Time Course of Thrombolysis Induced by Intravenous Bolus or Infusion of Tissue Plasminogen Activator in a Rabbit Jugular Vein Thrombosis Model

Jean-Paul Clozel, Thomas Tschopp, Eric Luedin, and Paul Holvoet

Tissue plasminogen activator is a thrombolytic agent that has been shown to be efficient in patients with myocardial infarction or pulmonary embolus. However, little is known about the time course and the dose dependency of its thrombolytic effect. The goal of our study was to investigate the time course of the thrombolysis induced by increasing doses of tissue plasminogen activator (t-PA) given either as a continuous infusion (0.0625–1 mg/kg) or as a bolus (0.05–0.4 mg/kg). For this purpose, we modified a previously described rabbit jugular vein thrombosis model by using an external gamma counter to follow continuously the thrombolysis. After administration of t-PA as either an infusion or a bolus, the rate and the extent of thrombolysis were dose dependent. The thrombus size decreased regularly following an exponential curve and reached a lower asymptote implicating an unlysable thrombus. As expected, after bolus injection, t-PA was rapidly inhibited resulting in a duration of action of approximately 15 minutes; this was independent of the dose. Surprisingly, during continuous infusion of t-PA for as long as 4 hours, the duration of action was limited to about 2 hours, although the plasma t-PA activity levels remained stable. Although the rate of inhibition was lower and thus the duration of action was longer during continuous infusion of t-PA than after a bolus injection, the extent of thrombolysis was similar when the same dose of t-PA was given as either a bolus or an infusion. These findings could be attributed to the higher initial rate of thrombolysis observed after a bolus injection. The present results underline the importance of using an experimental model where the time course of thrombolysis can be monitored to characterize the thrombolytic effects of a drug. (Circulation 1989;79:125–133)

Tissue plasminogen activator (t-PA) is a potent thrombolytic drug effective in patients with myocardial infarction.1–4 Usually, t-PA is given as a continuous infusion over 90–180 minutes. However, little is known about the time course and the duration of the thrombolysis induced by t-PA. The experimental thrombolysis models that have been described, such as the rabbit jugular vein thrombus model,5,6 the dog femoral vein thrombus model,7 or the rabbit pulmonary embolus model,8 allow a quantification of the extent of the thrombolysis at only one time point in each animal. In the dog9,10 or in the nonhuman primate11 coronary artery thrombus model, sequential coronary arteriographies can be performed, but the size of the thrombus cannot be assessed accurately; thrombolysis is usually estimated indirectly by evaluating flow characteristics. Moreover, it has been shown in rabbits12 and in humans13 that thrombolysis was not directly related to plasma functional activity of t-PA. After a bolus administration of t-PA, thrombolysis can go on even when plasma functional activity of t-PA is not measurable.12,13 Thus, plasma functional activity of t-PA is not useful to monitor the thrombolytic effect of t-PA. Therefore, we modified a previously described rabbit jugular vein thrombus model6 by using an external gamma counter to follow precisely the time course of the thrombolysis, and we evaluated the thrombolysis after giving increasing doses of t-PA as either a continuous infusion or a bolus.

Materials and Methods

Experimental Procedure

Burgundy rabbits with a body weight of 2.3–3 kg were anesthetized by intravenous injection of 35 mg/kg pentobarbital (Vetanarcol, Veterinaria AG,
Zurich, Switzerland). Additional pentobarbital was given when needed to maintain anesthesia. The rabbit was tracheotomized, and its lungs were ventilated by a mixture of 50% room air and 50% oxygen. A catheter was introduced into a femoral vein for infusing drugs, and another catheter was implanted into the femoral artery for blood sampling. Uptake of $^{125}$I by the thyroid gland was blocked by administration of sodium iodide (0.5 ml i.v. 2% solution).

