The Presence of a Right-to-Left Shunt Is Associated With Dramatic Improvement After Thrombolytic Therapy in Patients With Acute Ischemic Stroke

Kazumi Kimura, MD; Yasuyuki Iguchi, MD; Kensaku Shibazaki, MD; Yuka Terasawa, MD; Junya Aoki, MD; Noriko Matsumoto, MD

Background and Purpose—The efficacy of pharmacological thrombolysis using tissue plasminogen activator depends on the relative fibrin content of the thrombus. We investigated whether patients with stroke with a right-to-left shunt (RLS), whose embolic source was associated with fibrin-rich thrombus formed in the venous system, were more likely to improve dramatically after thrombolytic therapy than those without RLS.

Methods—Patients with acute stroke treated with tissue plasminogen activator were assessed prospectively to determine the clinical factors associated with “dramatic improvement” after tissue plasminogen activator administration. “Dramatic improvement” was defined as a ≥10-point reduction in the total National Institutes of Health Stroke Scale score or a total National Institutes of Health Stroke Scale score of 0 or 1 at 7 days. The presence of an RLS was determined using contrast transcranial Doppler within 6 hours of stroke onset.

Results—Forty-four patients (26 males; mean age; 73.0 ± 10.7 years; baseline National Institutes of Health Stroke Scale score, 13.4 ± 6.6) were enrolled. Twenty-one patients had dramatic improvement (D group). Contrast transcranial Doppler demonstrated an RLS in 17 (35.4%) patients. On multivariate logistic regression analysis using hyperlipidemia, atrial fibrillation, RLS, DWI-ASPECTS (>8), baseline National Institutes of Health Stroke Scale score (<10), and glucose (<120 mg/dL) as variables with a P<0.1 on univariate analysis, RLS (OR, 5.9; CI,1.3 to 27.3; P=0.022) was the only independent factor associated with dramatic improvement.

Conclusion—The presence of an RLS on contrast transcranial Doppler was an independent factor associated with dramatic improvement after tissue plasminogen activator administration. (Stroke. 2009;40:303-305.)

Key Words: atrial fibrillation ■ outcome ■ right-to-left shunting ■ TCD ■ tissue plasminogen activator

Intravenous administration of tissue plasminogen activator (tPA) can improve clinical outcomes in patients with acute ischemic stroke. However, the clinical markers associated with dramatic improvement after tPA therapy have not been identified.

One potential cause of embolic stroke is a right-to-left shunt such as a patent foramen ovale, which is termed paradoxical embolism. In paradoxical embolism, most of the thrombus is produced in the deep venous system and is rich in fibrin. The action of tPA is considered to be fibrin-dependent because of its favorable binding constant for fibrin-bound plasminogen and its activation of plasminogen in association with fibrin. Therefore, we hypothesized that tPA thrombolysis was more effective in patients with stroke with a right-to-left shunt than in patients without a right-to-left shunt. Contrast transcranial Doppler (c-TCD) examination was performed to evaluate the presence of a right-to-left shunt within 6 hours of stroke onset. The association between dramatic recovery after tPA thrombolysis and the presence of a right-to-left shunt on c-TCD was investigated.

Subjects and Methods

Consecutive patients with acute anterior circulation stroke treated with tPA within 3 hours of stroke onset between October 2006 and January 2008 were studied.

The following clinical data were collected from all patients: (1) patient age and gender; (2) arterial blood pressure before tPA infusion; (3) National Institutes of Health Stroke Scale (NIHSS) score before and 7 days after tPA infusion; (4) vascular risk factors, including hypertension, diabetes mellitus, and hyperlipidemia; (5) presence of potential cardiac embolic sources; (6) presence of a right-to-left shunt on c-TCD; (7) stroke subtype using modified Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria; (8) laboratory parameters before tPA infusion; (9) administration of antithrombotic agents such as antiplatelet agents and warfarin; (10) baseline diffusion-weighted imaging findings before tPA infusion using DWI-ASPECTS® and M1 occlusion, M2 occlusion, and internal cerebral artery occlusion on initial MR angiography were identified; and (11) the presence of deep venous thrombosis by ultrasonography within 24 hours after tPA infusion. The inclusion and exclusion criteria for the use of intravenous tPA were in accordance with those of the Japan Alteplase Clinical Trial.

