Pharmacodynamics of Thrombolysis With Recombinant Tissue-Type Plasminogen Activator
Correlation With Characteristics of and Clinical Outcomes in Patients With Acute Myocardial Infarction

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Coagulation analysis was performed on blood samples from 386 patients with acute myocardial infarction drawn before, during, and after a continuous intravenous infusion of 150 mg recombinant tissue-type plasminogen activator (rt-PA) (Activase®). Plasma rt-PA rose to peak levels of 2.1±3.1 μg/ml (mean±SD). Fibrinogen levels measured by coagulation rate and by sulfite precipitation decreased from baseline levels of 3.0±0.9 and 3.2±1.0 g/l, respectively, to nadir levels of 1.4±0.75 and 1.8±0.92 g/l, respectively, and were associated with peak levels in serum of fibrinogen-degradation products (FDP) of 230±470 μg/ml. Forty percent of patients experienced a nadir functional-fibrinogen level of less than 1.0 g/l, whereas 20% fell below 0.5 g/l. Nadir fibrinogen levels did not correlate with patency of the infarct-related coronary artery at 90 minutes or with risk of coronary vessel reocclusion within 7–10 days. However, the risk of coronary artery reocclusion was inversely related to the baseline functional fibrinogen level (p=0.0008), with the magnitude of its drop to nadir level (p=0.0003) as well as to peak levels of FDP (p=0.038). Quantitative blood loss correlated with all markers for systemic fibrinogenolysis including nadir fibrinogen level (r=−0.20, p=0.0011), percent decrease of fibrinogen (r=−0.22, p=0.001), and peak FDP levels (r=0.14, p=0.020). Both patients who experienced intracranial hemorrhage presented with high baseline fibrinogen levels and experienced extensive degradation of coagulable fibrinogen. Overall, patients at greatest risk of systemic fibrinogenolysis tended to be relatively older women with lower body weight. Peak plasma levels of t-PA antigen were weakly correlated with nadir-fibrinogen levels (r=0.11, p=0.041) and peak FDP levels (r=0.12, p=0.020), and also tended to be higher in older women of lower body weight. Plasma levels of t-PA antigen were higher in nonoperated patients experiencing “major” bleeding (3.4 versus 2.2 μg/ml, p=0.002). These results indicate that changes in coagulation parameters are highly variable in the setting of thrombolytic treatment with t-PA of acute myocardial infarction, precluding their use for predictive monitoring of therapy in individual patients. Nonetheless, the overall pattern of pharmacodynamic behavior of rt-PA within a given population and its correlation with selected major clinical outcomes, particularly with risk of reocclusion and bleeding, will be most useful for the design of alternative administration schemes. (Circulation 1989;80:1222–1230)
The recognition of the critical role of coronary thrombosis in acute myocardial infarction has led to more recent active investigation of the therapeutic potential of thrombolytic therapy in this setting. Randomized, placebo-controlled studies have now demonstrated that timely administration of streptokinase, anistreplase (APSAC), or recombinant tissue-type plasminogen activator (rt-PA) significantly improves survival after myocardial infarction. Results of comparative studies have demonstrated that the use of rt-PA leads to more rapid coronary thrombolysis than that of streptokinase. Although mortality results are not yet available for trials directly comparing these agents, rt-PA has been frequently used in ongoing clinical trials targeted toward the better definition of coronary thrombolysis and its additive therapy in the overall management of acute myocardial infarction.

The major limitation on the use of thrombolytic therapy has been its hemorrhagic side effects. Because the first-generation agents streptokinase and urokinase do not preferentially activate plasminogen in the presence of fibrin as opposed to circulating blood, their use has been associated with degradation of systemic coagulation components and induction of the so-called "lytic state." In fact, maximal efficiency of their action has required the presence of evidence of systemic fibrinogenolysis.

More recently, second-generation thrombolytic agents such as t-PA have emerged with recognized biochemical properties that confer the potential for relative fibrin-specific activation of plasminogen. Exploitation of this feature during thrombolysis raised hopes of increased efficacy with decreased toxicity resulting from sparing of the systemic hemostatic system. However, initial studies have now clearly shown that bleeding cannot be totally eliminated with the use of rt-PA, and in fact, bleeding has also emerged as its major limitation.