The artificial thrombus in the jugular vein was produced as described by Collen et al. Briefly, the external jugular vein was exposed through a paramedial incision in the neck and carefully dissected. Small side branches were ligated, and the facial vein was cannulated. A polyester thread (Novolene 4.0, SSC Neuhausen, Switzerland) was introduced inside the jugular vein to maintain the clot in place during lysis. Two clamps were positioned at the proximal and distal part of the jugular vein segment (~4 cm length), which was then emptied of all blood by suction through the facial vein catheter. Then $^{125}$I-labeled human fibrinogen (Amersham, England) containing ~800,000 cpm was mixed with fresh rabbit blood and 10 IU thrombin (F. Hoffmann-La Roche, Basel, Switzerland) and injected into the jugular vein segment through the facial vein catheter. The clot was aged for 30 minutes before both vessel clamps were removed. Then 100 IU/kg heparin (Liquemin, F. Hoffmann-La Roche, Basel, Switzerland) was given intravenously to prevent further incorporation of fibrinogen into the clot. Fifteen minutes after removing the clamps, administration of t-PA was started. Wild-type one-chain t-PA (Biopool, Umea, Sweden) was dissolved in 0.3 M NaCl containing 0.05% Tween 80. Its specific activity was 680,000 IU/mg protein.

Assessment of Thrombolysis

Thrombolysis was evaluated by monitoring continuously the decrease of thrombus radioactivity as a measure of the decrease of thrombus size. For this purpose, a gamma detector (Model 8SHAIM/2, Harshaw, Solon, Ohio) connected to a multichannel analyzer (Model ND62, Nuclear Data, Schaumburg, Illinois) was positioned 2 cm over the jugular vein a few minutes after introduction of the radioactive clot into the isolated jugular vein segment. Then the radioactivity was continuously recorded with a counting time of 45 seconds (Figure 1). The decrease of radioactivity was displayed on the multichannel analyzer and recorded on a floppy disk. Thereafter, all data were transferred on a computer (Model 3091, IBM) for further analysis. Stability of the clot was assessed by measuring the radioactivity for 15 minutes after opening of the clamps.

At the end of the experiments, the residual thrombus was removed, and the background radioactivity of the remaining preparation was measured with the detector in the same position as during the thrombolysis experiment (Figure 1). At the end of some experiments, the extent of the thrombolysis was calculated not only from the radioactivity measured with the external gamma counter but also by comparing the residual radioactivity incorporated inside the thrombus at the end of the experiment with the radioactivity initially incorporated in the thrombus as described by Collen et al.

Curve Fitting

The data were analyzed by nonlinear regression (statistical analysis system, SAS Institute, Cary, North Carolina). The following regression model
for the size of the thrombus fitted the experimental results well:

$$T(t) = Ae^{-\gamma t} + (100\% - A)$$

where $T$ is thrombus size (% baseline), $t$ is time, $A$ is lysable fraction, $(100\% - A)$ is unlysable fraction (determined theoretically by the lower asymptote), and $\gamma$ is time constant.

With this regression model for each animal, $A$ and $\gamma$ were determined. To characterize the thrombolysis process, the following variables were calculated (Figure 2): the extent of lysis at time 120 and 240 minutes; the initial rate of lysis $\Delta T/\Delta t$ (at time $t = 0$) equals $A \cdot \gamma$, and the time at which 90% of the total lysis was obtained ($t_{90\%}$) equals $\ln(10)/\gamma$. This variable was chosen to characterize the duration of action of t-PA because the last 10% of the lysis are very slow and thus difficult to differentiate from the spontaneous lysis. In this model, both the size of the thrombus and the rate of lysis decreased exponentially with the same time course. The half-life ($t_{50\%}$) for both decreases could be calculated as $\ln(2)/\gamma$.

