Coronary Thrombolysis with Recombinant Tissue Plasminogen Activator*  
Intracoronary vs Intravenous Administration  

We employed a canine model of coronary thrombosis, induced by injection of radioactive blood clot, via a catheter placed in the left anterior descending coronary artery, to compare effects of recombinant tissue plasminogen activator (rtPA) administered intravenously and administered directly into the coronary circulation. A control group did not receive rtPA. Compared with controls, both rtPA regimens induced coronary thrombolysis. However, compared with intravenous administration, rate and extent of coronary thrombolysis were increased with intracoronary administration. Most likely, the enhanced thrombolysis with intracoronary administration is explained by an increase in delivery of the drug to the thrombus.

(Chest 1991; 100:201-06)

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Numerous studies have investigated intravenous administration of thrombotolytic agents in treatment of acute myocardial infarction. One recent randomized study compared the rates of reperfusion obtained with intravenous administration of recombinant tissue plasminogen activator (rtPA) (40, 20, and 20 mg in consecutive hours) or streptokinase (SK, 1.5 million units over 1 h) in patients with acute myocardial infarction. Ninety minutes after onset of therapy, totally or subtotally occluded infarct-related arteries had opened in 62 percent of rtPA-treated patients and 31 percent of SK-treated patients. The rate of reperfusion with rtPA was much higher in vessels with subtotal occlusion compared with those with total occlusion, 90 percent vs 56 percent, respectively, at 90 minutes. The difference in reperfusion rates between subtotally and totally occluded vessels may be explained by differences in regional vascular resistance. In support of this possibility are results from a recent study of canine pulmonary embolism indicating that rtPA-induced thrombolysis predominantly occurred in partially as opposed to totally obstructed vascular units. Another recent canine study demonstrated that an increase in flow and thus rtPA delivery to thrombus markedly enhanced rtPA-induced pulmonary thrombolysis.

The above studies suggest two principles that may influence the effectiveness of rtPA-induced coronary thrombolysis: (1) regional myocardial blood flow and thus rtPA delivery and thrombolysis are inversely related to the coronary vascular resistance; and (2) for a given coronary vascular resistance, the rate of rtPA delivery to thrombus, over at least a finite dose range, will influence the rate of thrombolysis. Accordingly, for a given dose of rtPA, compared with intravenous administration, intracoronary administration should enhance the rate of thrombolysis. On the other hand, one canine study demonstrated that the rates of coronary thrombolysis were similar with intracoronary or intravenous administration of rtPA. In that study, however, a relatively high dose of rtPA was employed and it is conceivable that even with intravenous administration there was full saturation of the fibrin receptors with rtPA. In support of this possibility are several previous canine studies of pulmonary embolism which demonstrate the presence of an upper limit to the dose thrombolytic-rate relationship with rtPA.

The current study tests the hypothesis that compared with intravenous administration, rate of thrombolysis will increase with intracoronary administration of rtPA.

**METHODS**

Eighteen dogs (24 to 36 kg) were anesthetized with intravenous pentobarbital (30 mg/kg) that was supplemented as required to maintain apnea. Each dog was mechanically ventilated in a right
lateral decubitus position via an endotracheal tube with 100 percent O2 with a tidal volume of 15 ml/kg. The respiratory rate was adjusted to maintain PaCO2 between 25 and 45 mm Hg. Metabolic acidosis was treated with sodium bicarbonate to maintain arterial pH greater than 7.28. A catheter was inserted into the left femoral artery for measurement of blood pressure (BP) and for removal of 20 ml of blood for autologous clot formation. Blood, for gas analysis, was also removed via this catheter throughout the experiment. Intravenous lines were inserted into the left and right femoral veins for infusion of 10 percent dextrose, hetastarch, lidocaine when needed, and rtPA or saline solution according to the randomization. Two thermistor-tipped flow-directed Swan-Ganz catheters were inserted via the left external jugular vein. One was positioned in the proximal pulmonary artery for measuring thermal diluted cardiac output (CO). The other was positioned in the right atrium (RA) for injection of saline solution boluses used for CO determination (Columbus Instruments, Columbus, Ohio). ECG, lead 2, was used to monitor rate and rhythm. Lidocaine was given as required for ventricular ectopies.

