Combination of Platelet Fibrinogen Receptor Antagonist and Direct Thrombin Inhibitor at Low Doses Markedly Improves Thrombolysis

Francesca A. Nicolini, MD, PhD; Philmo Lee, BS; Gaddiel Rios, BS; Kandice Kottke-Marchant, MD, PhD; Eric J. Topol, MD

**Background** We evaluated the effects of a novel platelet fibrinogen receptor antagonist, Integrelin, and a direct thrombin inhibitor, recombinant hirudin, given together with recombinant tissue plasminogen activator (rTPA) in a canine experimental model of intracoronary thrombosis. We tested the hypothesis that combination of both agents at low doses would have an additive antithrombotic effect, resulting in a significant improvement in the efficacy of rTPA.

**Methods and Results** Thirty-two dogs with an electrically induced coronary thrombus were treated with rTPA (1 mg/kg over 20 minutes) together with one of the following adjunctive treatments in a random fashion. Eight dogs received saline for 90 minutes; Integrelin (5 μg · kg⁻¹ · min⁻¹ for 90 minutes) was given to 8 dogs; 8 dogs received recombinant hirudin (20 μg · kg⁻¹ · min⁻¹ for 90 minutes); and 8 dogs were treated with a low-dose combination of Integrelin (2.5 μg · kg⁻¹ · min⁻¹) plus recombinant hirudin (10 μg · kg⁻¹ · min⁻¹) for 90 minutes. Integrelin or recombinant hirudin, when given as single adjunct to rTPA, enhanced the lysis of the occlusive thrombus, causing full restoration of coronary blood flow (100% of its baseline value) for 29±16 and 26±5 minutes, respectively, whereas coronary blood flow was fully restored for only 5±1 minutes in dogs receiving rTPA plus saline (both P<.05). However, either Integrelin or recombinant hirudin failed to modify the reocclusion rate (57% and 63%, respectively) compared with saline (83%; all P=NS). Conversely, the low-dose combination therapy led to complete restoration of coronary blood flow for 92±19 minutes (P<.01 versus all treatments) and significantly reduced the reocclusion rate (25%; P<.05 versus saline).

**Conclusions** These data show that inhibition of specific pathways of platelet and thrombin activity improves the extent and duration of rTPA-induced thrombolysis in the electrolytic canine model. Furthermore, our findings suggest that low doses of platelet IIb/IIIa and direct thrombin antagonists in combination may be used successfully during thrombolysis.

**Key Words** plasminogen activators • Integrelin • hirudin • thrombolysis
the coronary blood flow (CBF). Thrombosis was induced using the electrolytic injury technique. Briefly, the endothelium of the Cx was damaged by gently rubbing the artery distal to the flow probe. A coronary electrode, consisting of a silver-coated copper wire with a 26-gauge needle tip, was inserted into the Cx, ensuring its contact with the intraluminal surface of the vessel. The electrode was then connected in series with a 250 000-Ω variable resistor to the positive terminal of a 9-V nickel-cadmium battery. The circuit was closed, securing the negative terminal to the subcutaneous tissue of the dog. Distal to the flow probe and the electrode, a vascular occluder was placed on the vessel and then adjusted to totally reduce the peak reactive hyperemia following a 15-second period of total occlusion, without affecting the resting flow (Fig 1). Formation of thrombus was initiated by delivery of 100 μA continuous anodal current to the tip of the coronary electrode until the CBF was zero. The occluder was gradually removed, and then electric stimulation was suspended. Mean aortic blood pressure was continuously monitored with a pressure transducer (Spectramed Inc, Oxnard, Calif) connected to a catheter placed in the ascending aorta via a carotid artery. The heart rate was monitored through lead II of the ECG. All the hemodynamic parameters were continuously recorded on a multichannel recorder (MFE, Salem, NH). Catheters were inserted in both femoral veins and advanced into the inferior vena cava for infusion of the different therapeutic regimens and collection of blood samples.