Neurologists prospectively determined the patients’ NIHSS scores before and 7 days after tPA infusion. Three measures of clinical recovery based on modified methods used in previous study were...
Thirteen patients had a posterior circulation stroke. Three patients were excluded because of insufficient transcranial Doppler studies. As a result, 48 patients (26 males, 22 females; mean age, 73.0 ± 10.7 years) were enrolled. The times from symptom onset to the initial MRI study and tPA bolus were 95.6 ± 30.5 minutes and 143.0 ± 27.8 minutes, respectively.

Dramatic improvement, good improvement, and worsening at Day 7 were observed in 21, 9, and 8 patients, respectively. Therefore, the D group had 21 patients and the non-D group had 27 patients. One non-D group patient had a symptomatic cerebral hemorrhage. C-TCD demonstrated a right-to-left shunt in 17 (35.4%) patients. The initial MR angiogram demonstrated occluded brain arteries in 37 patients (77.1%) and no occlusive lesions in 11 patients (22.9%). Table 1 shows the characteristics of patients with and without a right-to-left shunt. Patients with a right-to-left shunt more frequently had dramatic improvement (64.7% versus 32.3%, \( P = 0.030 \)) on Day 7. On the other hand, internal cerebral artery occlusion was more frequently seen in patients without a right-to-left shunt than in patients with a right-to-left shunt (35.5% versus 0%, \( P = 0.004 \)).

### Results

A total of 65 consecutive patients with stroke were treated with tPA. One patient was excluded because he had a pacemaker. Thirteen patients had a posterior circulation stroke. Three patients were excluded because of insufficient transcranial Doppler studies. As a result, 48 patients (26 males, 22 females; mean age, 73.0 ± 10.7 years) were enrolled. The times from symptom onset to the initial MRI study and tPA bolus were 95.6 ± 30.5 minutes and 143.0 ± 27.8 minutes, respectively.

Dramatic improvement, good improvement, and worsening at Day 7 were observed in 21, 9, and 8 patients, respectively. Therefore, the D group had 21 patients and the non-D group had 27 patients. One non-D group patient had a symptomatic cerebral hemorrhage. C-TCD demonstrated a right-to-left shunt in 17 (35.4%) patients. The initial MR angiogram demonstrated occluded brain arteries in 37 patients (77.1%) and no occlusive lesions in 11 patients (22.9%). Table 1 shows the characteristics of patients with and without a right-to-left shunt. Patients with a right-to-left shunt more frequently had dramatic improvement (64.7% versus 32.3%, \( P = 0.030 \)). On the other hand, internal cerebral artery occlusion was more frequently seen in patients without a right-to-left shunt than in patients with a right-to-left shunt (35.5% versus 0%, \( P = 0.004 \)).
On multivariate logistic regression analysis using hyperlipidemia, AF, a right-to-left shunt, DWI ASPECTS (>8), baseline NIHSS score (<10), and glucose (<120 mg/dL) as variables that had a $P<0.1$ on univariate analysis, a right-to-left shunt (OR, 5.9; CI, 1.3 to 27.3; $P=0.022$) was found to be the only independent factor associated with dramatic improvement (Table 3).

### Discussion

In the present study, the presence of a right-to-left shunt, which was demonstrated in 35.4% of patients, was found to be associated with neurological dramatic improvement after tPA infusion.

