Prostacyclin Analogue Iloprost Decreases Thrombolytic Potential of Tissue-Type Plasminogen Activator in Canine Coronary Thrombosis

F.A. Nicolini, MD, J.L. Mehta, MD, PhD, W.W. Nichols, PhD, T.G.P. Saldeen, MD, PhD, and M. Grant, MD

Platelets play an important role in the formation of a coronary thrombus and reocclusion after thrombolysis. Therefore, we examined the thrombolytic potential of concomitant intravenous administration of potent platelet inhibitor iloprost, a prostacyclin analogue, with tissue-type plasminogen activator (t-PA; n=8) and t-PA alone (n=9) in dogs with an electrically induced occlusive coronary artery thrombus. t-PA (0.75 mg/kg) was given over 20 minutes, and iloprost (4 μg/kg) was given over 40 minutes. Reperfusion rate was 63% (five of eight dogs) in the t-PA plus iloprost group and 67% (six of nine dogs) in the t-PA alone group (p=NS). The time to thrombolysis (or reperfusion) in the t-PA plus iloprost group was almost twice as great as in the t-PA alone group (33.0±13.3 vs. 18.5±6.7 minutes, mean±SD, p<0.02), and the duration of reperfusion was much shorter (3.4±1.8 vs. 39.3±17.4 minutes, p<0.005). Peak coronary artery blood flow after reperfusion in the t-PA plus iloprost group was also less (20±17 ml/min) than in the t-PA alone group (58±21 ml/min, p<0.005). Reocclusion occurred in all dogs given t-PA with iloprost despite potent synergistic platelet inhibitory effects of t-PA and iloprost, whereas four of six dogs given t-PA alone reoccluded. Neither regimen exerted a significant beneficial effect on regional myocardial shortening during coronary reperfusion. Plasma levels of t-PA were lower when iloprost was given with t-PA (1,022±360 vs. 1,459±270 ng/ml in t-PA alone group, p<0.05). The detrimental effects of iloprost identified in this study may relate to the reduction in plasma t-PA concentrations by its degradation in the liver caused by the prostacyclin analogue iloprost. (Circulation 1990;81:1115–1122)

An occlusive thrombus in the atherosclerotic coronary artery is believed to be the precipitating factor in the genesis of unstable angina and acute myocardial infarction in a vast majority of patients. This is based on angiographic, angioscopic, and pathologic examination of the offending coronary artery.1–3 Accordingly, therapy of such patients includes use of thrombolytic agents, such as streptokinase or tissue-type plasminogen activator (t-PA).4–7 Because the occlusive thrombus consists

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primarily of platelets and fibrin mass, antiplatelet agents8,9 and anticoagulants10 are also widely used in the management of acute myocardial ischemia.

In vivo thrombosis is associated with evidence of platelet activation and release of platelet products in the systemic circulation.11 Thrombolysis also is accompanied by release of large amounts of thromboxane A2,12 presumably because of intense platelet activation at the site of the initial thrombus. Accordingly, thrombolytic therapy may be followed by use of agents that inhibit platelet activity. In animal models of occlusive intracoronary thrombosis, the efficacy of thrombolytic therapy has been shown to be enhanced by administration of thromboxane A2 inhibitors,13 prostacyclin,14 thrombin inhibitors,15 or heparin.14

The purpose of this study was to compare the effects of thrombolysis with t-PA alone with t-PA given in combination with iloprost, a prostacyclin analogue, in a canine model of coronary artery thrombosis. Our studies demonstrate that concurrent
administration of iloprost with t-PA may be less efficacious than t-PA alone.

