Change in Hemostatic Markers After Recombinant Tissue-Type Plasminogen Activator Is Not Associated With the Chance of Recanalization

Joan Martí-Fàbregas, PhD; Montserrat Borrell, PhD; Dolores Cocho, MD; Sergi Martínez-Ramírez, MD; Mercè Martínez-Corral, MD; Jordi Fontcuberta, PhD; Josep-Lluís Martí-Vilalta, PhD

Background and Purpose—We evaluated the association between recombinant tissue-type plasminogen activator recanalization and change in hemostatic markers.

Methods—We studied 40 patients. Recanalization was measured with transcranial Doppler. We evaluated the change in markers of coagulation (fibrinogen) and fibrinolysis (thrombin activatable fibrinolysis inhibitor and α2-antiplasmin) in patients with ischemic stroke treated with recombinant tissue-type plasminogen activator. Samples were obtained before and 90 minutes after recombinant tissue-type plasminogen activator infusion.

Results—The analyses (2-way analysis of variance) showed that the change in the value of each marker did not depend on the vascular patency status.

Conclusion—From a practical point of view, the measurement of these hemostatic markers is probably not useful for predicting recanalization. (Stroke. 2008;39:234-236.)

Key Words: cerebral ischemia | hemostasis | recanalization | reperfusion | thrombolysis

In different studies, there is a great deal of variability in the percentage of early partial or total recanalization with recombinant tissue-type plasminogen activator (rtPA) that is achieved in only 34% to 78% of patients.1,2 One hypothesis is that efficient recanalization is likely only if certain changes in hemostatic levels are achieved in comparison with baseline levels. A recently reported study suggested that hemostatic activation is associated with clinical outcome in patients treated with intravenous rtPA,3 although no data about vascular patency was provided.

We report our results on the use of some specific markers of coagulation and fibrinolysis before and after rtPA administration. We tested the hypothesis that the chances of recanalization would be higher with a lower fibrinolytic inhibitor activity or a lower coagulation activity after the administration of rtPA.

Materials and Methods

We prospectively studied consecutive patients treated with intravenous rtPA within 3 hours of the onset of symptoms of ischemic stroke using the standard dose of 0.9 mg/kg. The vascular status was assessed at baseline and within the first 6 hours with transcranial Doppler, and all had a proximal or distal middle cerebral artery occlusion before the infusion. We used the criteria provided by the Thrombolysis in Brain Infarction classification.4 We defined “complete recanalization” as an increase in the blood flow from distal (Thrombolysis in Brain Infarction II/III) or proximal (Thrombolysis in Brain Infarction 0/I) occlusion to normal flow (Thrombolysis in Brain Infarction IV/V) and “partial recanalization” as an increase from proximal occlusion to distal occlusion.

The severity of the neurological deficit was measured as the National Institutes of Health Stroke Scale score. The ethics committee at our hospital approved the design of the study and the patients or their legal representatives gave written consent to participate.

Laboratory Assessment

Before the administration of rtPA and 30 minutes after the rtPA infusion was finished, we collected blood samples by venipuncture in 1/10 of 0.129 mol/L sodium citrate as an anticoagulant. The after-infusion blood sample was collected with aprotinin, a protease inhibitor. Platelet-poor plasma was obtained by centrifugation and was frozen at −40°C until used. A normal plasma pool was prepared by mixing plasma from 100 healthy blood donors. We measured fibrinogen (von Clauss method with thrombin; BioMerieux), α2-antiplasmin (chromogenic method; Chromogenix, Mölndal), and functional thrombin activatable fibrinolysis inhibitor (Actichrome TAFI kit; American Diagnostica, using the normal plasma pool as a standard). The results were expressed as percentage of normal plasma.

Statistical Analyses

For each marker, we calculated the values at baseline and after rtPA and the difference between both samples. From these measurements, we calculated the percentage of change. Mean and SD of continuous variables were compared between the 2 groups (partial/total recan-
Results of the 2-way analysis of variance. Change in the value of each marker depending on the vascular patency status (recanalization, solid line; no recanalization, dashed line).

