three adjunct treatment groups (Table 2). Reocclusion occurred within 90 minutes in five of seven control dogs, but occurred in none given RGDY. Furthermore, RGDY significantly decreased the frequency of cyclic partial occlusions. Aspirin yielded similar results (Table 2). Thus, antiplatelet agents prevented reocclusion in all of the dogs in which thrombi were induced by vascular injury (n=12, p=0.002, versus control).

Thrombolysis and Rethrombosis After Copper Wire–Induced Thrombosis

In contrast to results with the vascular injury preparation, all 18 dogs in which stable thrombotic occlusion was obtained after implantation of a copper wire exhibited recanalization of the occluded artery after infusion of t-PA (Table 1). The time of onset of occlusion, time of onset of recanalization,
and extent of recanalization were not significantly different among dogs in the three adjunct treatment groups (Table 3). Although the incidence of complete reocclusion and frequency of cyclic partial occlusions were decreased modestly by RGDY or aspirin, differences from control were not significant (Table 3). Recanalization occurred in five of 12 dogs (42%) in which thrombi were induced with the copper wire despite treatment with antiplatelet agents ($p=0.15$, versus control), a significantly higher incidence than was observed in the vascular injury preparation ($p=0.04$).

**Hemodynamics and Hematology**

Infusion of RGDY was associated with a modest decrease in mean arterial blood pressure that averaged $15\pm7\%$ (SD) after 90 minutes ($n=3$; range, 7–25%). A concomitant but less marked increase in heart rate (8%) was observed also. The percent change of hematocrit throughout the study was not significantly different in dogs given RGDY or aspirin compared with control dogs (data not shown).

**Platelet Aggregation Ex Vivo**

At least 98% of platelet aggregation induced ex vivo by collagen was inhibited by both RGDY and aspirin compared with a decrease of less than 10% in control dogs (Figure 1). The median threshold concentration of collagen was 5.6 μg/ml in control dogs ($n=11$) and more than 22.2 μg/ml in dogs given either RGDY ($n=9$) or aspirin ($n=10$). Two of the 11 control dogs had threshold concentrations of collagen greater than or equal to 11.1 μg/ml compared with nine of nine dogs and nine of 10 dogs given RGDY and aspirin, respectively.

The platelet aggregation response returned to normal within 1 hour after discontinuation of the infusion of RGDY (Figure 2).

**Microscopic Analysis of Thrombi**

Scanning electron microscopy revealed that the reoccluding thrombi after electrically induced vascular injury comprised a central region (near the electrode) rich in activated platelets contiguous proximally and distally with a more fibrin-rich matrix containing platelets and erythrocytes (Figure 3, Table 4). In contrast, reoccluding thrombi induced with the copper wire were more homogeneous throughout their length and consisted primarily of fibrin with interspersed platelets and erythrocytes (Figure 4, Table 4).

Thrombi induced by electrical current that failed to lyse after the infusion of t-PA were studied, as well. Grossly, they appeared as a grayish-white mass that filled the arterial lumen. Scanning electron microscopy showed the proximal portion of

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**Table 2. Characteristics of Femoral Arterial Occlusion, Recanalization, and Reocclusion After Electrically Induced Vascular Injury**

<table>
<thead>
<tr>
<th>Adjunctive agent</th>
<th>Occlusion-time of onset after current (min)</th>
<th>Recanalization</th>
<th>Reocclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time of maximal flow after start of infusion of t-PA (min)</td>
<td>Maximal flow velocity (% of baseline)</td>
<td>Frequency of partial occlusions (n/hr)</td>
</tr>
<tr>
<td>Saline (control) (n=7)</td>
<td>69.9±24.4</td>
<td>22.9±9.4</td>
<td>95.1±9.5</td>
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<tr>
<td>RGDY (n=6)</td>
<td>80.2±38.3</td>
<td>27.0±8.8</td>
<td>98.0±4.9</td>
</tr>
<tr>
<td>Aspirin (n=6)</td>
<td>90.2±58.0</td>
<td>30.5±3.0</td>
<td>94.2±10.9</td>
</tr>
<tr>
<td>All RGDY or aspirin (n=12)</td>
<td>85.2±47.2</td>
<td>28.7±6.5</td>
<td>96.1±8.3</td>
</tr>
</tbody>
</table>

Values are given as mean±SD.

