Mediation of reocclusion by thromboxane A2 and serotonin after thrombolysis with tissue-type plasminogen activator in a canine preparation of coronary thrombosis

PAOLO GOLINO, M.D.,* JULIET H. ASHTON, PH.D., PIA GLAS-GREENWALT, M.D., JANICE McNATT, L. MAXIMILIAN BUJA, M.D., AND JAMES T. WILLERSON, M.D.

ABSTRACT Human recombinant tissue-type plasminogen activator (rt-PA) has been shown to be an effective and safe agent for coronary thrombolysis in patients with acute myocardial infarction. However, thrombolysis is associated with a high rate of acute reocclusion after discontinuation of rt-PA. The goals of the present study were to assess whether reocclusion after thrombolysis is caused by intracoronary platelet aggregation and to determine the role of thromboxane A2 (TxA2) and serotonin (5HT) in mediating this phenomenon. Accordingly, coronary thrombosis was induced in anesthetized, open-chest dogs by insertion of a copper coil into the left anterior descending coronary artery (LAD). LAD blood flow was monitored throughout the experiment by means of a Doppler flow probe placed proximally to the coil. Thrombolysis was achieved with rt-PA (0.05 mg/kg bolus + μg/kg/min infusion) in 23 ± 3 min. rt-PA was then discontinued and each animal received a bolus of heparin (150 U/kg) every hour. Reperfusion was followed by repeated cycles of gradual occlusions followed by spontaneous restorations of blood flow (cyclic flow variations, CFVs) before a persistent occlusion recurred. In control dogs (n = 6), heparin alone did not prevent CFVs and reocclusion time was 25 ± 4 min. Administration of an intravenous bolus of 0.2 ± 0.06 mg/kg SQ29548, a TxA2/prostaglandin H2-receptor antagonist, and an intravenous bolus of 0.2 ± 0.04 mg/kg ketanserin, a 5HT2-receptor antagonist, completely abolished CFVs in six of six dogs and reocclusion time was greater than 158 ± 14 min (p < .01). Administration of a bolus of SQ29548 (0.2 ± 0.05 mg/kg) and LY53857, a different 5HT2-receptor antagonist (0.1 ± 0.02 mg/kg), followed by continuous infusion of both drugs (0.2 mg/kg and 0.1 mg/kg/hr over 3 hr, respectively) completely abolished CFVs and prevented reocclusion throughout the experimental period in five of five dogs. SQ29548 alone prevented reocclusion in only two of five dogs, ketanserin did not prevent reocclusion in any of four dogs, and LY53857 was effective in only one of four dogs. We conclude that reocclusion after thrombolysis may occur despite heparin therapy and is, at least in part, mediated by TxA2 and 5HT in this preparation of coronary thrombosis. TxA2- and 5HT2-receptor antagonists given together prevent and/or markedly delay reocclusion after thrombolysis.


CORONARY THROMBOLYSIS has recently received great attention for its potential reduction of the extent of necrosis after myocardial ischemia. Thrombolysis can be accomplished by infusion of streptoki-
with intravenous streptokinase when the former is administered 4 to 5 hr after symptom onset and that reperfusion is accomplished with much less pronounced systemic fibrinogen depletion. However, a major problem has emerged from these initial trials; that is, despite a reperfusion frequency between 61% and 85%, acute coronary reocclusion developed in 20% to 45% of these patients, even when patients were fully heparinized. Recently, a prolonged maintenance infusion of rt-PA has been shown to decrease the frequency of coronary reocclusion, but this problem is still far from being solved.

Fitzgerald et al., in a recent preliminary report, measured urinary concentrations of 2,3-dinor thromboxane (Tx) B2 (as an index of platelet activation) in patients with acute myocardial infarction undergoing thrombolytic therapy. These authors found a significant increase in the urinary concentration of 2,3-dinor-TxB2 after thrombolysis, which probably reflects a marked platelet activation at the time of reperfusion.

The goal of the present study was to test the hypothesis that intracoronary platelet activation after thrombolysis may lead to reocclusion in spite of adequate anticoagulant therapy. Additionally, we wanted to establish the role played by TxA2 and serotonin (5HT) secreted by platelets in mediating the reocclusion. A third goal of this study was to establish whether activated platelets present in the thrombus can increase the vasomotor tone of the coronary artery through a release of vasoconstricting substances, such as TxA2 and 5HT.