**Methods**

**Coronary Artery Thrombosis**

Seventeen male mongrel dogs (average weight, 21 kg) were anesthetized with pentobarbital sodium (30 mg/kg), intubated, and placed on positive pressure ventilation with a respirator (Harvard Apparatus, South Natick, Massachusetts). A thoracotomy was performed in the fifth left intercostal space, and the heart was suspended in a pericardial cradle. The left anterior descending coronary artery (LAD) was isolated distal to the first diagonal branch. An ultrasonic Doppler (Crystal Biotech, Holliston, Massachusetts) flow probe was placed on the LAD for measurement of coronary blood flow. An intracoronary thrombus was induced by use of the technique initially described by Romson et al\(^{16}\) and subsequently used by us\(^{17}\) and others.\(^{18}\) Briefly, the LAD was gently rubbed to disrupt the endothelium distal to the flow probe. A silver-coated copper wire with a 25-gauge needle tip (approximately 4 mm) bent 90° was inserted distal to the flow probe into the LAD and pulled back to ensure contact of the electrode with the intimal surface of the vessel. This electrode was connected in series with a 250,000-Ω variable resistor to the anode (positive terminal) of a 9-V nickel-cadmium battery. The cathode (negative terminal) was secured to subcutaneous tissue. In all animals, an external plastic occluder was placed on the LAD distal to the flow probe and electrode to reduce peak reactive hyperemia after a 10-second total occlusion by about 50%. The thrombus formation was initiated with passage of DC current (100 μA) through the intracoronary electrode until LAD blood flow was zero for at least 30 minutes with the electric current turned off and the plastic occluder removed.

In the core of LAD-supplied myocardium, myocardial segmental shortening was measured by placement of ultrasonic crystals in the midmyocardium. The orientation of the crystals, separated by 1.0–1.5 cm, lay transverse to the long ventricular axis and was aligned so that the optimal acoustic signal was obtained.\(^{19}\) End-diastolic segmental length (EDL) and end-systolic segmental length (ESL) were measured at aortic valve opening and closing, respectively, as determined from the ascending aortic pressure waveform.\(^{20,21}\) Regional myocardial segmental function was determined as \([(EDL−ESL)/EDL]×100\). Catheters were inserted into both femoral veins and advanced into the inferior vena cava and used for drug infusion and collection of blood samples.

**Hemodynamic Measurements**

In addition to continuous measurement of coronary blood flow, ascending aortic pressure was measured by inserting a catheter-tip pressure transducer (Millar, Houston, Texas) into a carotid artery and advancing it to the aortic root. Heart rate was calculated from lead II of the electrocardiogram. The recordings were made on a Honeywell multi-channel recorder.

**Administration of t-PA and Iloprost**

After the in situ intracoronary thrombus was fully occlusive as indicated by zero blood flow with the electric current on, the external occluder was gradually removed, and the current was abruptly turned off. The animals were given intravenous normal saline for 30 minutes, and the stability of thrombus (lack of spontaneous dissolution) was confirmed. Thereafter, the animals were randomly given t-PA (0.75 mg/kg over 20 minutes) alone \((n=9)\) or t-PA (0.75 mg/kg over 20 minutes) plus iloprost \((4 \mu g/kg over 40 minutes) \(n=8\)\). Iloprost was infused for 40 minutes to induce coronary vasodilation and to inhibit platelet aggregation over a prolonged period, in case t-PA caused thrombolysis. After administration of the drugs, the animal was observed for 1 hour for evidence of coronary reocclusion. Lidocaine was administered to control ventricular arrhythmias during reperfusion, as necessary.

The dose of iloprost \((100 ng/kg/min)\) was chosen based on preliminary experiments in which this dose caused a decrease of approximately 10% in mean arterial pressure and had little effect on coronary blood flow. Higher doses caused marked reductions in mean arterial pressure and coronary blood flow.

**Measurements of Plasma t-PA and Plasminogen-Activator Inhibitor Levels**

Samples of peripheral venous blood were collected in sterile disposable plastic syringes (Becton Dickinson, Rutherford, New Jersey), transferred into polypropylene tubes, and immediately placed on ice. Test tubes contained 0.5 ml indomethacin \((30 \mu M)\) and EDTA \((4.5 mM)\) to which 5 ml blood was added. Blood samples were collected before thrombus formation, after thrombus formation, and at the end of t-PA or t-PA plus iloprost infusion.