It is also now apparent that during thrombolytic therapy with rt-PA, although relative fibrin-specificity is retained, some patients will experience variably extensive systemic fibrinolytic activation with concomitant fibrinogen degradation. A role for this process in the bleeding associated with rt-PA has been hypothesized. However, accurate evaluation of the relation has been limited by problems with both in vitro artifacts, due to the high levels of rt-PA contained in blood samples collected during infusion and also to varying methodology for the assay of fibrinogen, the common precursor for both fibrin and plasmin-mediated fibrinogen-degradation products. To address these problems, a sample collection and assay system has now been developed for more accurate monitoring of these patients. The goals of the present study were to carefully characterize the alterations in the coagulation system induced by rt-PA and to investigate the relation of measured changes in coagulation assays to both demographic patient characteristics and clinical outcomes of thrombolytic therapy.

**Methods**

**Patient Population**

The patients enrolled in this study (TAMI-1) have been described in detail elsewhere. Briefly, patients presenting with symptoms of ischemic chest pain of 30 minutes to 6 hours duration with electrocardiographic ST-segment elevation of at least 0.1 mV in at least two adjacent leads were eligible for therapy with rt-PA as herein described. Patients were excluded for the usual contraindications to thrombolytic therapy, especially preexisting risk of hemorrhage, age over 75 years, or previous coronary bypass surgery.

**Treatment Protocol**

Treatment was immediately initiated with intravenous single-chain rt-PA (sc-PA) after informed patient consent. The first 176 patients received rt-PA continuously at rates of 60 mg for the first hour, 20 mg/hr for the next 2 hours, and 10 mg/hr for the next 5 hours (protocol 1). The last 210 patients received 1 mg/kg up to a maximum of 90 mg for the first hour, followed by the remainder of a 150-mg total dose over the next 5 hours (protocol 2). All patients received 10% of their first-hour dose as an initial intravenous bolus. All patients received heparin by continuous intravenous infusion to prolong the partial thromboplastin time to 1.5–2 times control, for a minimum of 24 hours. Aspirin (325 mg/day), dipyridamole (75 mg t.i.d.), diltiazem (30–60 mg q.i.d.), and lidocaine were given to all patients.

**Coagulation Assay Protocol**

Whole blood was collected at baseline, at 3 hours, within the last hour of maintenance infusion (7–8 hours for protocol 1 and 5–6 hours for protocol 2), and at 12 hours after initiation of rt-PA infusion. Blood was drawn into 0.01 M citrate anticoagulant containing 2 μM d-Phe-Pro-Arg-chloromethyl ketone (PPACK) as previously described, to avoid in vitro assay artifacts. Samples were kept on ice and centrifuged cell-free within 1 hour; then, plasma was harvested and stored frozen at −20°C. Samples were kept frozen until thawing in the central coagulation laboratory immediately before performance of coagulation assays. Fibrinogen levels were measured by the functional clotting rate assay of Clauss, as modified by Vermylen et al and by sulfite precipitation. Fibrinogen-degradation products were measured with a hemagglutination-inhibition immunoassay on serum obtained by mixing plasma with an equal volume of thrombin final concentration (65 units/ml plasma) and aprotinin final concentration (1,500 KIU/ml plasma) for 2 hours at 37°C. t-PA antigen levels were measured on once-refrozen samples with an enzyme-linked
imunosorbent assay (ELISA) based on three murine monoclonal antibodies.21

Clinical End Point Determination

Early coronary patency was determined by angiography at 90 minutes after the start of the infusion of rt-PA. Classification of perfusion was performed by a core laboratory using the TIMI grading system,8 with grade 2 or 3 considered patent. The occurrence of reocclusion of vessels patent at the time of departure from the catheterization laboratory was determined by repeat coronary angiography carried out at 7–10 days after rt-PA infusion, or sooner if recurrent ischemia occurred. Major bleeding was defined as observed blood loss of more than 500 ml or any intracranial hemorrhage. Episodes of intracranial hemorrhage were documented by CT scanning, as indicated by the onset of new neurologic deficit(s). All major hemorrhagic events were reviewed for classification by a primary and secondary study nurse, as well as by the coordinating center in the case of discrepancy. Total quantitative blood loss was expressed in arbitrary units (AU) defined as the sum of the number of transfused units of packed red blood cells and one third of the decrease in hematocrit from admission to its 48-hour nadir.22 Other markers of quantitative blood loss such as nadir hematocrit, drop in hematocrit, and units transfused were also used but found to be less useful than the AU classification.