**Plasma Measurements**

During the experiment, 3-ml blood samples were withdrawn into 1/10 vol 108 mM citrate at times 0 (15 minutes after opening the clamps of the jugular vein), 15, 30, 60, 90, 120, and 240 minutes. Two-milliliter blood fractions were centrifuged immediately, and 100-μl aliquots of the plasma were acidified and used to measure t-PA activity. Then, 900-μl aliquots of the plasma were collected on PPACK (d-Phe-Pro-Arg-CH₂Cl, Calbiochem, Lucerne, Switzerland) and used to measure plasma fibrinogen, plasminogen, and $\alpha_2$-antiplasmin levels. In this way, all the in vitro effects associated with systemic plasminogen activation were avoided.\(^{14}\)

The third milliliter was used, as mentioned before, to measure the \(^{125}\)I radioactivity.

The plasminogen activation activity (functional activity) in plasma was measured in an S-2251 substrate–based functional assay.\(^{15}\) Plasma fibrinogen concentrations were measured with a coagulation rate assay.\(^{16}\) The residual fibrinogen concentration was expressed as a percent of the pretreatment value. Plasminogen was determined with a chromogenic substrate S-2251 as originally described by Mussoni et al.\(^{17}\) The content of $\alpha_2$-antiplasmin was determined functionally with the chromogenic substrate S-2251.\(^{18}\)

The concentrations of plasminogen and $\alpha_2$-antiplasmin in the plasma samples of the various rabbits collected before treatment varied between 50% and 150% (plasminogen) and 90% and 150% ($\alpha_2$-antiplasmin) in relation to the content of a pooled reference plasma. The contents of plasminogen and $\alpha_2$-antiplasmin in the samples obtained before treatment were therefore normalized, and those obtained after treatment are given as a percentage of the value measured before treatment (time 0).

**Study Design and Statistical Analysis**

Ten different groups of four rabbits each received in a random order increasing doses of t-PA given either as a 2-ml bolus (from 0.05 to 0.4 mg/kg in 1 minute) or as a continuous infusion (from 0.0625 to 1 mg/kg in 20 ml beginning with 10% of the total dose given as a bolus within 1 minute and 90% as a continuous infusion over 4 hours). One control group received the t-PA vehicle. The radioactivity of the thrombus was measured for 4 hours after t-PA infusion and for 2 hours after t-PA bolus injection. The dose-response relation for the variables characterizing the thrombolysis can be represented by linear regression. The plasma measurements in the different t-PA groups

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**Figure 2.** Curve fitting of the thrombolysis during an intravenous infusion of tissue plasminogen activator (t-PA) (same experiment as in Figure 1), a control injection of t-PA vehicle, or a bolus injection of 0.4 mg/kg t-PA. These three experiments have been performed in three different rabbits. The size of the thrombus (measured by the radioactivity and indicated by the dots) could be fitted (indicated by the solid line) to the regression model $T(t) = Ae^{-\gamma t} + (100\% - A)$ where $t$ is time, $(100\% - A)$ is unlysable fraction (determined theoretically by the lower asymptote), and $\gamma$ is time constant. The calculation procedure for $T_{10\%}$ and $T_{90\%}$ is shown only for the infusion experiment.
were compared with those obtained in the control group by analysis of variance at the multiple significance level of 0.05 for many-one comparisons. All the results are expressed as mean ± SEM.

Results

Thrombolysis

In the control group, the incorporated clots were lysed extremely slowly. The extent of thrombolysis was less than 11% in 240 minutes (Figure 2). In contrast, after infusion (Figures 1 and 2) or a bolus injection (Figure 2) of t-PA, the radioactivity incorporated in the clot decreased rapidly because of lysis of the thrombus. This decrease was regular, and no large part of the thrombus was embolized in the venous circulation. After continuous infusion (Figure 3) or bolus injection (Figure 4), the radioactivity curve was best-fitted by an exponential regression model.