Blood samples were immediately centrifuged at 1,500g for 10 minutes; plasma samples were stored at \(-70°C\) for measurement of t-PA, which was completed within 4 weeks of blood collection.

The immubind t-PA enzyme-linked immunosorbent assay kit (American Diagnostica, New York) was used to quantify t-PA antigen. The immubind t-PA kit measures both free t-PA and circulating t-PA/antibody complex. We used the double antibody principle, which is unique for its design in using quenching and normal antibodies as a control for t-PA specificity. This method allows one to rule out false positives when measuring t-PA antigen in test samples.

The assay measures t-PA antigen in a range of 0.015–0.3 ng/well. Maximal sensitivity is 0.07 ng t-PA/ml, which allows for considerable dilution if necessary.
Ten microliters of undiluted conditioned media was added to a well prefilled with goat anti-human t-PA immunoglobulin G and incubated for 3 hours. During the incubation period, the t-PA antigen in the sample binds to the anti–t-PA immunoglobulin G. Horseradish peroxidase labeled anti–t-PA is added in the next step and incubated for 2 hours. Here, the conjugate binds to free antigenic determinants on the t-PA molecule present. After washing, the amount of peroxidase present is proportional to the amount of t-PA antigen. Substrate is then added to the wells and to the amount of t-PA antigen bound in the well. To determine the amount of t-PA in the conditioned media, the samples were compared against a standard curve generated with standard t-PA.

Plasma levels of a fast-acting inhibitor of plasminogen activator (PAI-1) were also measured in the same samples by amidolytic assay with purified t-PA and a chromogenic substrate. In brief, t-PA is added to multiple solutions of plasma, and residual t-PA activity is subsequently determined by use of the plasmin substrate p-Val-Leu-Lys-p-nitroaniline (S2251), a gift from Kabi-Vitrum AB, Stockholm, Sweden. PAI-1 is the amount inhibiting 1 unit of t-PA in this system. This method has been described previously.22

Platelet Aggregation Studies

To determine the effects of t-PA and iloprost on canine platelet aggregation, peripheral venous blood was collected in 3.8% sodium citrate. Platelet aggregation in whole blood was determined by impedance aggregometry with a whole blood platelet aggregometer (model 540, Chronolog, Havertown, Pennsylvania).23 Platelet aggregation was measured after formation of coronary thrombus and after t-PA or t-PA plus iloprost. The stimulus for whole blood platelet aggregation was ADP (10 μM).

To determine the direct effects of t-PA and iloprost, platelet aggregation in platelet-rich plasma was measured. The stimuli used were ADP alone and epinephrine plus ADP. The combination of aggregatory stimuli was used because ADP or epinephrine alone caused minimal aggregation. In these experiments, platelet-rich plasma was incubated with t-PA alone, iloprost alone, or their combination for 1 minute before the addition of aggregatory stimuli.

Agents

Iloprost was obtained from Schering AG, West Berlin, FRG, and dissolved in saline; subsequent dilutions were made just before its use. t-PA was produced by recombinant DNA technology by Genentech, South San Francisco, California, and was supplied in vials containing 50 mg t-PA.

Data Analysis

Data were analyzed with regard to the maximum coronary blood flow as well as its duration after reperfusion and time from the formation of thrombus to the infusion of agent and time to restoration of flow. Frequency of thrombolysis and reocclusion were analyzed by Fisher’s exact test. Effects of thrombosis and of thrombolytic regimen on myocardial function and t-PA and PAI-1 levels were compared by Student’s t test. All data are expressed in mean±SD.