Statistical Methods

All values are expressed as mean±SD, median with range, or both. Comparison of groups of continuous variables was made by Pearson’s correlation. Comparison of patient outcome groups with continuous coagulation variables was made by Wilcoxon rank-sum test.

Results

The major clinical outcomes of this patient group have been reported elsewhere.16,23 Briefly, a patent coronary artery was found in 72.6% of patients, with reocclusion occurring within 7–10 days in 15.3%. Major bleeding occurred in 14.2% of all (n=386) and in 10.3% of noncoronary artery bypass-grafted (n=302) patients. Transfusion of more than 2 units was required in 20.5% of all and in 10.4% of nonsurgical patients. Total blood loss as described in “Methods” was 5.7±4.6 AU in all and 4.5±3.4 AU in nonsurgical patients. Cerebrovascular accidents occurred in four nonsurgical patients, of which two were tomographically demonstrated as intracranial hemorrhage.

The results of coagulation assays are shown in Figure 1. Plasma rt-PA levels rose to 2.1±3.1 µg/ml (mean±SD) at 3 hours but fell to 1.0±1.3 µg/ml at the end of maintenance infusion (5 or 8 hours). Plasma fibrinogen measured by clotting-rate assay (Clauss) fell 50% from baseline to 1.5±0.78 g/l at 3 hours and remained relatively constant through the maintenance infusion and until 12 hours after the start of infusion. A very similar pattern was seen when fibrinogen was measured instead by sulfite precipitation, although actual values were 10–20% higher than measured with the functional assay. Fibrinogen-degradation products were recovered in serum commensurate with loss of both functional and precipitable fibrinogen.

The timing and extent of loss of systemic fibrinogen are shown in Table 1. In the majority of patients, nadir fibrinogen values were found during rt-PA infusion. However, peak fibrinogen-degradation products values (not shown) were observed at 3 hours in 60% of the patients, suggesting that most of the fibrinogen degradation occurred during the initial phase of higher-rate infusion. The correlation of systemic fibrinogenolysis with peak levels of rt-PA is shown in Table 2. Nadir functional and precipitable fibrinogen both correlated weakly (r=−0.11 and −0.14) but significantly

![Figure 1. Bar graphs of changes in coagulation parameters during rt-PA infusion in plasma obtained from blood collected on citrate and PPACK. t-PA Ag, t-PA antigen; FB-C, fibrinogen measured by coagulation rate assay (Clauss); FB-S, fibrinogen measured by precipitation (Sulfite); FDP, fibrinogen-degradation products. Values shown represent mean, and vertical bars represent SD.](image-url)
TABLE 2. Correlation of Coagulation Parameters

<table>
<thead>
<tr>
<th>Assay</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>With peak t-PA antigen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir Clauss</td>
<td>-0.11</td>
<td>0.041</td>
</tr>
<tr>
<td>Nadir sulfite</td>
<td>-0.14</td>
<td>0.066</td>
</tr>
<tr>
<td>Δ Clauss</td>
<td>0.072</td>
<td>0.21</td>
</tr>
<tr>
<td>Δ Sulfite</td>
<td>0.092</td>
<td>0.11</td>
</tr>
<tr>
<td>Peak FDP</td>
<td>0.12</td>
<td>0.020</td>
</tr>
<tr>
<td>With peak FDP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nadir Clauss</td>
<td>-0.54</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nadir sulfite</td>
<td>-0.34</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Δ Clauss</td>
<td>0.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Δ Sulfite</td>
<td>0.50</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

FDP, fibrinogen-degradation products.
Values given represent mean±SD with the following dimensions: fibrinogen, g/l; FDP, μg/ml.

(p=0.04 and 0.006) with peak rt-PA levels. Stronger and more significant relations were observed between measured fibrinogen-degradation products and nadir levels of, as well as absolute changes in, circulating fibrinogen.