The extent of thrombolysis at the end of a 4-hour infusion of t-PA depended on the dose \( (p<0.001) \), ranging from 16.5±2.1% for a 0.0625 mg/kg dose to 86.7±2.2% for a 0.5 mg/kg dose. Increasing the dose to up to 1 mg/kg did not result in a higher percentage of lysis. The initial rate of lysis was also dose dependent \( (p<0.01) \), ranging from 0.51±0.05%/min for 0.0625 mg/kg to 2.06±0.15%/min for 1 mg/kg. In contrast, the duration of action as assessed by the \( T_{10} \)
values was not significantly dependent on the dose. The rate of lysis decreased exponentially with time, and the values for the half-life of this decrease (T50) were dose independent and ranged from 22 to 41 minutes (Table 1).

Similarly, the extent of lysis measured at 2 hours after bolus injection of t-PA depended also on the dose (p<0.001), which ranged from 17.9±1.4% for a 0.05 mg/kg dose to 54.4±4.8% for a 0.4 mg/kg dose. The initial rate of lysis was also dose dependent (p<0.01), ranging from 1.13±0.16%/min for a 0.05 mg/kg dose to 3.94±0.20%/min for a 0.4 mg/kg dose. The values were about twice as high as those obtained after infusion of equivalent amounts of t-PA. The duration of action was again independent of the dose. The rate of lysis decreased exponentially, and the values for the half-life of this decrease were independent of the dose and ranged from 9 to 12 minutes (Table 2).

The slope of the linear regression curve for the relation between the extent of lysis obtained at 120 minutes and the dose was similar after t-PA infusion and t-PA bolus injection. Figure 5 shows the correlation between the extent of thrombolysis as calculated from the radioactivity measured with the external gamma counter and the extent of thrombolysis as calculated according to Collen et al. The linear regression correlation coefficient r was 0.965.

Plasma Measurements

During infusion of t-PA, the plasma plasminogen activation activity of t-PA increased dose dependently and remained stable between 30 and 240 minutes of infusion (Figure 6). Infusion of t-PA did not result in a significant systemic activation of plasminogen and consumption of α2-antiplasmin. Only at the highest dose (1 mg/kg) was degradation of fibrinogen significant with a decrease of 26% at 120 minutes (p<0.05) and 31% at 240 minutes (p<0.05) (Figure 6).

After bolus injection of t-PA, the plasminogen activation activity also increased dose dependently (Figure 7). However, at 30 minutes after bolus injection, t-PA activity was undetectable for all doses. Plasma fibrinogen, plasminogen, and α2-antiplasmin levels did not change significantly (Figure 7) after bolus injection of t-PA.

Discussion

The present results show that with an external gamma counter, it is possible to not only quantify the extent but to also identify the time course of the thrombolysis in a rabbit jugular vein thrombosis model. Determination of this time course showed clearly that the rate of thrombolysis decreased exponentially with time, even when t-PA was infused continuously to maintain a constant plasma t-PA functional activity. We have also confirmed the previous studies that have shown that t-PA could induce thrombolysis without causing a peripheral consumption of coagulation factors.

The use of an external gamma counter provides two clear advantages compared to the classic method where the thrombolysis is evaluated at the end of the experiment by measuring the radioactivity of the remaining clot. It allows not only control for the whole experimental procedure in order to detect any technical problem but also for measurement of the whole time course of the thrombolysis. Various technical problems can occur in this venous thrombosis model. The radioactive fibrinogen injected into the jugular vein segment can be only partly

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Lysed fraction at 240 min (%)</th>
<th>T90 (min)</th>
<th>Initial rate of lysis (%/min)</th>
<th>T50 (min)</th>
<th>Unlysable fraction (%)</th>
</tr>
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<tr>
<td>Control</td>
<td>7±1</td>
<td>1,310±661</td>
<td>0.06±0.02</td>
<td>394±199</td>
<td>79±7</td>
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<td>0.125</td>
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T90, time at which 90% of the total lysis was obtained; T50, time at which 50% of the total lysis was obtained.