After catheterization, all dogs received a 2-ml intravenous injection of pancuronium (2 mg/ml). A 15-cm incision was made between the left fifth and sixth intercostal space to expose the heart. A 2- to 3-cm H2O-positive end expiratory pressure was applied after thoracotomy. A 2.5-cm incision was made in the pericardium to expose the left main coronary artery. The left anterior descending artery was cleaned by blunt dissection and a piece of Corticelli tape was threaded underneath the artery to steady it during cannulation with a 20 G 1/4-inch intravenous placement catheter (Cathion IV Critikon Canada, Inc, Markham, ON). Following cannulation, the catheter was supported by two small strips of Teflon felt (Meadox Medicals, Inc, Oakland, NY), one on either side of the catheter, and secured to the pericardium. This catheter was used for injection of 0.3 g radioactive clot and for rtPA therapy or saline solution according to randomization. Figure 1 illustrates this particular preparation. Following intracoronary catheter placement, the dogs were allowed to stabilize for 30 minutes.

All catheters were connected to transducers (Statham P231D) that were leveled to the mid sternum. The ECG was continuously recorded. The output from all transducers was displayed on a 12-channel oscillograph with recorder (Electronics for Medicine).

Radioactive Autologous Blood Clot Preparation

Each technetium-99m sulfur colloid (TSC) preparation (TSC) preparation was prepared by boiling 3.0 ml of 1 N HCl, 3.0 ml of Na2S03·5H2O and 10.0-11.0 Gbq of technetium-99m pertechnetate in 90 ml of saline solution for 3.5 minutes. After ice bath cooling for 5 min, 0.3 ml of human serum albumin and 8.0 ml of phosphate buffer were added. The purity of the TSC preparations was determined to be 98.4 percent ± 0.3 percent by instant thin layer chromatography using methyl ethyl ketone as the solvent. TSC was chosen to label the clot because of its known affinity for fibrin strands, and because the colloidal particles when released as a result of clot lysis are rapidly cleared by the reticuloendothelial system (serum 1/2-life approximately 2 min) making correction for blood background radioactivity unnecessary.12,13

To prepare the TSC-labeled clot, 20 ml of blood from the dog was drawn in a 30-ml syringe. Approximately 180 MBq of TSC (0.4 ml) was added to the syringe of blood. The syringe was capped and turned end-over-end 30 times to ensure thorough mixing of the TSC in the blood. Clotting of the blood was done by simultaneously dripping the radioactive blood and 1,250 units (1.25 ml) of thrombin into a plastic cup 5 cm in diameter. The mixture was allowed to stand until the clot formed assumed a "Jello-like" consistency, a process that takes approximately 1.5 hours. Excess fluid was decanted and discarded. The clot was cut to give a small piece of approximately 0.3 g containing 4.0 to 5.0 MBq of TSC. The small piece of clot was placed in a 5-ml syringe, and 2 ml of saline solution was drawn into the syringe to facilitate injection of the clot into the coronary artery.

Protocol

After stabilization, baseline measurements (BP and CO) were taken. Subsequently, radioactive autologous clot was injected into the left anterior descending (LAD) artery, via the catheter. The clot was injected and flushed through the catheter with normal saline solution. The preparation was allowed to stabilize for 20 min. At this point, dogs were randomized to one of the three groups. The control group received saline solution, both 30 ml intravenous and intracoronary over 30 min. The second and third group dogs received 0.25 mg/kg of rtPA, 10 percent as a bolus and 90 percent in 30 ml of saline solution over 30 min. The rtPA intravenous group received rtPA intravenously and saline solution via the intracoronary catheter and the rtPA intracoronary group received rtPA through the intracoronary catheter and saline solution intravenously. We employed 0.25 mg/kg of rtPA because pilot studies had demonstrated that intravenous administration of this dose did not cause a maximum rate of thrombolysis. This allowed us to best investigate the relative efficacy of these two modes of administration. Following rtPA or saline solution infusion, all dogs received heparin 100 U/kg over 1 min and then saline solution 100 ml/h for the duration of the experiment.

Hemodynamic measurements (BR CO) were taken at the following times: before clot injection; after clot injection (20 min after clot injection); and 30 and 90 minutes after onset of rtPA drug therapy.

Assessment of Coronary Thrombolysis

Monitoring of cardiac radioactivity was achieved with a mobile gamma camera (Picker Dayna IV, Picker International Canada, Inc, Winnipeg, MB), equipped with a parallel hole collimator, coupled to a mobile computer (Medical Data Systems A+, Medtronic of Canada Ltd, Richmond, BC). Dynamic images were acquired in a 64 x 64 byte mode for 2 h at a rate of 60 s per frame. In each study, a region of interest was placed about the heart. To assess total thrombolysis, counts were summed over the 10 min just prior to

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administration of rtPA and were compared with a decay-corrected image from the final 10 min. To assess the rate of coronary thrombolysis, a marker was placed at the onset and end of rtPA infusion and a linear best-fit curve between these coordinates was generated by the computer. Thus, the slope of the time-activity curve defined the rate of clot lysis during drug infusion. This relationship is expressed in terms of the percentage of decline of total counts per 30 min. The time delay from rtPA administration to the start of thrombolysis was determined by measuring the time difference between the onset of infusion and a visual change in slope of the time-activity curve.