Administration of Thrombolytic Regimens

Formation of a fully occlusive coronary thrombus was indicated by zero flow. After the vascular occluder was removed and the electric stimulation was turned off, the dogs were allowed to receive intravenous saline for 30 minutes to confirm the stability of thrombus. Then, dogs received rTPA (1 mg/kg over 20 minutes) plus one of the following adjunctive treatments in a random fashion. The control group of 8 dogs was given saline at the rate of 0.6 mL/min for 90 minutes; 8 dogs received Integrelin at the dosage of 5 μg·kg⁻¹·min⁻¹ for 90 minutes; 8 dogs, recombinant hirudin at the dosage of 20 μg·kg⁻¹·min⁻¹ for 90 minutes; and the combination of Integrelin, at the dosage of 2.5 μg·kg⁻¹·min⁻¹, plus recombinant hirudin, at the dosage of 10 μg·kg⁻¹·min⁻¹, was given to the remaining 8 dogs (Fig 2).

None of the animals received aspirin or heparin. In the combination group, the doses of Integrelin and recombinant hirudin were chosen to be exactly half of those given in the monotherapy regimens.

Thrombolysis was defined as restoration of CBF to at least 30% of the baseline value, occurring at any time after the onset of rTPA infusion. Reocclusion was defined as occurrence of zero blood flow after successful initial thrombolysis.

Dogs were observed for a 2-hour period from the occurrence of thrombolysis for evidence of coronary reocclusion. As such, if reocclusion did not occur, the maximal duration of reperfusion was 120 minutes. In those dogs in which restoration of CBF was intermittent because of the cyclic flow variations, the total duration of reperfusion was calculated as the length of time during which blood flow was greater than zero during the 2-hour period after onset of reperfusion. Two hours after the onset of thrombolysis, dogs with persistent zero blood flow as well as dogs with cyclic flow variations were considered to have reocclusion of the coronary artery. Lidocaine was administered as necessary to control ventricular arrhythmias during the study.

Studies of Platelet Aggregation and Coagulation Activity

Platelet Aggregation

Peripheral venous blood samples were collected in 3.88% sodium citrate (9:1 v/v), and platelet-rich plasma (PRP) was obtained by centrifuging the blood at 150g for 15 minutes at 24°C. Platelet-poor plasma (PPP) was obtained by further centrifugation at 1500g for 15 minutes. Platelet counts in PRP were adjusted to 2.5×10⁶ cells/mL. Aggregation was determined in a light transmission aggregometer (Chronolog Corp, Havertown, Pa) in response to epinephrine (5 μmol/L) plus ADP (20 μmol/L). The combination of aggregatory stimuli was used because either ADP or epinephrine alone causes minimal aggregation in dog platelets.¹³

Coagulation Activity

Whole blood samples for prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen assay, and thrombin-antithrombin complex (TAT) were drawn into 3.88% sodium citrate (9:1 v/v) plus aprotinin (2000 IU/mL). PPP was obtained by centrifugation at 2000g for 15 minutes at 4°C. Samples for fibrinopeptide A (FPA) were collected in a mixture of EDTA, 143 μmol/L aprotinin, and 1.4 μmol/L D-phenylalanyl-L-propyl-L-arginine chloromethyl ketone (PPACK). PPP was obtained by centrifugation at 2000g for 15 minutes at 4°C. Plasma was frozen at −70°C until assayed.

The PT determination was performed on the ST4 Coagulation Timer (Diagnostica Stago, Parsippany, NJ). Thromboplastin C (0.2 mL; Baxter/Dade Diagnostics, Miami, Fla) was
TABLE 1. Thrombolytic Effects of tPA With Saline, Integrelin, Recombinant Hirudin, and Their Low-Dose Combination

<table>
<thead>
<tr>
<th></th>
<th>rTPA + Saline, 0.6 mL/min</th>
<th>rTPA + Integrerlin, 5 µg · kg⁻¹ · min⁻¹</th>
<th>rTPA + Recombinant Hirudin, 20 µg · kg⁻¹ · min⁻¹</th>
<th>rTPA + Integrerin and Recombinant Hirudin, 2.5 and 10 µg · kg⁻¹ · min⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CBF, mL/min</td>
<td>31±4</td>
<td>33±4</td>
<td>36±3</td>
<td>29±3</td>
</tr>
<tr>
<td>Time to reflow, min</td>
<td>34±4</td>
<td>38±4</td>
<td>37±7</td>
<td>30±4</td>
</tr>
<tr>
<td>Peak CBF, mL/min</td>
<td>46±6</td>
<td>44±3</td>
<td>40±6</td>
<td>53±9</td>
</tr>
<tr>
<td>Reperfusion rate, %</td>
<td>75</td>
<td>88</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Recocclusion rate, %</td>
<td>83</td>
<td>57</td>
<td>63</td>
<td>25*</td>
</tr>
</tbody>
</table>

rTPA indicates recombinant tissue plasminogen activator; CBF, coronary blood flow. Values are given in mean±SEM. *
P<.05 vs saline.

added to 0.1 mL of citrated plasma, and the subsequent clotting time was measured.

