Reperfusion Half-Life
A Novel Pharmacodynamic Measure of Thrombolytic Activity

José G. Merino, MD, MPhil; Lawrence L. Latour, PhD; Li An, PhD; Amie W. Hsia, MD; Dong-Wha Kang, MD; Steven Warach, MD, PhD

Background and Purpose—We hypothesized that the probability of reperfusion can be modeled by an exponential decay (ie, half-life) function and that this reperfusion half-life is decreased by thrombolytic treatment.

Methods—Serial perfusion MRI scans were evaluated for evidence of reperfusion in intravenous tissue plasminogen activator-treated (n=45) and untreated (n=103) patients. The cumulative probability of reperfusion for each group was fit with exponential decay functions. The resulting reperfusion half-life (ie, the time it takes half the sample to reperfuse) was calculated.

Results—In untreated patients, a monoexponential decay function fit the data well (R²=0.95) with a half-life of 29.1 hours. In tissue plasminogen activator-treated patients, the data were best fit with a biexponential decay function (R²=0.99) that had a fast and a slow component. The fast component is attributable to tissue plasminogen activator therapy and has a half-life of 0.71 hours, whereas the slow component was similar to that of the untreated group. Approximately 3.5 hours after the start of treatment, the effect of tissue plasminogen activator on the probability of reperfusion was negligible.

Conclusion—The probability of reperfusion can be well described by the reperfusion half-life. Determination of the fast component reperfusion half-life may be an approach to compare the relative potency of different thrombolytic agents.

Key Words: MRI ■ reperfusion ■ stroke ■ thrombolytic therapy

Tissue reperfusion is the goal of acute stroke therapies, and prompt reperfusion is associated with smaller final infarct volume and improved outcome.1,2 Reperfusion is a naturally occurring dynamic process that can be augmented and accelerated in some patients using a thrombolytic agent.1,3–5 Among untreated patients, the probability of finding a penumbral pattern decreases gradually over time,6 and the probability of a favorable response to intravenous tissue plasminogen activator (tPA) also declines logarithmically as time from stroke onset to initiation of treatment increases. Many biological processes, including drug kinetics, follow an exponential decay model, and we hypothesized that reperfusion of ischemic stroke does as well.7

The purpose of this study was to parameterize the time–reperfusion relationship in tPA-treated patients. We hypothesized that (1) the rate of spontaneous reperfusion can be modeled using an exponential decay function from which the reperfusion half-life, the time it takes for half the patients to have reperfusion, can be calculated; and that (2) treatment with intravenous tPA will shift the curve to the left, leading to a shorter reperfusion half-life.

Methods

Patients
This is an analysis of data collected prospectively as part of a natural history study approved by the Institutional Review Board at the National Institute of Neurological Diseases and Stroke and Suburban Hospital. All patients or their authorized representative signed informed consent. We considered all consecutive patients with ischemic stroke who had a baseline MRI with diffusion- and perfusion (PWI)-weighted images within 24 hours of onset and at least one follow-up PWI within 1 week. We included patients who were treated in a standard fashion as per the clinical pathway of the National Institutes of Health Stroke Program at Suburban Hospital, including those who received intravenous tPA consistent with current guidelines.8 We excluded patients treated with intraarterial thrombolytics or who were enrolled in clinical trials, patients who despite a clinical diagnosis of stroke had negative diffusion-weighted and PWI images at baseline, and patients with brainstem or lacunar stroke.

Imaging
Imaging was performed in a 1.5-Tesla MRI scanner. Typical MRI parameters and the methodology used to generate mean transit time maps from the PWI using the first over zeroeth moment have been previously described.2 Three readers reviewed the images in 2 stages. In the first stage, we identified patients who had imaging...
exclusion criteria using baseline diffusion-weighted images, PWI, gradient recalled echo, and fluid-attenuated inversion recovery images of potentially eligible patients. In the second stage, we reviewed the baseline diffusion-weighted images and baseline and follow-up mean transit time maps of patients not excluded in the first stage to determine whether reperfusion had occurred with respect to baseline (a dichotomous outcome). For this analysis, we were interested in any degree of visually apparent reperfusion, which we believe represents a decrease of the mean transit time delay volume of at least 20% to 30%, a change in volume associated with good clinical outcome.2–5

Statistical Analysis and Modeling
We analyzed patients in 2 groups: treated versus not treated with intravenous tPA. We compared groups using Student t, the Mann–Whitney, or Fisher exact test, as appropriate, and calculated the cumulative probability of reperfusion (the complement of the probability of survival) using standard Kaplan–Meier methodology. For the survival analysis, we considered the time to reperfusion as the midpoint between the last scan without reperfusion and the first scan in which reperfusion was noted. Patients who at baseline had a diffusion-weighted lesion but a normal PWI were included in the analysis, and the midpoint between the onset of symptoms and the baseline scan was taken as the time of reperfusion. We fit mono- and biexponential decay models using a nonlinear least squares algorithm using an IDL program with a Levenberg-Marquardt nonlinear least-square fitting subroutine (see Supplemental Table I, available online at http://stroke.ahajournals.org for details) and calculated a decay constant (τ) and the reperfusion half-life, as described in Supplemental Table I.9 Initially, we fit a monoexponential function, and if this did not fit the data well, we used a biexponential one.