The relation of these coagulation parameters with the major clinical outcomes are shown in Tables 3–6. There was no significant difference between any assay result in patients with patency of the infarct-related coronary artery at 90 minutes (Table 3), with the exception of a tendency toward a higher plasma rt-PA antigen level at the end of the maintenance infusion (1.1±1.5 versus 0.8±0.9 μg/ml, p=0.05). Results of assays in patients experiencing reocclusion versus no reocclusion within 7–10 days are shown in Table 4. Reocclusion rates in the patient groups with immediate versus delayed angioplasty (99 and 98 patients, respectively) were very similar (11% versus 13%), so both groups were pooled for analysis with the patient group having thrombolitically patent infarct-related arteries that were not randomized due to unsuitable anatomy (98 patients) or that were mechanically patent from rescue angioplasty (74 patients). Patients without reocclusion displayed a significantly greater drop in functional fibrinogen from baseline (Δ Clauss) (1.8±1.1 versus 1.2±1.0 g/l, p=0.0003), as well as higher peak generation of fibrinogen-degradation products (310±550 versus 200±450 μg/ml, p=0.038). Nadir functional fibrinogen (1.2±0.8 versus 1.4±0.7 g/l) was not significantly different for the two groups. Because a larger drop in fibrinogen could result from either a lower nadir or a higher baseline value and because nadir fibrinogen values by either method were similar in both groups, the analysis was further extended to include baseline functional fibrinogen. As can be seen, patients with no reocclusion did present with a significantly higher baseline fibrinogen level as measured by the Clauss method (3.1±1.0 versus 2.6±0.7 g/l, p=0.0008).

The relation of assay results to hemorrhagic outcome was first analyzed by comparison of patients with or without major bleeding. As shown in Table 5, among all patients, rt-PA levels tended to be higher, nadir fibrinogen levels significantly lower, and the change in fibrinogen significantly more in those with major bleeding. When the analysis was restricted to nonsurgical patients only, the difference in rt-PA levels was both more profound and statistically significant, especially at peak levels, but the differences in nadir fibrinogen and in absolute changes in fibrinogen were less profound. The relation between bleeding and peak fibrinogen-degradation products was very similar in both categories for both groups.

Alternatively, quantitative blood loss, defined as the sum of units of packed red cells transfused and one third of the decrease in hematocrit (approximate number of units lost but not replaced) from admission to nadir was also compared with changes in coagulation assays (Table 6). This approximation of total blood loss was found to correlate (r=0.43) significantly (p=0.0001) with protocol-defined major bleeding. Both in all patients and in nonsurgical patients, quantitative bleeding correlated most strongly with nadir levels of functional fibrinogen, as well as with its absolute decrease. In addition, in nonsurgical patients, there was a significant correlation between total blood loss with the plasma

TABLE 3. Relation of Changes in Coagulation Parameters With Coronary Patency at 90 Minutes

<table>
<thead>
<tr>
<th>Assay</th>
<th>Reocclusion (n=55)</th>
<th>No reocclusion (n=104)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak t-PA AG</td>
<td>2.1±2.1</td>
<td>2.5±5.1</td>
<td>0.70</td>
</tr>
<tr>
<td>5–8 Hr t-PA AG</td>
<td>1.1±1.5</td>
<td>0.8±0.9</td>
<td>0.05</td>
</tr>
<tr>
<td>Nadir Clauss</td>
<td>1.3±0.8</td>
<td>1.4±0.7</td>
<td>0.14</td>
</tr>
<tr>
<td>Nadir sulfite</td>
<td>1.6±0.8</td>
<td>1.7±0.9</td>
<td>0.26</td>
</tr>
<tr>
<td>Δ Clauss</td>
<td>1.8±1.1</td>
<td>1.6±1.1</td>
<td>0.25</td>
</tr>
<tr>
<td>Δ Sulfite</td>
<td>1.7±1.1</td>
<td>1.6±1.2</td>
<td>0.38</td>
</tr>
<tr>
<td>Peak FDP</td>
<td>280±510</td>
<td>250±510</td>
<td>0.34</td>
</tr>
</tbody>
</table>

FDP, fibrinogen-degradation products.
Values given represent mean±SD with the following dimensions: t-PA AG, μg/ml; Fibrinogen, g/l; FDP, μg/ml.