**Statistical Analysis**

The total clot lysis and rate of clot lysis during infusion was compared by one-way analysis of variance (ANOVA). Hemodynamic parameters were analyzed for a change with embolization by a paired t test. Time delay from rtPA administration to onset of thrombolysis was analyzed by an unpaired t test. To assess the statistical significance of treatment with rtPA-IC, rtPA-IV, and control on hemodynamics, a two-day ANOVA was used (NCSS—repeated measure ANOVA split plot design). There were two independent variables: groups (three levels: rtPA-IC, rtPA-IV, and control) and conditions (three levels: before rtPA, 30 and 90 min after rtPA). The ANOVA was used between-within two-factor mixed design in that between-subject (groups) and within-subject (conditions) comparisons were obtained. A Tukey's Studentized range test was used to examine for significant differences between the means.

**RESULTS**

Both rtPA regimens elicited early coronary thrombolysis. Both intracoronary and intravenous administration elicited thrombolysis within minutes of rtPA administration, 3.8 ± 1.15 and 4.0 ± 2.8 (mean ± SE), respectively.

Figure 2 illustrates mean (±SE) effects of intracoronary and intravenous administration of rtPA on the rate of coronary thrombolysis. As described in the "methods" section, the values depicted are those obtained during the 30-min drug infusion interval. Also depicted is the mean rate of thrombolysis in the control group. Note that the rate of lysis in controls that did not receive rtPA is much less than in the treated dogs. Compared with intravenous administration, the rate of coronary thrombolysis was significantly increased (p < 0.01) with intracoronary administration of rtPA. The mean rate of coronary thrombolysis was increased twofold with intracoronary vs intravenous administration. The count-time coordinates obtained during drug infusion are well described by linear regression analysis (r). All r values are in excess of 0.97 and all time-activity relationships were significant at p < 0.01.

Figure 3 illustrates representative samples. Note that the rate of lysis during intracoronary and intravenous administration is relatively constant. Note that compared with intravenous administration, the rate of thrombolysis was significantly increased with intracoronary administration. With one exception, with both treatment regimens shortly after discontinuation...
of rtPA therapy, the rate of coronary thrombolysis attenuated and became relatively constant. In one dog in the intravenous group, shortly after the rtPA infusion was discontinued, the rate of coronary thrombolysis actually increased for a period of approximately 12 min.

Figure 4 illustrates mean (± SE) values for total clot lysis over 90 min. Note that in the control group, intrinsic thrombolysis was minimal. On the other hand, compared with controls, both intravenous and intracoronary administration of rtPA induced significant thrombolysis (both p<0.01 compared with controls). Compared with intravenous administration, intracoronary administration significantly increased total thrombolysis, p<0.05.

Following embolization, there was a decrease in CO, mean change from 2.8 to 2.3 L/min (p<0.05).

Table 1 depicts mean (± SE) values of CO and BP measured at the designated times in each group. Note that over the course of the experiment, CO fell in controls and in dogs treated with intracoronary rtPA. As depicted, over time, there was a small but significant change in BP in the group given intracoronary rtPA. However, there were no significant differences between groups.

Table 1—Effects of Time and Treatment on Cardiac Output (CO) and Blood Pressure (BP)*

<table>
<thead>
<tr>
<th>Groups</th>
<th>Pre-rtPA</th>
<th>rtPA 30 min</th>
<th>rtPA 90 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO, L/min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>2.6±0.3</td>
<td>2.2±0.2</td>
<td>1.9±0.2†</td>
</tr>
<tr>
<td>rtPA IV</td>
<td>2.0±0.2</td>
<td>2.0±0.2</td>
<td>1.8±0.1</td>
</tr>
<tr>
<td>rtPA IC</td>
<td>2.4±0.3</td>
<td>2.2±0.2</td>
<td>2.0±0.2‡</td>
</tr>
<tr>
<td>Mean BP, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>110±9.0</td>
<td>109±5.0</td>
<td>113±8.0</td>
</tr>
<tr>
<td>rtPA IV</td>
<td>123±6.0</td>
<td>123±6.0</td>
<td>119±7.0</td>
</tr>
<tr>
<td>rtPA IC</td>
<td>116±11.0</td>
<td>110±9.0</td>
<td>98±6.0‡</td>
</tr>
</tbody>
</table>

*pValues are mean ± SE; †IV = intravenous; ‡IC = intracoronary.