Methods

Experimental preparation. The study was performed in 37 open-chest mongrel dogs of 25 to 40 kg in body weight. Dogs were anesthetized with sodium pentobarbital, 30 mg/kg iv, intubated, and ventilated with room air through a Harvard respirator. Polyethylene catheters were inserted through the right carotid artery and the jugular vein for monitoring systemic arterial pressure and administration of fluids and drugs, respectively. A left thoracotomy was performed at the fifth intercostal space and the heart was suspended in a pericardial cradle. A segment of the left anterior descending artery (LAD) was carefully isolated from the surrounding tissue and a pulsed Doppler flow probe was placed around it. Baseline hemodynamics, including those of heart rate, systemic blood pressure, and mean and phasic LAD blood flow velocity were recorded on a four-channel recorder (Hewlett-Packard Co., model 9270). Then, through a left carotid arterial cutdown, a No. 7F Amplatz L1 left coronary catheter (Cordis Corp., Miami) was positioned into the left coronary ostium under fluoroscopic control. An 0.025 inch Teflon-coated guide wire (Cook Co., Bloomington, IN) was advanced in the LAD, and the catheter was removed. A copper coil of appropriate size made by wrapping a 24-gauge uncoated copper wire around needles of different sizes and this coil was positioned in the LAD immediately distal to the Doppler flow probe over the guide wire with the use of a flexible catheter tubing. Care was taken to make sure that no side branches originated from the LAD segment between the flow probe and the copper coil. The guidewire was removed and lidocaine (2 mg/kg) was given as an intravenous bolus followed by a 1 mg/min infusion.

Reocclusion protocol. Hemodynamic measurements were repeated and, after a 15 min waiting period to document persistence of the thrombus, the dogs received a bolus of 0.05 mg/kg of human rt-PA (Knoll Pharmaceuticals Co., Whippany, NJ), followed by an infusion of 5 μg/kg/min for up to 90 min or until the thrombus was dissolved. This dose was chosen because it is associated with a high rate of reperfusion, i.e., greater than 80%, and a minimal depletion of plasma fibrinogen. When flow through the LAD was reestablished (about 70% of the control value), rt-PA infusion was discontinued, and all dogs received a bolus of heparin at the dose of 150 U/kg. Heparin administration was repeated every hour. The animals were then randomly assigned to one of six groups. Six dogs, receiving no further treatment, were controls (group I); six dogs received an intravenous bolus of 0.2 ± 0.06 mg/kg SQ29548 (Squibb Pharmaceuticals, Princeton, NJ), a potent and selective TxA2/prostaglandin H2-receptor antagonist, and an intravenous bolus of 0.2 ± 0.04 mg/kg of ketanserin, a 5HT-receptor antagonist (group II-A); five dogs received an intravenous bolus of SQ29548 (0.2 ± 0.05 mg/kg) and LY385787 (Eli Lilly Pharmaceuticals Co., Indianapolis) (0.1 ± 0.02 mg/kg), a different, selective 5HT-receptor antagonist, followed by an infusion of both drugs at doses of 0.2 and 0.1 mg/kg/hr, respectively, over a 3 hr period (group II-B); five dogs received an intravenous bolus of SQ295458 only (group III); and eight dogs were treated with an intravenous bolus (0.2 ± 0.04 mg/kg) of ketanserin (group IV-A, n = 4) or LY53857 (0.1 ± 0.02 mg/kg) (group IV-B, n = 4). Three dogs died of ventricular fibrillation during the coronary occlusion period and in four other dogs, rt-PA failed to dissolve the thrombus at the end of the 90 min infusion. These dogs were excluded from statistical analysis. Hemodynamics and LAD blood flow were monitored throughout the experiment until reocclusion occurred (in which case the observation period was extended for 30 additional minutes to make sure that the thrombus was persistent) or for up to 3 hr.

Coronary vasoconstriction protocol. To determine whether intracoronary platelet activation during thrombus formation may cause vasoconstriction of large epicardial coronary vessels, the LAD diameter just below the copper coil was measured in five dogs by means of a pair of ultrasonic crystals. The technique and its relative limitations have been described elsewhere. Briefly, a pair of miniature 7 MHz ultrasonic crystals (Triton Technology, San Diego) attached to a Dacron backing was sutured to the adventitia of opposing sides of the LAD just below the copper coil. The LAD diameter was measured continuously with an ultrasonic dimension gauge (Triton Technology, Model 120.2, San Diego). The instrument generates a voltage linearly proportional to the transit time of acoustic impulses traveling at the sonic velocity of ~1.5 × 105 mm/sec between the crystals, thus giving a record of instantaneous external coronary arterial diameter. The internal cross-sectional area was calculated by measurement of the external diameter, the length of the vessel, and its weight. To distinguish a passive decrease in LAD diameter due to a reduction of coronary distending pressure from actual vasoconstriction due to activation of arterial smooth muscle cells, we compared coronary artery dimensions obtained after formation of the thrombus to those recorded during a 10 sec occlusion of the LAD produced by a suture snare placed proximally to the Doppler flow probe. The latter measurement was made early in the experiments before the insertion of the coil.