TABLE 4. Relation of Changes in Coagulation Parameters With Coronary Reocclusion

<table>
<thead>
<tr>
<th>Assay</th>
<th>Reocclusion (n=55)</th>
<th>No reocclusion (n=304)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak t-PA AG</td>
<td>2.0±1.9</td>
<td>2.1±2.0</td>
<td>0.19</td>
</tr>
<tr>
<td>5–8 Hr t-PA AG</td>
<td>0.9±1.0</td>
<td>1.0±1.4</td>
<td>0.81</td>
</tr>
<tr>
<td>Nadir Clauss</td>
<td>1.4±0.7</td>
<td>1.2±0.8</td>
<td>0.066</td>
</tr>
<tr>
<td>Nadir sulfite</td>
<td>1.7±0.8</td>
<td>1.6±0.8</td>
<td>0.19</td>
</tr>
<tr>
<td>Δ Clauss</td>
<td>1.2±1.0</td>
<td>1.8±1.1</td>
<td>0.0003</td>
</tr>
<tr>
<td>Δ Sulfite</td>
<td>1.4±1.1</td>
<td>1.7±1.1</td>
<td>0.11</td>
</tr>
<tr>
<td>Peak FDP</td>
<td>200±450</td>
<td>310±550</td>
<td>0.038</td>
</tr>
<tr>
<td>Baseline Clauss</td>
<td>2.6±0.7</td>
<td>3.1±1.0</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

FDP, fibrinogen-degradation products.
Values given represent mean±SD with the following dimensions: t-PA AG, μg/ml; Fibrinogen, g/l; FDP, μg/ml.
rt-PA level at the end of the infusion and with the peak fibrinogen-degradation products level.

Four patients in this study experienced a cerebrovascular accident, which was diagnosed with CT scanning in two as an intracranial hemorrhage. The new neurologic deficit in both of the latter patients occurred between 6 and 8 hours after the start of the rt-PA infusion. Both were older (ages, 63 and 74 years), Caucasian women with chronic hypertension. Both had relatively high baseline functional fibrinogen levels (5.0 and 4.0 g/l), and each had experienced marked fibrinogen degradation by 3 hours (0.48 and 0.72 g/l). Both patients displayed markedly elevated peak fibrinogen-degradation products levels (770 and 400 μg/ml).

Because of the overall association of systemic fibrinogenolytic assay changes with both increased bleeding and reduced risk of reocclusion, further analysis was undertaken to determine the relation between baseline demographic features of patients and changes in coagulation measured after rt-PA infusion (Tables 7 and 8). Systemic fibrinogenolysis, as reflected by lower nadir fibrinogen, greater drop in fibrinogen, and higher levels of fibrinogen-degradation products, was more likely to occur in older women with lower body weight. These changes were less marked in diabetics or smokers and were not affected by a history of uncontrolled hypertension, infarct location, or peripheral vascular disease (Table 7). The patients more likely to experience systemic fibrinogenolysis (older women with lower body weight) also tended to have higher rt-PA levels at the end of the infusion. However, there were no significant differences in the changes in coagulation assays with the use of a weight-adjusted rather than fixed first-hour dose (Table 7), which nonetheless was associated with significantly lower peak blood rt-PA levels. No correlation was observed between the ejection fraction at 90 minutes and changes in blood coagulation parameters.

**Discussion**

The major goal of our study was to evaluate the relations among a variety of coagulation assays and clinical outcomes that are likely to be affected during thrombolytic therapy with rt-PA. This effort was facilitated by two important features. First, blood samples were collected on the protease inhibitor PPACK, which rapidly inactivates the rt-PA molecule and thereby prevents subsequent in vitro assay artifact. Second, this study comprised a large patient population, which was similarly treated with respect to thrombolytic therapy and carefully characterized for major clinical outcomes. Detailed angiographic determination of early coronary patency and subsequent reocclusion and prospective evaluation of clinically defined bleeding or quantitative blood loss were particularly important. Together, these data have allowed both improved assessment of the pharmacodynamics of rt-PA and the analysis of its relation to these significant clinical events.

Direct comparison of the results of our study with coagulation data obtained during previous studies with rt-PA11,13,14,24–27 is difficult because of varying methodologies of sample collection and assay performance, especially for the quantification of fibrinogen. In addition, the use of different preparations and dose regimens of rt-PA has added further
complexity to the analysis. Nonetheless, in the present study, we have adequately assessed the impact of dosage schemes of rt-PA that achieve a high rate of early coronary patency on hemostasis.