Results

Comparative Thrombolytic Effects of t-PA and Iloprost Plus t-PA

Table 1. Thrombolytic Effects of Tissue-Type Plasminogen Activator With and Without Iloprost

<table>
<thead>
<tr>
<th>Time</th>
<th>t-PA Without Iloprost</th>
<th>t-PA With Iloprost</th>
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<tbody>
<tr>
<td>Prethrombus CBF (ml/min)</td>
<td>25±10</td>
<td>24±7</td>
</tr>
<tr>
<td>Time to zero flow (min)</td>
<td>36±6</td>
<td>38±5</td>
</tr>
<tr>
<td>Time to infusion (min)</td>
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<td>36±4</td>
</tr>
<tr>
<td>Reperfusion rate (number of dogs; %)</td>
<td>6/9; 67</td>
<td>5/8; 63</td>
</tr>
<tr>
<td>Time to reflow (min)</td>
<td>18.5±6.7</td>
<td>33.0±13.3*</td>
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<tr>
<td>Duration of reflow (min)</td>
<td>39±17.4</td>
<td>3.4±1.8†</td>
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<td>Peak restored CBF (ml/min)</td>
<td>58±21</td>
<td>20±17†</td>
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<tr>
<td>Restored CBF (% of prethrombus flow)</td>
<td>190±93</td>
<td>90±93‡</td>
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<tr>
<td>Reocclusion rate (%)</td>
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<td>100</td>
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Data are mean±SD.

*p<0.02 compared with t-PA without iloprost.
†p<0.005 compared with t-PA without iloprost.
‡p<0.05 compared with t-PA without iloprost.

Of flow. Frequency of thrombolysis and reocclusion were analyzed by Fisher’s exact test. Effects of thrombosis and of thrombolytic regimen on myocardial function and t-PA and PAI-1 levels were compared by Student’s t test. All data are expressed in mean±SD.

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Data are mean±SD.

*p<0.02 compared with t-PA without iloprost.
†p<0.005 compared with t-PA without iloprost.
‡p<0.05 compared with t-PA without iloprost.

Of flow. Frequency of thrombolysis and reocclusion were analyzed by Fisher’s exact test. Effects of thrombosis and of thrombolytic regimen on myocardial function and t-PA and PAI-1 levels were compared by Student’s t test. All data are expressed in mean±SD.

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<td>Restored CBF (% of prethrombus flow)</td>
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*p<0.02 compared with t-PA without iloprost.
†p<0.005 compared with t-PA without iloprost.
‡p<0.05 compared with t-PA without iloprost.

Of flow. Frequency of thrombolysis and reocclusion were analyzed by Fisher’s exact test. Effects of thrombosis and of thrombolytic regimen on myocardial function and t-PA and PAI-1 levels were compared by Student’s t test. All data are expressed in mean±SD.
Combination of iloprost plus t-PA caused reperfusion in five of eight dogs (reperfusion rate, 63%; p=NS vs. t-PA alone). Mean time to reflow was longer (33.0±13.3 min) compared with t-PA alone (p<0.005). The reestablished blood flow was maintained for a very short time (3.4±1.8 minutes; p<0.02 vs. t-PA alone). The peak coronary blood flow in dogs with reperfusion was also lower (20±17 ml/min; p<0.005 compared with t-PA alone) and amounted to 90±93% of prethrombus blood flow (p<0.05 vs. t-PA alone). An experiment showing minimal effects of t-PA when given with iloprost is shown in Figure 2.

In dogs treated with t-PA alone or t-PA plus iloprost, the restored blood flow showed fine fluctuations throughout the period of reflow until the flow returned to baseline zero state (Figures 1 and 2).

**Effect on Myocardial Function and Systemic Hemodynamics**

Complete occlusion of the coronary artery resulted in increase in EDL and ESL. The segmental function was paradoxical (EDL<ESL) in each animal. t-PA had only modest effects on systemic hemodynamics and myocardial function (Table 2). Heart rate was unchanged, and the arterial pressure was slightly (p=NS) lower. t-PA, when successful in thrombolysis, caused a small decrease (p<0.05) in EDL (from 13.4±1.9 to 12.9±1.9 mm) and ESL (from 14.8±2.5 to 14.5±2.4 mm). However, segmental shortening was unaffected (from −10.7±5.1 to −11.9±4.2%). Iloprost plus t-PA, as expected, caused a transient (5–10-minute) reduction (approximately 10%) in mean arterial pressure, but heart rate was unchanged. Myocardial function as reflected in segmental shortening (from −9.9±19.2 to −8.0±12.0%) was not affected by administration of iloprost plus t-PA.