<table>
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<tr>
<th>Dose (mg/kg)</th>
<th>Lysed fraction at 120 min (%)</th>
<th>T90 (min)</th>
<th>Initial rate of lysis (%/min)</th>
<th>T50 (min)</th>
<th>Unlysable fraction (%)</th>
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<td>32±2</td>
<td>3.94±0.20</td>
<td>9±1</td>
<td>46±5</td>
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</tbody>
</table>

T90, time at which 90% of the total lysis was obtained; T50, time at which 50% of the total lysis was obtained.
incorporated into the thrombus. Then, when the clamps are opened, the fibrinogen not incorporated in the thrombus is liberated into the blood. Therefore, the true initial radioactivity of the thrombus is smaller than the total radioactivity of the injected fibrinogen, leading to overestimation of the thrombolysis. With an external gamma counter, it is possible to measure exactly this initial radioactivity. Moreover, before starting the administration of a drug, the stability of the thrombus can be checked.

Finally, any breakage of the thrombus that could occur despite the wool or the surgical silk included inside the thrombus could be detected. In the method described by Collen et al,\textsuperscript{6} the amount of fibrinogen not incorporated into the thrombus was evaluated by multiplying blood radioactivity measured 1 minute after opening the clamps by the theoretical blood volume of the rabbit. This calculation was checked at the end of the experiment by making a careful isotope recovery balance.\textsuperscript{6} Such a balance is not needed in our model where the initial radioactivity of the thrombus is directly measured.

In addition to these technical advantages, the main improvement brought about by the use of an external gamma counter was that the exact time course of thrombolysis induced by t-PA could be measured in vivo. This thrombolysis was extremely regular. No large parts of the thrombus embolized into the venous circulation; the curve could be fitted to an exponential regression model. This would theoretically result in the case where the lysed amount of thrombus per unit of time is proportional to the remaining lysable fraction of the thrombus. In
theory, this could be expected if the percentage of the remaining lysable fraction of the thrombus lysed by unit of time was constant. Surprisingly, in the present study, the curves never tended toward 100% lysis. Instead, they tended toward an asymptotic value—"the unlysable fraction"—which was dose related. The presence of such an asymptote combined with the exponential equation means that the rate of lysis (expressed as the percentage of the remaining thrombus lysed per unit of time) decreased exponentially with time. Thus, during a continuous infusion of t-PA, after about 120 minutes, the rate of lysis was extremely slow or equal to zero. Depending on the dose, the thrombolysis stopped at different levels. Therefore, one could conclude that the limitation of the thrombolysis was not due to a technical artifact. If the thrombolysis had been nearly complete, it would have been impossible to observe a further lysis. But this was not the case because with the lowest doses of t-PA the extent of the lysis was less than 40%, and with the highest doses, the extent of the lysis was over 70%. This also could not be due to a progressive degradation of the t-PA that was infused because the plasma functional activities were constant during the infusion. It is also difficult to believe that this decrease of the rate of lysis was due to the progressive aging of the clot because in the same model we were able to obtain lysis of the same extent when the t-PA treatment was started as late as 2 hours after opening the clamps of the jugular vein segment (data not shown). Moreover, it has been shown in a similar model that the thrombus could still be lysed after 24 hours of aging.⁶

Our results do not agree with those obtained in a similar model by Agnelli et al.¹² These authors found a duration of action of t-PA more than 90 minutes after a bolus injection of 75,000 IU DNA recombinant t-PA by measuring the thrombolysis at different time points, and we found a duration of action of about 35 minutes. However, in the study of Agnelli et al.,¹² the thrombolysis could not be followed on-line in the same rabbit. Moreover, in their study, the thrombolysis was measured at 30, 120, and 240 minutes. At 120 minutes, the lysis was nearly complete. Therefore, it was not possible to exclude that this extensive thrombolysis was obtained earlier than at 120 minutes and that the thrombolysis thereafter was minimal. Nevertheless, even if we find a shorter duration of action of t-PA

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**Figure 7.** Plots of plasma measurements after tissue plasminogen activator (t-PA) bolus injection. The bolus injections have been made at time 0. Groups mean values are indicated.
than previously described, we can still confirm that the duration of the in vivo thrombolytic effect of t-PA was longer than the duration of the presence of measurable activity of t-PA in plasma. This has been shown before in the rabbit and in humans. 