$^*p=0.02$ versus control.

$^\dagger p=0.04$ versus control.

$^\ddagger p=0.01$ versus control.

$^\S p=0.002$ versus control.

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**Table 3. Characteristics of Femoral Arterial Occlusion, Recanalization, and Reocclusion After Implantation of a Copper Wire**

<table>
<thead>
<tr>
<th>Adjunctive agent</th>
<th>Occlusion-time of onset after wire implant (min)</th>
<th>Recanalization</th>
<th>Reocclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Time of maximal flow after start of infusion of t-PA (min)</td>
<td>Maximal flow velocity (% of baseline)</td>
<td>Frequency of partial occlusions (n/hr)</td>
</tr>
<tr>
<td>Saline (control) (n=6)</td>
<td>16.5±18.8</td>
<td>23.3±13.2</td>
<td>98.5±2.5</td>
</tr>
<tr>
<td>RGDY (n=6)</td>
<td>25.3±31.6</td>
<td>22.0±13.7</td>
<td>90.0±11.4</td>
</tr>
<tr>
<td>Aspirin (n=6)</td>
<td>28.5±34.3</td>
<td>18.8±19.8</td>
<td>86.2±22.1</td>
</tr>
<tr>
<td>All RGDY or aspirin (n=12)</td>
<td>26.9±31.4</td>
<td>20.4±16.3</td>
<td>88.1±16.9</td>
</tr>
</tbody>
</table>

Values are given as mean±SD.
these thrombi to be similar in composition to the core of the reoccluding thrombus formed with the same preparation, that is, they were composed almost totally of platelets (Figure 5).

Discussion

Several experimental animal preparations have been used to assess the efficacy of agents in vivo for induction of thrombolysis and prevention of rethrombosis in arteries. Few studies have systematically characterized thrombi morphologically, however, and agents generally have not been tested under diverse conditions that produce thrombi of disparate composition. Results of this study show that the efficacy of both t-PA (in eliciting thrombolysis) and antiplatelet agents (in preventing rethrombosis) is affected by conditions giving rise to morphologically distinct thrombi. Under conditions that produce platelet-rich thrombi, recanalization with t-PA is impaired (Table 1), and reocclusion after successful thrombolysis is prevented by antiplatelet agents (Table 2). In contrast, under conditions producing fibrin-rich thrombi, recanalization occurs universally (Table 1), yet reocclusion is frequent even in the presence of antiplatelet agents (Table 3). These results suggest that potential pharmacologic
TABLE 4. Morphologic Score of Reoccluding Thrombi

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Thrombus region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Central</td>
</tr>
<tr>
<td>Vascular injury-induced thrombosis (n=4)</td>
<td>4.8±0.3</td>
</tr>
<tr>
<td>Copper wire--induced thrombosis (n=4)</td>
<td>2.3±0.8†</td>
</tr>
</tbody>
</table>

Values are given as mean±SD.

*1, 0% platelets, 100% fibrin; 2, 25% platelets, 75% fibrin; 3, 50% platelets, 50% fibrin; 4, 75% platelets, 25% fibrin; 5, 100% platelets, 0% fibrin.

†p=0.002 versus vascular injury--induced thrombosis.

approaches for induction of thrombolysis and prevention of rethrombosis should be assessed under selected conditions that elicit reproducible thrombi composed of disparate proportions of platelets and fibrin analogous to those likely to be encountered in specific clinical circumstances. Furthermore, our data indicate that results of studies in experimental animals and perhaps patients should be evaluated with reference to the composition of occluding thrombi.