Fibrinolytic studies. Venous blood samples (4.5 ml) for measurement of fibrinogen, plasminogen, α2-antiplasmin,
fibrinogen degradation products (FDPs), and partial thromboplastin time were collected in 0.5 (0.1M) sodium citrate before insertion of the copper coil and immediately after stopping the rt-PA infusion. Samples were placed immediately on ice and promptly centrifuged at 3000 g for 10 min. To inhibit activation of the fibrinolytic system in vitro, the plasma was then transferred to polyethylene test tubes supplemented with aprotinin at a final concentration of 200 kallikrein inhibitor units/ml plasma. All plasma samples were frozen at −20°C until assay.

**Statistical analysis.** Results are expressed as the mean ± SEM. Analysis of variance was used for multiple comparisons among groups. For comparisons of hemodynamics, LAD blood flows, and fibrinolytic profiles among groups, a two-way analysis of variance for a design with repeated measures was used.

**Results**

**Induction of LAD thrombi and thrombolysis.** After positioning the copper coil in the LAD, a persistent coronary thrombus developed in 2 ± 1 min (range 0 to 12 min). This was associated with cyanosis and systolic bulging of the portion of myocardium supplied by the LAD. Three dogs died during the LAD occlusion of ventricular fibrillation and their data were excluded from the study. rt-PA given as a bolus (0.05 mg/kg) followed by an infusion of 5 µg/kg/min successfully lysed the coronary thrombi in approximately 90% of the animals (37 of 41 dogs) in 23 ± 2 min. The four dogs in whom rt-PA failed to produce reperfusion were not included in the study. The rt-PA infusion was maintained until the LAD blood flow velocity was approximately 70% of the control value.

**LAD blood flow and hemodynamics.** Before placement of the copper coil into the coronary artery, LAD blood flow showed a stable and constant pattern (figure 1, A). Coronary blood flow approached zero after intracoronary positioning of the coil and thrombus formation (figure 1, B). After successful thrombolysis (figure 1, C), and with the coil still in place, LAD blood flow showed a typical pattern characterized by gradual decreases of flow to almost zero values, followed by spontaneous restorations of blood flow (cyclic flow variations, CFVs) (figure 1, D). This pattern was observed for several minutes until permanent reocclusion occurred (figure 1, D). Reocclusion was defined as a very low LAD flow state (i.e., < 1% of the control value) that lasted for 30 min or longer. In group I dogs, heparin alone (150 U/kg) given at the moment of reperfusion did not prevent the subsequent development of CFVs. Reocclusion time, defined as the time elapsed between the onset of reperfusion and the occurrence of persistent reocclusion, was 25 ± 4 min (table 1). In group II-A dogs, the addition of a bolus of both SQ29548 and ketanserin to heparin was very effective in abolishing CFVs and preventing reocclusion in six of six dogs (figure 2). Four dogs in this group had stable LAD flow until the end of the experiment, i.e., 180 min after discontinuation of rt-PA. In the other two dogs reocclusion occurred 117 and 112 min after reperfusion. Therefore, the reocclusion time for dogs in this group was greater than 158 ± 14 min (p < .01 vs group I dogs; table 1). In all group II-B dogs, the administration of a bolus of SQ29548 and LY53857 followed by a continuous infusion of both drugs resulted in a stable LAD flow pattern throughout the experimental period, i.e., 180 min (table 1). Administration of heparin and either SQ29548, ketanserin, or LY53857 (groups III, IV-A, and IV-B, respectively) was much less protective in abolishing CFVs and preventing reocclusion than the administration of the two receptor antagonists together (table 1).