Determination of aPTT was performed on the ST4 Coagulation Timer. Dade Actin FSL (0.1 mL; Baxter/Dade Diagnostics) was incubated with 0.1 mL of citrated plasma at 37°C for 3 minutes. Then, 0.1 mL of 0.2 mol/L CaCl₂ was added to the incubation mixture, and the subsequent clotting time was measured.

FPA is released after thrombin catalyzes the transformation of fibrinogen to fibrin. Thus, FPA is a marker for thrombin activity. FPA concentrations were measured in plasma samples after fibrinogen was removed by treatment with bentonite according to a modified procedure based on competitive enzyme-linked immunoassay.

Fibrinogen was determined in plasma using the von Clauss method using the ST4 Coagulation Timer. TAT complexes are protease–antithrombin III complexes formed after thrombin generation and are markers for in vivo thrombin generation and activity. TAT complex levels were determined in plasma using a commercially available enzyme-linked immunosorbent assay kit (Asserachrom ATM, American Bioproduct Co, Parsippany, NJ). Species cross-reactivity for both FPA and TAT was tested. Nonanticoagulated canine and human blood samples were allowed to clot for 15 minutes. Serum was prepared by centrifugation at 2000g for 15 minutes at 4°C. Catecholamine samples showed 40% to 50% cross-reactivity for FPA and 80% to 100% cross-reactivity for TAT compared with human samples.

Blood samples for the above determinations were collected at the following time points: before thrombus formation (as baseline), on termination of rTPA infusion, and at the end of the adjunctive therapy administration (Fig 2).

**Agents**

rTPA was produced by recombinant DNA technology and kindly supplied by Genentech (South San Francisco, Calif) in vials containing 50 mg of rTPA. Integrelin was supplied by COR Therapeutics, Inc, South San Francisco, Calif, in vials of 20 mg. Recombinant hirudin (10 mg per vial) was obtained from CIBA-GEIGY, Summit, NJ. Dilutions of the agents were made in saline, according to dog's body weight, just before use.

**Data Analysis**

Data were analyzed with regard to the maximal CBF, its duration, and the time from the infusion of drug to the onset of reperfusion (time to reflow) using ANOVA for repeated measures followed by t test for unpaired and paired observations where applicable. In addition, the magnitude of restored CBF, calculated over time during reperfusion, was chosen to quantify the extent of thrombolysis. Frequency of reperfusion and reocclusion were analyzed by Fisher's Exact Test. Effects of treatments on platelet aggregation and coagulation studies were analyzed by Student's t test. All data are expressed as mean±SEM. Two-sided *P<.05 was considered statistically significant.

**Results**

Comparative Effects of Saline, Integrelin, Recombinant Hirudin, and Low Doses of Integrelin Plus Recombinant Hirudin on rTPA-Induced Thrombolysis

The comparative thrombolytic effects of the four regimens are shown in Table 1 and Figs 3 and 5. CBF

![Fig 3. Bar graph of effects of recombinant tissue plasminogen activator (rTPA) with saline, Integrelin, recombinant (r) hirudin, and their combination in low dose on thrombolysis and duration of reflow. The magnitude of restored coronary blood flow (CBF) was calculated over the time of reperfusion to obtain an index of initial lysis. Dogs receiving the active adjunctive treatment showed greater lysis of the occlusive thrombus compared with those receiving saline (left and middle). Furthermore, low-dose combination of Integrelin plus recombinant hirudin significantly enhanced the total duration of reperfusion compared with all treatments.](http://circ.ahajournals.org/doi/10.1161/01.CIR.89.4.1804)
before thrombus formation was similar among the four groups of dogs (all \( P=\text{NS} \)). None of the treatments were effective in improving time to reflow, peak CBF, and the reperfusion rate compared with rTPA plus saline (all \( P=\text{NS} \)) (Table 1). However, low doses of Integrelin plus recombinant hirudin, given together with rTPA, prolonged the duration of reperfusion (\( P<.05 \) versus all treatments) and reduced the reocclusion rate (\( P<.05 \) versus saline), whereas administration of Integrelin or recombinant hirudin did not (all \( P=\text{NS} \) versus saline) (Table 1 and Fig 3).