**Plasma t-PA and PAI-1 Levels**

Plasma t-PA levels decreased markedly at the time of formation of stable occlusive coronary thrombus in each dog (Table 3). Administration of t-PA resulted in high levels of t-PA in systemic plasma. The levels of t-PA in plasma were lower when t-PA was administered with iloprost than when t-PA was given without iloprost (p<0.02).

PAI-1 levels increased (p<0.02) on thrombus formation in each dog (Table 3). On administration of t-PA with or without iloprost, PAI-1 levels decreased markedly.

**Effect of t-PA and t-PA Plus Iloprost Infusion on Platelet Aggregation**

Platelet aggregation in whole blood, measured by impedance aggregometry, was 12.0±3.5 Ω after formation of coronary thrombus (n=9). In dogs given t-PA alone, platelet aggregation was 6.2±3.2 Ω (n=4, p<0.05). In five dogs given iloprost plus t-PA, platelet aggregation was much lower (1.2±0.5 Ω; p<0.01 compared with control; p<0.02 vs. t-PA alone).

The results of the effects of t-PA and iloprost on platelet aggregation in platelet-rich plasma are shown in Table 4. Both t-PA and iloprost exerted a concentration-dependent inhibitory effect on canine platelet aggregation. Iloprost (0.5 ng/ml), which alone had no effect on platelet aggregation, signifi-
significant \( (p<0.05) \) potentiated the platelet-inhibitory effects of t-PA.

**Discussion**

The coronary thrombus formed on delivery of anodal current to the deendothelialized surface is due to activation of platelets and their deposition on the intimal surface\(^{16,17} \). The initial platelet thrombus enlarges with incorporation of other blood components until blood flow reaches zero. The important role of platelets in coronary thrombosis is apparent from the fluctuation in coronary blood flow before

**TABLE 2. Systemic and Myocardial Effects of Tissue-Type Plasminogen Activator Alone and With Iloprost in Dogs With Reperfusion**

<table>
<thead>
<tr>
<th></th>
<th>t-PA group ( (n=6) )</th>
<th>Iloprost+t-PA group ( (n=5) )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During reperfusion</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>160±24</td>
<td>162±22</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>104±11</td>
<td>98±15</td>
</tr>
<tr>
<td>Segment length change (%)</td>
<td>-10.7±5.1</td>
<td>-11.9±4.2</td>
</tr>
</tbody>
</table>

Data are mean±SD.  
*\( p<0.05 \) vs. before reperfusion.

**TABLE 3. Systemic Plasma Tissue-Type Plasminogen Activator and Plasminogen-Activator Inhibitor Levels**

<table>
<thead>
<tr>
<th></th>
<th>t-PA alone group</th>
<th>t-PA+ioprost group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t-PA (ng/ml)</td>
<td>PAI-1 (units/ml)</td>
</tr>
<tr>
<td>Before thrombosis</td>
<td>18.3±4.2</td>
<td>15.9±2.1</td>
</tr>
<tr>
<td>After 30 minutes of thrombosis</td>
<td>6.8±3.1*</td>
<td>19.9±3.2*</td>
</tr>
<tr>
<td>After t-PA+t-PA+ioprost</td>
<td>1,459±270†</td>
<td>&lt;DL</td>
</tr>
</tbody>
</table>

Data are mean±SD.  
t-PA, tissue-type plasminogen activator; PAI-1, fast-acting inhibitor of plasminogen activator; DL, detection limit.  
*\( p<0.02 \) vs. before thrombosis.  
†\( p<0.02 \) after t-PA+ioprost vs. t-PA alone.
TABLE 4. Effects of Tissue-Type Plasminogen Activator and Iloprost on Platelet Aggregation