**DISCUSSION**

Our study compared the effects of intravenous vs intracoronary administration of rtPA on the rate and extent of coronary thrombolysis. We demonstrated that while both regimens were effective, compared with intravenous administration, the rate and extent of coronary thrombolysis were significantly increased with intracoronary administration. While several previous studies have compared intracoronary and intravenous administration of SK in treatment of coronary thrombosis, prior to the current study, only one canine study prospectively compared intravenous and intracoronary administration of tPA.7

As cited above, one recent clinical study compared the rates of reperfusion obtained with intravenous administration of SK and rtPA in patients presenting with acute myocardial infarction.1 Ninety minutes after onset of therapy, the rates of reperfusion with both drugs were much higher in patients with subtotal vascular occlusion (TIMI 1) than in patients with total occlusion of the infarct-related artery (TIMI 0). At 90 min, effective reperfusion occurred in 90 percent of rtPA-treated patients with subtotal vascular occlusion. In contrast, in those rtPA-treated patients who initially demonstrated total occlusion, effective reperfusion occurred in only 56 percent of patients. In patients treated with SK, the 90-min reperfusion rate was 26 percent in patients with totally occluded infarct-related arteries and 63 percent in patients with subtotal obstruction. Most likely, these differences in reperfusion rates are explained by differences in regional vascular resistances. Also, compared with thrombus causing total obstruction (TIMI 0), thrombus causing subtotal occlusion (TIMI 1) may present a greater surface area of thrombus on which the enzyme may act. Therefore, the enhanced thrombolysis in partially vs totally occluded vessels may be due to both a lower regional vascular resistance and to a greater surface area of exposed thrombus. A recent canine study employed the pulmonary artery pressure-flow relationship to investigate the mechanism of pulmonary hemodynamic improvement with rtPA in pulmonary embolism.5 From the pattern of improvement in pulmonary hemodynamics, the authors concluded that rtPA-induced thrombolysis predominantly occurred in partially as opposed to totally obstructed vascular units. These studies indicate that rtPA distribution and corresponding thrombolysis are functions of the distribution of blood flow, which is inversely related to the regional vascular resistance. Therefore, compared with totally obstructed vessels where resistance to blood flow is infinite, the binding of rtPA to fibrin and subsequent thrombolysis preferentially occurs where vascular obstruction is incomplete.

The above studies suggest that for a given dose of rtPA and constant vascular resistance, thrombolysis is
a direct function of delivery to the thrombolytic agent to the clot. A recent canine study of pulmonary embolism tested this hypothesis. Embolization with radioactive blood clot increased pulmonary artery pressure and decreased CO from 2.7 to 1.8 L/min. Following embolization, dogs were randomly divided into three groups: group 1 received 0.5 mg/kg of rtPA over 30 min; the six group 2 dogs were pretreated with hydralazine to increase CO; in the six group 3 dogs, CO was increased by opening a systemic fistula. Dogs in groups 2 and 3 received the same dose of rtPA as those in group 1. Following embolization, CO remained low in group 1 and increased with the interventions in groups 2 and 3. Mean 2-h time-averaged values were 1.9, 2.9, and 3.1 L/min, respectively. Corresponding to the increased flow in groups 2 and 3, rate and extent of pulmonary thrombolysis increased. During drug infusion, rate of thrombolysis was 30 percent lysis per hour in group 1 and 48 percent lysis per hour and 49 percent lysis per hour in groups 2 and 3, respectively. We concluded that an increase in flow enhanced rtPA-induced thrombolysis by increasing delivery of the thrombolytic agent to clot in partially obstructed vascular units.

Accordingly, compared with intravenous administration, intracoronary administration of a thrombolytic agent should enhance coronary thrombolysis. That is, despite high or infinite resistance to blood flow in the vicinity of coronary thrombus that may impair delivery of an intravenously administered drug, intracoronary administration should optimize delivery and thus efficacy of thrombolytic therapy. Several studies have compared intracoronary with intravenous administration of SK in treatment of acute myocardial infarction and intracoronary administration of SK is reported to be superior to intravenous administration in inducing coronary thrombolysis. However, even with intracoronary administration of SK, variable rates of reperfusion are reported. Most likely, these differences are due to several factors, including variation in dose, rate of infusion, location of thrombus, presence of collaterals, and ostial vs subselective drug infusion.