The experimental animal preparations used for induction of thrombosis in this study were not designed to mimic the pathophysiology of arterial thrombosis in human subjects, but rather to elicit predominantly platelet- or fibrin-rich thrombi for evaluation of specific therapeutic strategies under defined conditions. The methods used, application of anodal current to the endothelium and implantation of a copper wire, share a common mechanism of action in that both impart a positive charge to the surrounding environment. Positive charge attracts circulating blood elements including platelets, which possess a net negative surface charge and are thereby normally repelled by the negatively charged, intact endothelial surface. The differences in composition of thrombi in the two preparations probably relate to differences in the extent of intimal injury induced as well as to the three-dimensional spatial relations of the thrombogenic surfaces involved. Thermal injury induced by direct current probably exposes basement-membrane collagen and other prothrombotic constituents (e.g., tissue factor) resulting in massive activation of platelets as seen by scanning electron microscopy (Figure 3). Although

![Figure 4](http://circ.ahajournals.org/)

**Figure 4.** Scanning electron micrograph of a reoccluding thrombus formed after successful recanalization in a femoral artery containing copper wire implanted previously. Low-magnification inset shows wire in place with adjacent thrombus (inset). Higher magnification shows thrombus to be composed mainly of fibrin strands with some associated platelets and erythrocytes.
the implanted copper wire likely exerts less effect on the endothelium, its three-dimensional nature in the vessel lumen provides multiple thrombogenic surfaces for platelet attachment that are bridged by a fibrin meshwork, as observed microscopically (Figure 4). As a result, thrombi induced by the copper wire were relatively fibrin-rich compared with those induced by the electrode.

The resistance of some thrombi formed after electrode-induced vascular injury to lysis by t-PA was associated with the occurrence of a proximal region made up almost totally of platelets (Figure 5). Such a "cap" of platelets could be resistant to fibrinolysis and might effectively inhibit penetration of t-PA into the fibrin matrix of the thrombus. Analogous morphology might contribute to the observed failure of thrombolytic drugs to achieve coronary thrombolysis in some patients. Similar resistance of experimentally induced platelet-rich arterial thrombi to lysis with t-PA has been reported recently.16

Several studies have shown that platelet activation is likely to play a key role in the recurrence of thrombosis after initially successful thrombolysis.11-14,17 The platelet membrane GP IIb/IIIa receptors are attractive targets for inhibition of platelet aggregation because they mediate binding of fibrinogen, an obligatory component of normal aggregation in vivo.18 These receptors also mediate binding of von Willebrand factor and fibronectin, which may participate in platelet adhesion to the subendothelium and subsequent spreading.18 Association of several different adhesive proteins with the same receptor complex appears to result from recognition of a common amino acid sequence, Arg-Gly-Asp (RGD), in each. Thus, interaction of these proteins with GP IIb/IIIa receptors and subsequent platelet aggregation have been inhibited competitively by monoclonal antibodies to GP IIb/IIIa receptors19 and by naturally occurring and synthetic peptides containing the RGD sequence.20-22 In this study, RGDY was selected for its fourfold-higher antiplatelet potency compared with Arg-Gly-Asp-Ser, found naturally in fibrinogen and fibronectin.9 RGDY inhibited platelet function ex vivo completely but reversibly (Figures 1 and 2) and prevented reclosure under conditions that produced platelet-rich thrombi (Table 2). The rapid return of normal platelet function after discontinuation of RGDY compared with the irreversible inhibition induced by aspirin23 may be advantageous under certain circumstances.

Results with RGDY in the platelet-rich preparation corroborate previous studies showing that monoclonal antibodies to platelet GP IIb/IIIa receptors prevent rethrombosis after thrombolysis in a canine preparation of coronary arterial damage superimposed on high-grade stenosis.14,17 However, the
platelet inhibitory effect of antibodies is not short lived.19

The results with this novel peptide antagonist of GP IIb/IIIa receptors suggest that it may provide a short-acting, useful approach for adjunctive therapy designed to prevent reocclusion after pharmacologic thrombolysis. Our finding that RGDS was only partially effective in preventing reocclusion induced by fibrin-rich thrombi indicates that other adjuncts, perhaps incorporating antithrombin agents, may be required, as well. Use of experimental preparations, such as those described in this study, that induce thrombi with consistent but diverse composition and that can be implemented simultaneously in the same dog should facilitate direct comparison of the responses of different kinds of thrombi to promising adjunctive treatment regimens.

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References


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