**FIGURE 1.** Representative tracing of hemodynamic data obtained from a control dog. A, Before placement of the copper coil into the LAD, coronary blood flow shows a stable and constant pattern. B, After positioning the coil, LAD blood flow decreased to almost unrecordable values. C, During rt-PA infusion, the intracoronary thrombus was progressively lysed and blood flow through the LAD was restored. D, After discontinuation of the infusion of rt-PA, despite the administration of 150 U/kg of heparin, LAD blood flow showed a typical pattern of gradual decreases of flow to almost zero followed by spontaneous restorations of blood flow until a reocclusion occurred.

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TABLE 1
Reocclusion time and partial thromboplastin time (PTT) in dogs after thrombolysis with rt-PA

<table>
<thead>
<tr>
<th>Reocclusion time (min)</th>
<th>PTT (min)</th>
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<tbody>
<tr>
<td>Group I</td>
<td>Baseline</td>
</tr>
<tr>
<td>Group II-A</td>
<td>&gt;158 ± 14B</td>
</tr>
<tr>
<td>Group II-B</td>
<td>&gt;180</td>
</tr>
<tr>
<td>Group III</td>
<td>86 ± 38</td>
</tr>
<tr>
<td>Group IV-A</td>
<td>21 ± 3</td>
</tr>
<tr>
<td>Group IV-B</td>
<td>61 ± 39</td>
</tr>
</tbody>
</table>

Reocclusion time was defined as the time elapsed between reperfusion and the occurrence of a persistent reocclusion (i.e., >30 min). PTT was measured at baseline (i.e., before insertion of the coil into the LAD) and 3 hr after reperfusion or at the moment of reocclusion. See text for details.

*Numbers in parentheses indicate numbers of dogs in which the treatment completely abolished CFVs after thrombolysis.

p < .05 vs group I, III, IV-A, and IV-B dogs by analysis of variance test.

Hemodynamic findings in this study are summarized in table 2. Systemic arterial blood pressure significantly declined in group II and group III dogs during the experiment. The same trend was shown by the only dog in group IV-B whose LAD blood flow was stable to the end of the experimental period (table 1). This finding is not surprising if considering that in open-chest dogs receiving rt-PA, heparin, and antiplatelet drugs, some bleeding from surgical wounds occurs.

Coronary vasoconstriction. To demonstrate that platelet activation during thrombus formation can lead to coronary vasoconstriction, five dogs were instrumented with a pair of ultrasonic crystals sutured on the adventitia of the LAD just below the copper coil. Intracoronary development of thrombus was associated with a striking decrease in LAD diastolic cross-sectional area. To differentiate changes in LAD diameter merely due to a reduction in LAD distending pressure from those caused by enhanced contraction of arterial smooth muscle cells, LAD dimensions obtained when the thrombus was occluding the artery were compared with the same variables during a complete LAD occlusion induced by means of a suture snare placed proximal to the Doppler flow probe before insertion of the copper coil. Occlusion of the LAD by the suture snare caused a reduction of LAD diastolic cross-sectional area of 20 ± 4%, whereas formation of the thrombus was associated with a reduction of LAD cross-sectional area of 48 ± 6% (p < .001, figure 3). In two of five dogs instrumented with the sonar crystals, rt-PA failed to lyse the intracoronary thrombus, one dog died of ventricular fibrillation during the LAD occlusion, and the remaining two dogs were entered in groups III and IV-B, respectively.

Fibrinolytic studies. Results of assays of fibrinogen, plasminogen, α2-antiplasmin, and FDPs are summarized in figure 4. Fibrinogen, plasminogen, and α2-antiplasmin levels decreased with reperfusion, but only modestly (to an average of 85%, 74%, and 69% of preinfusion values, respectively).

Partial thromboplastin times for the different groups at baseline and with immediate reocclusion and after 3 hr of reperfusion are summarized in table 1. The hematocrits for each of the groups studied are listed in table 3.

**FIGURE 2.** Representative tracing of hemodynamic data obtained from a dog treated with SQ29548 and ketanserin. A, Baseline measurements. B, After placement of the copper coil into the LAD and thrombus formation. C, rt-PA administration caused lysis of the thrombus and restoration of blood flow. However, despite administration of 150 U/kg of heparin, LAD blood flow progressively decreased to low values again. D, Intravenous administration of SQ29548 and ketanserin (arrow) promptly restored a normal flow pattern.
TABLE 2