Results
In a period of 40 months, we evaluated 497 consecutive patients with ischemic stroke who had a baseline MRI and at least another PWI scan within 1 week of onset of symptoms. For this analysis, we excluded, before the first stage, 303 patients because they did not meet baseline inclusion/exclusion criteria and, after the first stage, 46 patients who had imaging exclusion criteria. Thus, 148 patients were included in the final sample and evaluated in the second stage: 45 who were treated with intravenous tPA and 103 who were not (Supplemental Table II). The median time to reperfusion in the untreated group was longer than in the tPA-treated group (24.7 hours; 95% CI, 20.1 to 29.3 hours versus 7.7 hours; 95% CI, 0 to 18.1 hours, respectively; P=0.004).

In the untreated group, the cumulative probability of reperfusion was well fit by a monoexponential function ($R^2=0.95, \tau=41.97$). The reperfusion half-life was 29.1 hours (Figure 1; Table). In contrast, the cumulative probability data from the tPA-treated group was less well fit by a monoexponential function ($R^2=0.83$). However, a biexponential function with fast and slow components of markedly different time constants fit the tPA data much better ($R^2=0.99$; Figure 2). The inflection point of the curve occurred 3.5 hours after onset of treatment; at this time, 97% of patients who would reperfuse at the fast rate had done so. Reperfusion occurred early in 41% of tPA-treated patients with a time constant, $\tau_1$, of 1.02 hours and a half-life of 0.7 hours after treatment. This is suggestive of the effect of tPA. Reperfusion occurred late in 54% of the tPA-treated patients with a time constant, $\tau_2$, of 42.18 hours and a half-life of 29.2 hours, which is similar to that of the untreated group. This suggests that in this fraction of patients, reperfusion occurred spontaneously through intrinsic mechanisms and was not due to the effect of tPA. From the model we estimate that the remaining 5% of patients had some reperfusion before the start of tPA at the spontaneous reperfusion rate.

Discussion
Time to reperfusion after acute stroke is well described by the reperfusion half-life, a novel pharmacodynamic variable.

Table. Time Constant and Reperfusion Half-Lives for the Spontaneous Reperfusion and the Intravenous tPA Groups

<table>
<thead>
<tr>
<th></th>
<th>Time Constant (τ)</th>
<th>Reperfusion Half-Life (t½)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous reperfusion</td>
<td>41.97</td>
<td>29.1 hour</td>
</tr>
<tr>
<td>Intravenous tPA (fast component)</td>
<td>1.02</td>
<td>0.7 hours*</td>
</tr>
<tr>
<td>Intravenous tPA (slow component)</td>
<td>42.18</td>
<td>29.2 hours*</td>
</tr>
</tbody>
</table>

*Time from start of intravenous tPA infusion.
Modeling the probability of reperfusion to calculate the reperfusion half-life can help differentiate spontaneous from therapy-induced reperfusion and may potentially be used to compare the effects of 2 drugs. We recognize that our findings must be replicated using different patient samples and measures of recanalization and reperfusion, and although we expect that the exact value of the time constants to vary, we believe that the principles underlying the model will hold.

The model described in this study can help determine the optimal imaging time to discriminate between responders and nonresponders. From the model we found that the optimal time to detect tPA-related reperfusion among patients treated was 3.5 hours, approximately 5 reperfusion half-lives. We speculate that the optimal imaging time is different for each thrombolytic agent, and future clinical trials that have an imaging outcome may be improved if the agent-specific optimal time to ascertain treatment-induced reperfusion is identified. Our findings, if replicated, can also be used in clinical practice; if a treated patient has not reperfused 3.5 hours after tPA, then another intervention may be warranted.

Our study has several limitations. Because reperfusion is a dynamic process, and imaging studies were only performed at discrete time points, the exact time of reperfusion is unknown. However, we used standard survival analysis methodology to determine the time to the event and, because our sample is large, this method yields a good estimate of the actual reperfusion time. Patients in the intravenous tPA-treated group were scanned earlier than patients in the spontaneous reperfusion group; this is unavoidable, because patients seen soon after symptom onset are scanned sooner and are more likely to receive thrombolytics. Because the baseline scan in the spontaneous reperfusion group was later, these patients were more likely to have unidentified partial reperfusion at baseline. In addition, these patients had fewer scans. Both factors may affect the slope of the reperfusion curve, but the fact that the spontaneous reperfusion rate is similar to the slow component among the tPA-treated patients gives us confidence that the differences in the timing and number of scans do not affect the validity of the model.

In conclusion, modeling the rate of reperfusion, and calculating the reperfusion half-life, provides a measure of the speed and duration of thrombolytic activity and may lead to improvements in the design of MRI-based clinical trials that use reperfusion as a marker of outcome.

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Disclosures

None.

References

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