### Table. Comparison of the Values* of Hemostatic Markers According to Recanalization

<table>
<thead>
<tr>
<th></th>
<th>Recanalization (n=19)</th>
<th>No Recanalization (n=21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen, g/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.78 (1.3)</td>
<td>3.60 (0.9)</td>
<td>0.77</td>
</tr>
<tr>
<td>After rtPA</td>
<td>2.78 (0.9)</td>
<td>2.49 (0.6)</td>
<td>0.27</td>
</tr>
<tr>
<td>Absolute change</td>
<td>0.99 (0.86)</td>
<td>1.11 (1.23)</td>
<td>0.83</td>
</tr>
<tr>
<td>Percent change</td>
<td>−23.8 (22.4)</td>
<td>−25.5 (24.9)</td>
<td>0.73</td>
</tr>
<tr>
<td>α2-antiplasmin, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>89.2 (16.6)</td>
<td>93.5 (16.1)</td>
<td>0.42</td>
</tr>
<tr>
<td>After rtPA</td>
<td>12.7 (16)</td>
<td>18.1 (13.2)</td>
<td>0.27</td>
</tr>
<tr>
<td>Absolute change</td>
<td>78.6 (23.4)</td>
<td>74.1 (17.5)</td>
<td>0.53</td>
</tr>
<tr>
<td>Percent change</td>
<td>−85.8 (18.8)</td>
<td>−80.68 (13.3)</td>
<td>0.35</td>
</tr>
<tr>
<td>Functional thrombin activatable fibrinolysis inhibitor, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>116.2 (29.3)</td>
<td>108.4 (29.2)</td>
<td>0.41</td>
</tr>
<tr>
<td>After rtPA</td>
<td>96.7 (31.9)</td>
<td>97.6 (26)</td>
<td>0.92</td>
</tr>
<tr>
<td>Absolute change</td>
<td>19.4 (22.9)</td>
<td>7.7 (30.1)</td>
<td>0.18</td>
</tr>
<tr>
<td>Percent change</td>
<td>−15.5 (19.7)</td>
<td>−3.1 (28.7)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

*Values expressed as mean (SD).

Our study included 40 patients, 21 men and 19 women, with a mean age of 67.8±11.2 years. The treatment was started at a mean of 150.4±36.1 minutes after the onset of symptoms. The median National Institutes of Health Stroke Scale score before treatment was 14.5. According to the TOAST criteria, the etiological classification was as follows: 20% large artery atherothrombosis, 52.5% cardiac embolism, 2.5% unusual, and 25% unknown. Before rtPA, 10 patients (25%) had a proximal occlusion, whereas 30 patients (75%) had distal occlusion. Partial (n=2) or total (n=17) recanalization was achieved in 19 (47.5%) of the patients. The Table shows that there were no differences between groups in any marker either in the absolute change after thrombolysis or in the percentage of change from the baseline to the control value.

The 2-way repeated-measures analysis showed a statistically significant decrease of each marker after thrombolysis (fibrinogen P<0.0001, α2-antiplasmin P<0.0001, functional thrombin activatable fibrinolysis inhibitor P=0.003) but with no association with recanalization (fibrinogen P=0.73, α2-antiplasmin P=0.53, functional thrombin activatable fibrinolysis inhibitor P=0.18; see Figure). Due to technical reasons, measurements of baseline and after-infusion α2-antiplasmin were available in only 33 patients. A multivariate analysis of variance test was performed with the 33 patients in whom we measured all 3 markers that confirmed a decrease of values over time (P<0.0001) but without a relationship to recanalization (P=0.68).

### Discussion

We found that the chance of recanalization was not affected by the changes in the levels of fibrinogen, α2-antiplasmin, and functional thrombin activatable fibrinolysis inhibitor after the administration of intravenous rtPA. To our knowledge, this is the first study that has attempted to analyze the effect of these changes on recanalization.

It is not surprising to find that recanalization is associated with clinical outcome. After an ischemic stroke, the likelihood of recanalization depends in large measure on the composition and size of the clot and on the time from onset to treatment. In addition, it seems reasonable to hypothesize that the baseline level of fibrinolytic inhibitors correlates inversely with the probability of recanalization, although no studies have reported the importance of the time sequence of changes of fibrinolysis inhibitors. Moreover, the failure of thrombolysis in ischemic heart disease has been associated with an insufficient reduction in the levels of fibrinogen.

Finally, a recent study found an association between hemostatic activation and clinical outcome. Although we also found a dynamic change in these hemostatic markers, we were unable to find an association between the level of these markers and the likelihood of recanalization.
One limitation of our study is the small sample of patients. Also, the levels of hemostatic markers in the blood samples may not be a reflection of the actual reactions occurring inside or near the clot. Obviously, there are markers of coagulation and fibrinolysis, other than those that we measured, that could affect recanalization. The degree, speed, and the exact timing of recanalization within 6 hours can affect the results also.\(^5\) We did not account for the exact location of the occlusion. Finally, we did not take into account the possibility that ultrasound could facilitate recanalization and the relevance of the etiology of stroke.

In summary, our study suggests that the measurement of fibrinogen and fibrinolysis inhibitors after treatment with rtPA does not add useful information from the practical or pathophysiological point of view in evaluating the likelihood of recanalization.

**Acknowledgments**

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**Disclosures**

None.

**References**

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