<table>
<thead>
<tr>
<th></th>
<th>ADP</th>
<th>Epinephrine+ADP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>25±6</td>
<td>94±6</td>
</tr>
<tr>
<td>t-PA 50 μg/ml</td>
<td>16±8*</td>
<td>80±4*</td>
</tr>
<tr>
<td>t-PA 100 μg/ml</td>
<td>10±4*</td>
<td>78±4*</td>
</tr>
<tr>
<td>Iloprost 0.5 ng/ml</td>
<td>25±5</td>
<td>87±5</td>
</tr>
<tr>
<td>Iloprost 2.0 ng/ml</td>
<td>5±4*</td>
<td>65±4*</td>
</tr>
<tr>
<td>t-PA+iлоprost 50 μg/ml+0.5 ng/ml</td>
<td>4±5†</td>
<td>56±13†</td>
</tr>
</tbody>
</table>

Data are expressed as mean±SD.

Platelet-rich plasma was incubated for 1 minute with tissue-type plasminogen activator (t-PA), iloprost, or their combination before stimulation with ADP alone (20 μM) or epinephrine (55 μM)+ADP (20 μM).

*p<0.05 compared with control.
†p<0.05 compared with the cumulative effects of t-PA and iloprost.

development of occlusive thrombus.17 Furthermore, the dissolution of the thrombus with t-PA or streptokinase is associated with periodic changes in blood flow, similar to those seen in narrowed endothe-
liarlized canine coronary arteries.24,25 The cyclic changes in blood flow are believed to be due to platelet accumulation in the coronary artery at the site of initial thrombus. Indeed, histology of the coronary artery after restoration of flow demonstrates a residual thrombus rich in platelets adherent to the intimal surface.17 Further evidence for the central role of platelets in thrombus formation are observations of the delayed formation of thrombus when thromboxane A2 inhibitors are given before delivery of electric current.18 These agents, when given after restoration of blood flow with thrombo-
lytic agents, reduce secondary platelet accumu-
lation.13 Prostacyclin, when administered after thrombolysis, also results in improvement in the effects of thrombolytic agents.14 In this setting, administration of heparin14 and thrombin inhibitors15 has also been shown to be very beneficial.

Before the discussion of the results of our study, it is pertinent to discuss the relevance of this model of canine coronary thrombosis to coronary occlusion in acute myocardial ischemia in man. Coronary arteries of patients with acute myocardial infarction invariably show underlying obstruction with atherosclerosis, endothelial tear, and an occlusive thrombus.26 The occulsive thrombus always begins with accumulation of platelets at the site of endothelial disruption. In the canine model of coronary thrombosis used in this study, the histology reveals several features of the human coronary thrombus (i.e., endothelial disruption and a platelet-rich thrombus formed at the site of placement of external occluder).17 The coronary artery is narrowed by placement of an external occluder to mimic atherosclerotic narrowing in humans. In addition, presence of an external occluder markedly facilitates the formation of an occulsive thrombus on delivery of electric current (time to coronary occlusion, 20–40 minutes with external narrowing vs. 2–4 hours without external narrowing). However, the occluder is removed before administration of the thrombolytic regimen, and stability of the occlusive thrombus is checked over a 30-minute period of saline administration. We showed earlier17 that the frequency of coronary blood flow restoration is markedly improved when the external occluder is removed (compared with when it is left on). Also noteworthy are important differences in platelet function in dogs and man. The canine platelets are less reactive than those of humans, and often, multiple agonists are needed to induce complete aggregation in dog platelet-rich plasma. In spite of the similarities and dissimilarities between canine coronary thrombus and human coronary thrombus, this model in dogs provides a method for evaluating the effect of a variety of thrombolytic regimens.13–18,27

The present study shows that the plasma levels of t-PA decrease concurrent with the passage of electrical current and thrombus formation. This reduction in endogenous t-PA levels may not only facilitate thrombus formation but also contribute to the propagation of thrombus, once it is formed. t-PA is formed in the vascular endothelium,28 and manual as well as electrical injury to the endothelium may be the basis of decrease in the plasma levels of t-PA. Concurrent with the reduction in t-PA levels, PAI-1 levels increased significantly with passage of electric current and reduction in blood flow. The major source of PAI-1 is platelets, and cyclical reductions in coronary blood flow strongly suggest platelet activation in the coronary arterial lumen, which results in total occlusion of the narrowed artery with disrupted endothelium. These alterations in hemostasis may cause important perturbations in the rheology of blood. Coupled with release of large amounts of thromboxane A2 during thrombolyis,12 reduction in t-PA and an increase in PAI-1 may be a mechanistic basis for reocclusion of the coronary artery after initial restoration of blood flow.