Hemodynamic variables in dogs before and after thrombolysis with rt-PA

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 6)</th>
<th></th>
<th>Group II-A (n = 6)</th>
<th></th>
<th>Group III (n = 5)</th>
<th></th>
<th>Group IV-A (n = 4)</th>
<th></th>
<th>Group IV-B (n = 4)</th>
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<tbody>
<tr>
<td></td>
<td>HR (bpm)</td>
<td>AOM (mm Hg)</td>
<td>PHF (%)</td>
<td>MNF (%)</td>
<td>HR (bpm)</td>
<td>AOM (mm Hg)</td>
<td>PHF (%)</td>
<td>MNF (%)</td>
<td>HR (bpm)</td>
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<tr>
<td>Control</td>
<td>150 ± 3</td>
<td>121 ± 4</td>
<td>100</td>
<td>100</td>
<td>140 ± 3</td>
<td>121 ± 5</td>
<td>100</td>
<td>100</td>
<td>149 ± 4</td>
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<tr>
<td>Occlusion</td>
<td>137 ± 4</td>
<td>113 ± 7</td>
<td>0.3 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>123 ± 9</td>
<td>106 ± 5</td>
<td>0.4 ± 0.3</td>
<td>0.3 ± 0.3</td>
<td>143 ± 4</td>
</tr>
<tr>
<td>Imm ref</td>
<td>139 ± 4</td>
<td>110 ± 7</td>
<td>67 ± 11</td>
<td>75 ± 17</td>
<td>122 ± 9</td>
<td>109 ± 8</td>
<td>85 ± 8</td>
<td>95 ± 12</td>
<td>143 ± 2</td>
</tr>
<tr>
<td>1 hr ref (0)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>141 ± 3</td>
<td>90 ± 12</td>
<td>75 ± 19</td>
<td>77 ± 22</td>
<td>146 ± 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1 hr ref (2)</td>
<td>90 ± 12</td>
<td>75 ± 19</td>
<td>77 ± 22</td>
<td>2 hr ref (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3 hr ref (4)</td>
<td>90 ± 14</td>
<td>74 ± 18</td>
<td>72 ± 19</td>
<td>3 hr ref (2)</td>
</tr>
</tbody>
</table>

HR = heart rate; AOM = aortic mean pressure; PHF = left anterior descending coronary artery peak flow velocity; MNF = left anterior descending coronary artery mean flow velocity.

Numbers in parentheses indicate dogs in which reocclusion did not occur after thrombolysis in the indicated time period.

*p < .05 vs respective control value.

Discussion

Recent studies have shown that rt-PA infused intravenously is an effective and safe agent for coronary thrombolysis in patients with acute myocardial infarction and the administration of rt-PA is associated with less extensive systemic fibrinogenolysis than commonly observed with streptokinase.3-7 However, the benefit of establishing coronary reperfusion is significantly offset by an acute spontaneous reocclusion rate of 20% to 45%, despite full heparinization.3-7 Gold et al.,8 in a recent study, demonstrated that in men with myocardial infarction treated with rt-PA, coronary reocclusion can be prevented by a maintenance infusion of low doses of rt-PA for up to 4 hr. These prolonged infusions, however, caused a significant depletion of circulating fibrinogen of up to 50% of the initial values.

The major findings of the present study are: (1) intracoronary platelet aggregation is responsible for reocclusion after thrombolysis with rt-PA in this experimental preparation of coronary thrombosis despite adequate anticoagulant therapy, (2) TxA2 and 5HT are important mediators of reocclusion and the combination of SQ29548, a TxA2/prostaglandin H2 receptor antagonist, and either LYS3857 or ketanserin, two different 5HT S2-receptor antagonists, prevents and/or markedly delays reocclusion after thrombolytic therapy, and (3) intracoronary activation of platelets during formation of a thrombus causes a marked vasoconstriction of the vessel in which the thrombus is forming.

In this study, a Doppler flow probe was used to monitor coronary blood flow throughout the experimental period. This allowed us to quantify coronary blood flow over time and to demonstrate that in this experimental preparation, LAD blood flow after thrombolysis is not stable, but instead shows a pattern of progressive declines of flow followed by spontaneous

FIGURE 3. Changes in LAD diastolic cross-sectional area in dogs with coronary occlusion induced by means of a suture snare placed around the artery (CAO) and after formation of intracoronary thrombus (thrombus) caused by the copper coil. Each dot represents one dog. See text for details.
increases in flow. These cyclical alterations in coronary blood flow were usually repeated a few times before a persistent coronary artery reocclusion occurred. The dynamic nature of this pattern makes it difficult to be detected by qualitative methods like coronary angiography, especially when angiographic examinations are repeated at relatively long time intervals. Administration of a full dose of heparin did not prevent the occurrence of either CFVs or reocclusion. However, antagonism of the TxA2/prostaglandin H2 and 5HT2 receptors with a bolus of SQ29548 and ketanserin was very effective in abolishing the CFVs after thrombolysis and delaying the occurrence of reocclusion: CFVs were abolished in six of six group II-A dogs and four of them had stable LAD flow throughout the experimental period (3 hr). In the remaining two dogs, the CFVs were also abolished, but reocclusion occurred earlier than 3 hr, probably because of a faster metabolism of the drug(s). In fact, when continuous infusions of LY53857 and SQ29548 were given after the initial bolus (group II-B), the reocclusion time was greater than 180 min in five of five dogs.