Although the peak CBF reached during the reperfusion was similar among the four groups of dogs (Table 1), we observed important differences in the magnitude of restored CBF over time during the reperfusion (Fig 3). In the rTPA-plus-saline group, CBF was restored to its baseline value for just 5±1 minutes. In the rTPA-plus-Integrelin and rTPA-plus-recombinant hirudin groups, the magnitude of CBF during reperfusion was greater than or equal to its baseline value for 29±16 and 26±5 minutes, respectively (both \( P<.05 \) versus rTPA-plus-saline group). These observations indicate that either Integrelin or recombinant hirudin, when associated with rTPA, produced greater lysis of the occlusive thrombus than the thrombolytic therapy alone. Furthermore, in dogs treated with rTPA plus Integrelin plus recombinant hirudin at low doses, CBF was restored to its baseline value for 92±19 minutes (\( P<.01 \) versus all treatments). This effect, along with the significant increase in the overall duration of reperfusion, suggests that inhibition of platelet- as well as thrombin-mediated activity effectively maximizes the thrombolytic effects of rTPA. The same statistical relation among the four groups of dogs was observed in choosing the CBF “cutoff” value as 50% of baseline (Fig 3).

**Platelet Aggregation and Coagulation Studies**

The results of PRP platelet aggregation in response to epinephrine plus ADP (5 and 20 \( \mu \text{mol/L} \), respectively) are

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**Fig 4.** Schematic of the coronary patency status in each experiment. Open bar indicates an open artery, and solid bar indicates an occluded artery. r-PA indicates recombinant tissue plasminogen activator; Rx, treatment.
shown in Table 2. After rTPA administration, platelet aggregation was markedly decreased in all groups of dogs. At the end of adjunctive therapy administration, however, in dogs receiving saline, platelet aggregation was higher than in all other groups \( (P<.05) \), indicating a short-acting effect of rTPA on platelet aggregation.\(^{22}\)

Table 3 shows the results on PT and aPTT. As expected, on rTPA administration, PT was increased in all dogs compared with the baseline value. Recombinant hirudin caused a further increase in PT. It is noteworthy that the increase in PT in dogs receiving high or low doses of recombinant hirudin occurred at different time points. Dogs receiving full doses of recombinant hirudin showed very high PT values by the end of rTPA administration \( (P<.05 \text{ vs all treatments}) \), whereas in dogs receiving low recombinant hirudin doses, prolongation of PT was detected only on termination of adjunctive therapy \( (P<.05 \text{ vs saline}) \). After rTPA administration, an increase in aPTT was also detected in all animals. However, in rTPA plus saline–treated dogs, the aPTT values were much lower than with the other treatments \( (P<.05) \). The increase in aPTT in rTPA plus Integrelin–treated dogs over that of those receiving rTPA plus saline may be due to a slightly lower mean fibrinogen concentration for this group. In an in vitro series of experiments (data not shown), Integrelin alone failed to have any effect on aPTT up to 20 \( \mu \text{mol/L} \). The increase in aPTT caused by recombinant hirudin was prompt in dogs receiving full recombinant hirudin doses and gradual, over time, in dogs receiving low doses of Integrelin plus recombinant hirudin (Table 3).

In all groups of dogs, rTPA administration, regardless of the adjunctive therapy, caused the same degree of fibrinogen depletion \( (60\% \text{ to } 65\%) \). Neither recombinant hirudin, Integrelin, nor the combination further decreased the plasma fibrinogen levels (data not shown).