In a preliminary study, Golino et al29 showed that iloprost administered to dogs with intracoronary thrombus, induced by placement of a copper coil in the coronary lumen, markedly potentiated the effects of t-PA in terms of time to thrombolysis and frequency of thrombolysis and reocclusion. Based on the important role of platelet activation in thrombo-
genesis, it would appear logical that iloprost would be beneficial. However, our studies show that iloprost administered concurrently with t-PA not only does not enhance the thrombolytic effects of t-PA but significantly attenuates the thrombolytic potential of t-PA. In this regard, our data are consistent with the preliminary observations of Kerins et al,27 who also showed reduction in thrombolytic potential of t-PA when iloprost was concurrently administered. Important differences between the studies by Golino et al29 and us are the different methodologies used to induce thrombosis (copper coil vs. electrical current) and the dose of iloprost used (200 vs. 100 ng/kg/min).
It is unlikely that these differences can account for the divergent results of their study and ours.

It can be speculated that reduction in arterial pressure with iloprost may stimulate catecholamine release, which in turn may activate platelets. It is an unlikely scenario because mild reduction in mean arterial pressure (approximately 10 mm Hg) observed in dogs receiving t-PA with iloprost usually does not induce platelet aggregation. Moreover, platelet aggregation as determined by impedance aggregometry was markedly inhibited in dogs receiving iloprost with t-PA compared with those receiving t-PA alone. Lastly, similar blood pressure-lowering doses of prostacyclin given after t-PA–induced thrombolysis generally sustain, rather than inhibit, coronary blood flow.14,27

Our study shows that iloprost causes about 30% reduction in the circulating levels of t-PA compared with t-PA alone; this reduction is probably caused by an increase in hepatic blood flow,30,31 which facilitates degradation of t-PA.32 The thrombolytic effects of t-PA in the coronary thrombus model used by us are dependent on the dose of t-PA, and therefore, it is likely that the relatively lower plasma levels of t-PA were the basis for reduction in the quality of thrombolysis when t-PA was given with iloprost. It is also possible that the coronary “steal” effects of iloprost33 contribute to a selective increase in blood flow to the region supplied by the patent coronary artery and diminution of flow in the region supplied by the occluded coronary artery. Although we did not measure myocardial blood flows in regions supplied by the patent and narrowed coronary arteries in the present study, our previous observations in dogs with narrowed coronary arteries clearly suggest that coronary “steal” does occur on administration of prostacyclin.34

Importantly, we observed a significant inhibitory effect of iloprost and t-PA on aggregation of canine platelets in vitro. Iloprost clearly potentiated the platelet aggregation inhibitory effect of t-PA. This was evident with the use of two different stimuli used to induce platelet aggregation. Furthermore, administration of iloprost with t-PA caused a greater inhibition of whole blood platelet aggregation in dogs receiving this regimen than in those who received t-PA alone. These observations imply that platelet inhibition alone is not adequate to restore blood flow in a totally occluded coronary artery. However, inhibition of platelet aggregation after thrombolysis has been achieved may potentiate the effects of thrombolytic therapy by preventing subsequent platelet accumulation in arteries with residual thrombi. These observations support the studies from the laboratory of Dr. Lucchesi13,14 relative to the salutary effects of thromboxane A2 inhibitors, prostacyclin and heparin, given soon after thrombolysis.

In summary, our observations suggest that iloprost given concurrently with t-PA attenuates the beneficial effects of t-PA alone in a canine model of electrically induced coronary thrombosis.

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References


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