The observed decrease of the rate of lysis with time could have been expected after a bolus injection of t-PA because it is known that the half-life of t-PA in rabbits, for example, is about 1.5–3 minutes. Therefore, as it was confirmed by the measurement of the t-PA functional activity, after a bolus injection of t-PA, the concentration of t-PA in plasma decreases rapidly; this could explain the rapidly decreasing rate of lysis. In contrast, during the infusion, the plasma concentration of t-PA was stable because new t-PA was continuously administered. Nevertheless, the rate of lysis was decreasing regularly. The design of our study did not allow us to explain this surprising finding. It is likely that the concentration of active t-PA bound on the clot determines the rate of lysis. In our study, part of the t-PA bound on the clot could have been inhibited and would have stayed on the clot and prevented new t-PA to bind to the thrombus. It is also possible that the fibrin binding sites for t-PA would not be any more accessible to the fresh t-PA that is infused.

In the present study, the thrombolysis induced by t-PA could be characterized by four factors: the extent of the lysis, the initial rate of lysis, the time at which 90% of the lysis had occurred, and the half-life of the decrease of the rate of thrombolysis. After either infusion or bolus injection of t-PA, the extent of the thrombolysis was approximately linearly related to the logarithm of the dose. Previous in vivo studies have also demonstrated a dose dependence of the thrombolytic effect. However, less than three doses were used, and a precise dose-response relation was difficult to assess. In vitro studies have also shown that the rate of lysis of a plasma clot depends closely on the concentration of t-PA. We also measured for each dose of t-PA the time at which 90% of the lysis had occurred. This variable was chosen to characterize the duration of action of t-PA because the last 10% of lysis is very slow and thus difficult to differentiate from the spontaneous lysis. The time at which 90% of the lysis had occurred was also dose independent after either bolus injection or intravenous infusion of t-PA. This was also true for the half-life of decrease of the rate of lysis.

Because the extent of lysis was log linearly related to the dose of t-PA for infusion as well as for bolus injection of t-PA, it was possible to compare the slopes. Surprisingly, the extent of lysis was not significantly different when t-PA was given as either a bolus or a slow infusion (p = 0.23). With the bolus injection, the initial rate of lysis was higher than with continuous infusion (at a comparable dose). However, after bolus injection, the duration of action was shorter than with an infusion (p < 0.001), which compensated for the higher initial lysis rate.

Thus, the final result was that intravenous infusion or bolus injection of t-PA resulted in a similar extent of thrombolysis. The results of our study could explain the findings of Agnelli et al12 that in a rabbit jugular vein thrombus model, improved thrombolysis could be obtained when t-PA was infused over a shorter period of time. Because the rate of lysis decreases continuously with time during even continuous infusion, it is likely that t-PA infused earlier is more efficient.

Currently, the main clinical indication of t-PA is the acute myocardial infarction. Acute myocardial infarction is due to the appearance of a thrombus inside a coronary artery. In the present study, we have used a venous thrombosis model with rheologic conditions different from those in a coronary artery. Therefore, our results cannot be extrapolated directly to the clinical situation. However, many clinical studies have shown that the delay of reopening of the coronary arteries after myocardial infarction is an important factor for the further clinical outcome. Therefore, the initial rate of thrombolysis might be a very important factor for the success of thrombolytic treatment. In conclusion, the present results show that not only the absolute extent of thrombolysis but also its time course should be evaluated in experimental models to characterize the effect of thrombolytic agents.

Acknowledgments

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