It has been suggested that the efficacy of pharmacological thrombolysis is dependent on the relative fibrin content. 12, 13 Therefore, fibrin-rich thrombi may be more resolved by tPA than platelet-rich thrombi. Thus, patients with acute stroke with a right-to-left shunt, whose embolic source is thought to be a fibrin-rich thrombus in the deep venous system, may more frequently have dramatic improvement after tPA thrombolysis. However, patients with AF having fibrin-rich clots did not frequently have dramatic recovery. Clot dissolution depends on clot size and age as well as thrombus composition. 14 Fresh and old clots have been shown to form in cardiac cavities, including the left atrium in cases with AF. 15 Furthermore, transesophageal echocardiography sometimes demonstrates large thrombi in the left atrium in patients with stroke with AF. Therefore, we believe that thrombus associated with AF sometimes contains old and large clot and may be resistant to tPA therapy.

The present study had several limitations. Because some patients with acute stroke with disturbed consciousness and aphasia could not perform the Valsalva maneuver, an adequate transcranial Doppler could not be performed in all patients. Thus, the frequency of a right-to-left shunt might have been underestimated. Second, of course, patients with a right-to-left shunt do not all always have paradoxical embolism. We could not find the deep venous thrombosis in any patients with a right-to-left shunt at all. The thrombus might be dissolved by tPA therapy. We may be able to find deep venous thrombosis before tPA infusion. Finally, the number of our patients was small. Therefore, we need a large sample study to confirm our results.

### Table 2. Characteristics of Patients With and Without a Right-to-Left Shunt

<table>
<thead>
<tr>
<th>Right-to-Left Shunting</th>
<th>Patients With (N=17)</th>
<th>Patients Without (N=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological recovery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dramatic improvement</td>
<td>11 (64.7%)</td>
<td>10 (32.3%)</td>
<td>0.030</td>
</tr>
<tr>
<td>Good improvement</td>
<td>1 (5.9%)</td>
<td>8 (25.8%)</td>
<td>0.130</td>
</tr>
<tr>
<td>Worsening</td>
<td>4 (23.5%)</td>
<td>4 (12.9%)</td>
<td>0.429</td>
</tr>
<tr>
<td>MR angiography before tPA infusion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery occlusion</td>
<td>0</td>
<td>11 (35.5%)</td>
<td>0.004</td>
</tr>
<tr>
<td>M1 occlusion</td>
<td>10 (58.8%)</td>
<td>10 (32.3%)</td>
<td>0.074</td>
</tr>
<tr>
<td>M2 occlusion</td>
<td>2 (11.8%)</td>
<td>4 (12.9%)</td>
<td>0.909</td>
</tr>
<tr>
<td>No occlusion</td>
<td>5 (29.4%)</td>
<td>6 (19.4%)</td>
<td>0.428</td>
</tr>
</tbody>
</table>

### Table 3. Multivariate Analysis of Variables Associated With Dramatic Response to tPA

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right-to-left shunt</td>
<td>5.93</td>
<td>1.289–27.293</td>
<td>0.022</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>4.98</td>
<td>0.499–49.601</td>
<td>0.171</td>
</tr>
<tr>
<td>AF</td>
<td>0.82</td>
<td>0.146–4.584</td>
<td>0.818</td>
</tr>
<tr>
<td>DWI ASPECTS &gt;8</td>
<td>2.19</td>
<td>0.453–10.565</td>
<td>0.330</td>
</tr>
<tr>
<td>NIHSS score &lt; baseline &lt;10</td>
<td>2.27</td>
<td>0.393–13.085</td>
<td>0.360</td>
</tr>
<tr>
<td>Glucose &lt;120 mg/dL</td>
<td>3.63</td>
<td>0.770–17.082</td>
<td>0.103</td>
</tr>
</tbody>
</table>

In conclusion, the presence of a right-to-left shunt detected by c-TCD was associated with neurological dramatic improvement after tPA treatment. C-TCD examination may be useful for predicting the outcome in patients with acute stroke treated with tPA.

### Disclosures

None.

### References

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