In addition to confirming that rt-PA is not absolutely fibrin specific when used at these high doses, this study revealed relatively extensive systemic fibrinogen degradation with 40% of patients experiencing a decrease of coagulable fibrinogen to less than 1 g/l. The degradation was less extensive when measured by precipitation, with 24% of patients decreasing to less than 1 g/l, similar to that found in the only other reported patient group receiving a total dose of 150 mg sc-rt-PA, in which 17% of the patients had a fibrinogen (measured by precipitation) drop to less than 1.5 g/l.14 Noteworthy is a preliminary report of coagulation analyses from the TIMI-IIB Trial, which has shown, using methodology very similar to that of this study, even greater systemic functional fibrinogen degradation (62% of patients decreasing to less than 1 g/l) at a total 150-mg dose of rt-PA but less extensive fibrinogen degradation (15% of patients decreasing to less than 1 g/l) when used at the currently approved dose of 100 mg.29 Of importance, the 150-mg dose given initially in TIMI-IIB was given as 90 mg during the first 1 hour, in contrast to our lower first-hour dose (60 mg or 1 mg/kg). This would support the importance of the magnitude of the early-phase rt-PA dose in inducing systemic fibrinogen degradation, also reflected by our observation of relatively early distribution of peak fibrinogen-degradation products levels (9% at 3 hours). Furthermore, the large interindividual variability of plasma rt-PA levels

### Table 8. Major Clinical Correlates With Hematologic Parameters

<table>
<thead>
<tr>
<th>Continuous variable</th>
<th>Assay</th>
<th>r</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>5–8 Hr t-PA</td>
<td>0.18</td>
<td>0.0007</td>
</tr>
<tr>
<td>Nadir Clauss</td>
<td>−0.10</td>
<td></td>
<td>0.050</td>
</tr>
<tr>
<td>Δ Clauss</td>
<td>0.18</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Peak FDP</td>
<td>0.19</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline Clauss</td>
<td>0.13</td>
<td></td>
<td>0.024</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>5–8 Hr t-PA</td>
<td>−0.17</td>
<td>0.002</td>
</tr>
<tr>
<td>Nadir Clauss</td>
<td>0.15</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>Δ Clauss</td>
<td>−0.20</td>
<td></td>
<td>0.006</td>
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<tr>
<td>Nadir sulfite</td>
<td>0.26</td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Δ Sulfite</td>
<td>−0.18</td>
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<td>0.002</td>
</tr>
<tr>
<td>Peak FDP</td>
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<td>0.019</td>
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<tr>
<td>Baseline Clauss</td>
<td>−0.10</td>
<td></td>
<td>0.076</td>
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FDP, fibrinogen-degradation products.

Values given represent mean=SD with the following dimensions: t-PA, μg/ml; fibrinogen, g/l; FDP, μg/ml.
and a weak correlation between plasma rt-PA levels and degradation of fibrinogen were again evident. Because of this high degree of variability, it was predicted that a large clinical data bank would be required to adequately evaluate the relations of such widely variable coagulation parameters with clinical outcomes.

No correlation was observed between the extent of systemic fibrinogen degradation and the frequency or coronary artery patency at 90 minutes, not unexpected in view of the fact that rt-PA is a relatively fibrin-specific thrombolytic agent with a higher degree of selectivity for plasminogen activation at the fibrin surface. This property distinguishes rt-PA from streptokinase, urokinase, and APSAC, which require systemic fibrinolytic activation for thrombolytic efficacy. A significant relation between coronary patency and the extent of fibrinogen breakdown was observed in the European cooperative studies; however, these were carried out with two-chain rt-PA and the correlation was weak.

The role of fibrinogen degradation in the process of reocclusion appears to be more complex. Although no significant difference was observed between levels of nadir fibrinogen by either method, both the relative drop in functional fibrinogen and levels of peak fibrinogen-degradation products were significantly greater in patients with sustained coronary patency. Supportive of the role of the amount of fibrinogen degradation, as opposed to the level of residual fibrinogen, as a key to risk of reocclusion is the impact of the level of baseline fibrinogen. Higher levels of baseline fibrinogen could theoretically provide more substrate for degradation, thus leading to increased generation of degradation products, known to have anticoagulant and antiplatelet effects. Indeed, a correlation between baseline fibrinogen and peak fibrinogen-degradation products did exist \( (r=0.16, p=0.005) \) in these patients. This result may be appropriately placed in the context of our recent observation of the reduced risk of reocclusion in patients treated with fibrinogenolytic doses of urokinase, in combination with doses of rt-PA capable of achieving high thrombolytic efficacy.