Thrombin activity, assessed by measuring changes in plasma FPA and TAT levels, is shown in Fig 5. In dogs receiving rTPA plus saline, at the end of rTPA administration \( (\text{approximately at the onset of thrombolysis}) \), FPA values were twice baseline. In rTPA-plus-Integrelin–treated dogs, after rTPA, FPA was increased by 71±21\% \( (P=\text{NS \ vs \ saline}) \). In both of these groups of dogs, FPA was still 50\% greater than the baseline value at the end of adjunctive therapy, indicating persistently high thrombin activity. On the other hand, full doses of recombinant hirudin virtually blocked any increase in FPA \( (P<.05 \text{ versus saline at any time point}) \). In the group of dogs receiving low doses of recombinant hirudin plus Integrelin, by the end of adjunctive therapy administration, FPA levels were similar to the baseline value and significantly lower than those in saline or Integrelin groups \( (P<.05) \). The TAT also showed a pattern consistent with that of FPA. Taken together, these data indicate that significant inhibition of thrombin activity was achieved in both groups of dogs treated with recombinant hirudin (Fig 5).

**Discussion**

In the present study, we showed that inhibition of specific pathways of platelet and thrombin activity successfully improves the extent and the duration of rTPA-

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**Table 2.** Effects of rTPA With Saline, Integrelin, Recombinant Hirudin, and Their Low-Dose Combination on PRP Platelet Aggregation

<table>
<thead>
<tr>
<th></th>
<th>PRP Platelet Aggregation, %</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td>rTPA + saline, 0.6 mL/min</td>
<td>76±5</td>
</tr>
<tr>
<td>rTPA + Integrelin, 5 ( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>68±10</td>
</tr>
<tr>
<td>rTPA + recombinant hirudin, 20 ( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>70±9</td>
</tr>
<tr>
<td>rTPA + Integrelin and recombinant hirudin, 2.5 and 10 ( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</td>
<td>71±10</td>
</tr>
</tbody>
</table>

rTPA indicates recombinant tissue plasminogen activator; PRP, platelet-rich plasma. Values are given in mean±SEM.

*\( P<.05 \) vs all treatments.

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**Table 3.** Effects of rTPA With Saline, Integrelin, Recombinant Hirudin, and Their Low-Dose Combination on PT and aPTT

<table>
<thead>
<tr>
<th></th>
<th>rTPA + Saline, 0.6 mL/min</th>
<th>rTPA + Integrelin, 5 ( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</th>
<th>rTPA + Recombinant Hirudin, 20 ( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</th>
<th>rTPA + Integrelin and Recombinant Hirudin, 2.5 and 10 ( \mu \text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PT, s</td>
<td>aPTT, s</td>
<td>PT, s</td>
<td>aPTT, s</td>
</tr>
<tr>
<td>Baseline</td>
<td>9±1</td>
<td>22±3</td>
<td>8±1</td>
<td>35±14</td>
</tr>
<tr>
<td>End rTPA</td>
<td>25±7</td>
<td>95±21*</td>
<td>26±8</td>
<td>138±25</td>
</tr>
<tr>
<td>End adjunctive treatment</td>
<td>14±4</td>
<td>99±30*</td>
<td>23±8</td>
<td>&gt;180</td>
</tr>
</tbody>
</table>

rTPA indicates recombinant tissue plasminogen activator; PT, prothrombin time; and aPTT, activated partial thromboplastin time. Values are given in mean±SEM.

*\( P<.05 \) vs all treatments.

†\( P<.05 \) vs saline.
induced coronary thrombolysis in the electrolytic canine model. Inhibition of platelet aggregation alone with Integrelin, as well as thrombin neutralization alone with recombinant hirudin, improved the magnitude of reflow over time (both treatments, \(P < 0.05\) versus saline) and therefore increased the initial lysis of the occlusive thrombus. However, both treatments failed to reduce significantly the reocclusion rate and thus did not prevent rethrombosis at the site of vascular injury. The major finding of this study is that combination of low doses of Integrelin plus recombinant hirudin given together with rTPA induced sustained and stable reperfusion in the vast majority of dogs, supporting the hypothesis of additive antithrombotic effect between Integrelin and recombinant hirudin.

Our data on recombinant hirudin are in keeping with the observation of Rote et al., who showed failure of high doses of recombinant hirudin to provide improvement of rTPA-mediated thrombolysis in a chronic canine electrolytic model. In this study, recombinant hirudin was administered up to 12 hours, and the patency of the infarct-related artery was studied 5 days later. Although the doses of recombinant hirudin used in our experiments were 10 times lower, we clearly showed through the coagulation studies the efficacy of such doses of recombinant hirudin in blocking thrombin activation (Table 3 and Fig 5).