Only one previous study has systematically investigated intracoronary vs intravenous administration of tPA (600,000 IU over 1 h) on coronary thrombolysis. Coronary thrombus was induced by advancing a copper coil into the LAD artery. Following the induction of thrombus, dogs were randomized to receive intracoronary or intravenous SK or tPA. Both intracoronary and intravenously administered tPA were superior to both regimens of SK. On the other hand, coronary thrombolysis was similar with intracoronary and intravenous administration of tPA. The authors speculated that the intravenous route of administration is as effective as the intracoronary route because of the activator's avidity and selectivity for binding to fibrin. In this study, however, a relatively high dose of tPA was employed and it is possible that even intravenous administration resulted in an excess of the drug-fibrin receptor ratio.

Several recent canine studies support this possibility. For example, in one recent study of embolic pulmonary hypertension, we compared rate and extent of pulmonary thrombolysis when 1 mg/kg of rtPA was infused over 15 (rtPA) and 90 min. Although during drug infusion the rate of clot lysis was increased twofold with rtPA, this difference was much less than the sixfold increase in concentration achieved with rtPA. In a more recent study employing the same model, we compared thrombolytic effects of 1 mg/kg of rtPA infused over 5 and 15 min. In this study, despite a threefold increase in drug concentration with the former regimen, during drug infusion, rates of pulmonary thrombolysis were similar. Similarly, in the most recent study, despite a twofold increase in rate of infusion of rtPA (rtPA 1 mg/kg and rtPA 2 mg/kg), the mean thrombotic rate observed during drug infusion was similar. These studies indicate that the rate of thrombolysis is not directly related to serum concentration, suggesting an effective upper limit to the dose-thrombolytic rate relationship.

In the current study, we employed a relatively low dose of rtPA and demonstrated that compared with intravenous administration, intracoronary administration enhanced rate and extent of coronary thrombolysis. However, it should be emphasized that the rate of thrombolysis with intracoronary administration was increased only twofold compared with that obtained with intravenous administration. While concentrations of rtPA were not measured, the local concentration obtained with intracoronary administration must be markedly higher than the intracoronary concentration obtained with intravenous administration. Most likely, despite intracoronary administration, a high vascular resistance in the vicinity of thrombus impaired rtPA delivery to clot. This possibility is supported by previous observations demonstrating variability in revascularization with intracoronary administration of SK.

In the current study, compared with intracoronary administration of rtPA, the presence of the indwelling coronary artery catheter located upstream from the clot would tend to bias against intravenous administration. That is, the catheter, by decreasing effective vascular cross-sectional area, would tend to increase local vascular resistance and thus impair the delivery of intravenously administered rtPA to the clot. On the other hand, this criticism should not detract from the study and its conclusions. The central hypothesis of the current study is that variations in regional vascular resistance will influence local blood flow and thus delivery and efficacy of the thrombolytic agent. 

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Crowley\textsuperscript{14} described mechanical factors, such as the presence of collaterals, location of thrombus, and subselective vs ostial catheter placement that may influence the effectiveness of intracoronary administration of a thrombolytic agent. Similarly, Tendera et al\textsuperscript{15} described factors influencing the probability of reperfusion with intracoronary ostial infusion of SK or urokinase in patients with acute myocardial infarction. The strongest predictor of reperfusion was site of occlusion (p = 0.004). Arteries with proximal occlusion recanalized 74 percent of the time vs 38 percent for distal occlusion. The authors speculated that the higher probability of proximal thrombolysis may be related to local availability of the thrombolytic agent and/or plasminogen. In a distal occlusion, a "cul-de-sac" phenomenon and/or run-off through proximal branches may prevent penetration of the thrombolytic agent to the clot.

While prompt intravenous administration of a thrombolytic agent is the treatment of choice for most patients with evolving acute myocardial infarction, in certain instances, urgent or emergent cardiac catheterization is believed to be indicated. The examples include doubts regarding diagnosis, prolonged symptoms without ECG changes, apparent failure of intravenous thrombolytic therapy, or a preference for direct mechanical intervention. In some of these patients, intracoronary administration of a thrombolytic agent may be appropriate therapy. In addition, thrombolytic obstruction complicating angioplasty is often treated by intracoronary administration of a thrombolytic agent. However, prospective studies comparing effectiveness of different agents have not been carried out.

Since the current study was carried out in experimental preparation, employing exogenously produced clot, we recommend caution in direct clinical extrapolation.

\textbf{ACKNOWLEDGMENT:} We are indebted to Usha Shick, B.Sc., Heidi La Pointe, ACT, and S. Ming Chan, Ph.D., for their excellent technical assistance in carrying out this study.

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