More consistent relations were observed between changes in coagulation assays and clinical bleeding or quantitative blood loss. Overall, blood plasma t-PA levels tended to be significantly higher in patients with major bleeding, especially when surgical patients were removed from analysis. Quantitative blood loss in this same nonsurgical patient group was significantly correlated with all three indexes of systemic fibrinogenolysis, that is, the nadir fibrinogen level, the absolute decrease in fibrinogen, and the peak value of fibrinogen-degradation products. Furthermore, intracranial hemorrhage was noted in two patients with large previous changes in these three parameters, including a profound degradation of functional fibrinogen but less extensive degradation of precipitable fibrinogen. Of interest, both patients presented with elevated baseline fibrinogen as measured by both methods. In fact, the second patient, with a level of 2.1 g/l, would have been estimated to still have a fibrinogen value within the limits of normal (1.5–3.0 g/l), if determined with the precipitation assay. It has been previously demonstrated that large fibrinogen-degradation products, such as Fragment X, that predominate during thrombolytic therapy with rt-PA are measured in precipitation assays but not in coagulation assays. Still, in a direct comparison of the two assay methods we found that although sulfite values tended to be slightly but consistently higher than those of the Clauss assay, this difference did not appear to be more pronounced at lower fibrinogen values observed during rt-PA treatment. Whether the marked dissociation between coagulable and precipitable fibrinogen levels observed in these two catastrophic occurrences is of mechanistic significance is unclear and will require further analysis in larger numbers of patients. Nonetheless, because of the stronger correlation with quantitative bleeding, we have selected the functional fibrinogen assay for ongoing investigation.

The contribution of the systemic fibrinogenolytic state to bleeding, although significant, should not be overstated from the present data. The risk of hemorrhage associated with thrombolytic therapy indeed appears to be more closely related to invasive procedures, demographic characteristics of the patient including older age, lower body weight, and female gender, in addition to the occurrence of systemic fibrinogen breakdown. Multiple regression analysis of all these factors has nonetheless shown that nadir functional fibrinogen levels are a weak but independent predictor of blood loss in this patient population. Of interest, as shown here, the patients most likely to experience fibrinogen degradation with rt-PA are older and lighter women, the same subgroup at highest risk for bleeding. It is possible that adjusting therapeutic protocols in these high-risk patients may well lead not only to improved pharmacodynamics but also, more important, to reduced toxicity.

Finally, it is important to develop a perspective on the role of laboratory monitoring during thrombolytic therapy in patients with acute myocardial infarction. Our goals in the present study were 1) to describe the coagulation assay changes that occur during thrombolytic therapy with rt-PA in a dose regimen with proven high efficacy for coronary thrombolysis in a large patient group, 2) to relate these observed changes to those predicted by the known molecular interactions of the components of the coagulation and fibrinolytic systems, 3) to relate these changes to the demographic characteristics of the patient, and 4) to relate these changes to the clinical outcome(s) of the population as a whole, as well as to those of the individual patient. The present study significantly extends knowledge with
respect to each of these goals, based on a large data base from a well-characterized quality-controlled clinical population and a blood sample bank as free of in vitro artifact as is currently possible to achieve. Notwithstanding these strengths, a high degree of interindividual variability in assay parameters and response to rt-PA infusion was still observed.

As a result, coagulation assay monitoring, which does carry a significant predictive value for certain clinical outcome(s) in a patient population, cannot be generally recommended for the individual patient receiving rt-PA. The single determination of a functional fibrinogen level at the end of the rt-PA infusion might be useful to facilitate more rapid management of bleeding complications, that is, the need for interruption of heparin anticoagulation only or the additional replacement of coagulation factors. However, fibrinogen assays will not, despite their relation to increased risk of bleeding, adequately predict its actual occurrence in a given patient. Still, the characterization of pharmacologic and clinical dynamics of rt-PA infusion in an aggregate patient population may prove useful in refining future investigations of rt-PA, alone or in combination with adjunctive therapy, aiming at more effective and safe thrombolytic therapy.

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Appendix

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Although Dr. Stump had no financial interest in Genentech, Inc, during the conduct of the study, he has since become its employee. Dr. Collen has an interest in a royalty bearing licensing agreement on t-PA between the University of Leuven, Belgium, and Genentech.

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References


2. GISSI (Gruppo Italiano per lo studio della streptochinasi nell’infarto miocardico): Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. Lancet 1986;1:397–401


Hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. 

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