Previous studies from our laboratory have demonstrated the importance of 5HT and TxA2 in mediating CFVs in experimentally stenosed, endothelially injured canine coronary arteries. Ketanserin and SQ29548 are very effective antithrombotic agents in vivo in the same experimental preparation. In a recent study, we also demonstrated that intracoronary platelet activation during CFVs causes marked coronary vasoconstriction at sites of platelet attachment. This vasoconstriction appears to be mediated by TxA and 5HT released by activated platelets, since SQ29548 and LY53857 completely reversed the enhanced coronary vasoconstriction. An interesting finding of the present study is that, in this experimental preparation, intracoronary thrombus formation may also trigger marked local vasoconstriction of large epicardial coronary arteries. The reduction in LAD cross-sectional area at the site of placement of the ultrasonic crystals was significantly more pronounced when a thrombus occluded the arterial lumen than during a brief, complete occlusion of the LAD induced by a suture snare, thus excluding the possibility that the decreased cross-sectional area during thrombus formation was merely the consequence of a reduction in coronary perfusion pressure.

It is interesting to note that in the present study neither SQ29548 nor ketanserin alone exerted significant protection against coronary artery reocclusion. LY53857 (another specific S2-receptor antagonist) also had a very weak protective effect when given by itself. However, the combination of SQ29548 and ketanserin or SQ29548 and LY53857 prevented or markedly delayed coronary artery reocclusion after thrombolysis. This is in agreement with a recent report demonstrating a positive synergistic antiplatelet effect of 5HT and TxA2 receptor blockade in vivo and an in vivo potentiating effect of TxA and 5HT in mediating one another’s influence on CFVs in the experimental preparation we have used. Platelet agonists interact with specific receptors on the platelet membrane, the activation of which leads, in turn, to an increase in the cytoplasmic concentration of Ca++. A specific intracellular Ca++ concentration must be reached to trigger secretion of products from dense and α-granules leading to platelet aggregation.

The clinical efficacy of coronary thrombolysis is clearly dependent on the rapidity with which it can be induced after the onset of thrombosis and ischemia and the rate of occurrence of early reocclusion. Considering that early reocclusion may occur in as many as 20% to 45% of the patients treated with rt-PA, it

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

**FIGURE 4.** Plasma levels of fibrinogen, plasminogen, and α2-antiplasmin (expressed as a percent of basal values) and FDPs (µg/ml) in dogs receiving rt-PA. Blood samples were obtained at baseline and immediately after discontinuing rt-PA infusion (n = 37).

**TABLE 3**

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline</th>
<th>1 hr after reperfusion</th>
<th>3 hr after reperfusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group II-A</td>
<td>39.4 ± 1.4</td>
<td>34.6 ± 1.4</td>
<td>28.8 ± 1.8</td>
</tr>
<tr>
<td>(6 dogs at baseline; 2 reoccluded; 4 dogs had continuous reperfusion)</td>
<td></td>
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<tr>
<td>Group II-B</td>
<td>37.8 ± 0.9</td>
<td>36.8 ± 1.4</td>
<td>30.8 ± 1.8</td>
</tr>
<tr>
<td>(5/5 dogs)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group III</td>
<td>36.0 ± 2.4</td>
<td>34.0 ± 1.4</td>
<td>29.7 ± 1.4</td>
</tr>
<tr>
<td>(2/5 dogs)</td>
<td></td>
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</tr>
</tbody>
</table>

*Numbers in parentheses refer to the number of dogs with patent coronary arteries compared with the total number of dogs treated.*
appears important to identify means to reduce the reocclusion rate. Although our data were obtained in an experimental setting, the observed differences were substantial. The marked effect of the combination of SQ29548 and ketanserin on acute coronary reocclusion after initial reperfusion in the preparation used in the present study may have important implications for future thrombolytic therapy in patients.

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References

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