The maximal degree of thrombin activity was observed, regardless of the treatment received, at the onset of reperfusion in all dogs (Fig 5). However, dogs receiving recombinant hirudin alone or in combination with Integrelin showed very minimal changes in both FPA and TAT plasma levels, suggesting that in these groups thrombin activity was inhibited throughout the experiment.\(^2\)

Platelets have been shown to play a central role in the occurrence of reocclusion after experimental thrombolysis.\(^2\) We found that platelet aggregation was markedly decreased at the end of rTPA in all dogs and that by the end of adjunctive therapy, platelet studies continued to show persistent inhibition in the groups of dogs receiving active treatments (Table 2). We could not determine the superiority of Integrelin in inducing platelet aggregation inhibition over recombinant hirudin alone or the combination of low doses of Integrelin plus recombinant hirudin because no difference was detected among these three groups of dogs at the end of adjunctive therapy. Nevertheless, recent reports indicate that dosages of even 1.0 to 1.5 \(\mu\)g \(\text{kg}^{-1} \cdot \text{min}^{-1}\) of Integrelin are sufficient to totally block ADP-induced platelet aggregation.\(^25\) In the present study, despite Integrelin's potent ex vivo antiplatelet effect and its increased extent of lysis of the occlusive thrombus in vivo, it failed to sustain the thrombolysis. These observations would imply that platelet inhibition alone is not adequate to prevent rethrombosis.\(^15,26,27\) The experimental data on the effect of platelet glycoprotein IIb/IIIa inhibition on thrombolysis are still controversial depending on the doses of the drugs, the models, and the thrombolytic agents used. Studies using a variety of platelet glycoprotein IIb/IIIa antagonists as adjunct to fibrinolytic agents showed either improvement\(^29-30\) or no benefit\(^31\) on thrombolysis. Very recently, Song et al.\(^32\) showed that Integrelin at the dosage of 4 \(\mu\)g \(\text{kg}^{-1} \cdot \text{min}^{-1}\) given together with streptokinase prevented occurrence of reocclusion in the femoral artery of dogs with electrically induced occlusive thrombus. Although the dose of Integrelin was very similar to that used in our study, the variance in the model (femoral versus coronary artery) along with the different thrombolytic agent used (streptokinase versus rTPA) may account for the discrepancy in the final result.

The results of the present study showed that the reocclusion rate was significantly decreased only in dogs...
treated with the low-dose combination of Integrin plus recombinant hirudin (Table 1). This observation along with the superior increase in the extent of lysis of the primary thrombus obtained in the group receiving the low-dose combination of platelet IIb/IIIa receptor antagonist and direct thrombin inhibitor suggest that the interaction between platelets and thrombin plays a major role in determining the efficacy of rTPA-induced thrombolysis.

Another aspect that deserves mention is that in this study, none of the active adjunctive treatments accelerated rTPA-induced thrombolysis. On the contrary, other reported efficacy of antiplatelet agents, direct antithrombin agents, or both in decreasing the time to reperfusion. This disagreement in the results may relate to a substantial difference in the model and in the administration of thrombolytic therapy. In the present study, to obtain a reperfusion rate comparable to that occurring in humans undergoing thrombolysis with rTPA, we removed the external occluder before initiation of thrombolytic therapy and gave rTPA as an accelerated regimen (20 versus 90 minutes as reported in the majority of the experimental studies). Under these circumstances, both the reperfusion rate and time to restoration of CBF are markedly improved.

In summary, the present study shows that the combination of Integrin plus recombinant hirudin led to sustained and stable reperfusion, indicating that concomitant inhibition of both thrombin and platelet-mediated activity ameliorates the thrombolytic effect of rTPA. Furthermore, because of the very different mechanisms of action of Integrin and recombinant hirudin, suggesting a strong additive antithrombotic effect of these two agents, our study shows that low doses of highly selective platelet and thrombin antagonists in combination may be effectively used during thrombolytic therapy.

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Combination of platelet fibrinogen receptor antagonist and direct thrombin inhibitor at low doses markedly improves thrombolysis.
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