Safety and Efficacy of Intravenous Tissue Plasminogen Activator and Heparin in Acute Middle Cerebral Artery Stroke

Rüdiger von Kummer, MD, and Werner Hacke, MD

Background and Purpose: There is little reported of the safety and efficacy of high-dose intravenous recombinant tissue plasminogen activator (alteplase) in combination with heparin anticoagulation in patients presenting with acute ischemic stroke.

Methods: Thirty-two patients with severe hemispheric stroke syndrome caused by angiographically proven middle cerebral artery and/or intracranial internal carotid artery occlusion were treated with 100 mg alteplase by intravenous infusion over 90 minutes within a mean±SD of 226±68 minutes after symptom onset. Recanalization was assessed by digital subtraction angiography in all patients immediately after treatment and by transcranial Doppler monitoring (n=30) and/or a third angiogram (n=5) 12-24 hours later.

Results: Complete or partial reperfusion was observed in 11 patients (34%) 90 minutes after the initiation of alteplase infusion and in 17 patients (53%) within 12-24 hours. Hemorrhagic infarction without clinical deterioration was detected by follow-up computed tomography in nine patients (28%). Fatal parenchymal hemorrhage occurred in three patients (9%) with huge middle cerebral artery infarcts. Serious hemorrhage from the puncture site occurred in two patients (6%). Good clinical outcome correlated with reperfusion (p<0.05) and the presence of grade 2 collateral blood flow (p<0.01).

Conclusions: When 100 mg of recombinant tissue plasminogen activator was given within the first 6 hours of acute stroke together with heparin the incidence of deleterious hemorrhage was <10%. Reperfusion and effective collateral blood flow seem to be two important factors associated with a small infarct volume and good clinical outcome. (Stroke 1992;23:646-652)

Key Words • cerebral ischemia • collateral circulation • plasminogen activator, tissue-type
Subjects and Methods

Between February 1989 and September 1991, 32 consecutive patients presenting with signs of severe hemispheric stroke (score of >18 on the stroke scale of the National Institute of Neurological Disorders and Stroke [NINDS]) were treated with the intravenous infusion of 100 mg rt-PA (alteplase, Thomae, Biberach, FRG) over 90 minutes. Inclusion and exclusion criteria have been adopted from the German rt-PA multicenter trial. Among the criteria were 1) informed consent given by the patient or his relatives, 2) patient age between 20 and 70 years, 3) clinical diagnosis of acute stroke occurring within 6 hours before treatment, 4) absence of hematomatologic disease and hemorrhage as documented by cranial computed tomography (CT), and 5) angiographic demonstration of the appropriate intracranial internal carotid artery (ICA), MCA trunk (M1), or MCA branch (M2) occlusion consistent with the patient's clinical presentation.

The rt-PA infusion was begun immediately after the angiographic documentation of arterial occlusion. Alteplase was given as a 15 mg bolus, followed by 50 mg over 30 minutes and 35 mg over the subsequent 60 minutes, as adopted from a German rt-PA-myocardial infarction study. Simultaneously with the alteplase, we injected a bolus of 5,000 units heparin and continued the heparin by infusing 1,000–1,500 units/hr, aiming to double the activated partial thromboplastin time (aPTT) in each patient. Heparin was discontinued when CT revealed parenchymal hemorrhage. Angiography was repeated immediately after completion of the rt-PA infusion. Reperfusion was graded as 0, no reperfusion; 1, occlusion with minimal reperfusion; 2, partial reperfusion; or 3, complete reperfusion of the MCA or ICA. Reperfusion was reassessed 12–24 hours after symptom onset by transcranial Doppler ultrasound (TCD) (n=30) and a third angiogram (n=5). In two patients neither angiography nor TCD could be performed the day after the stroke because of their poor clinical states. In these two patients MCA occlusion was confirmed by postmortem examination within 48 hours after the stroke.

The extent of perfusion deficit and collateral blood supply was assessed semiquantitatively from the first angiogram after the symptomatic carotid artery and the ipsilateral vertebral artery had been visualized and was graded as 0, no collaterals; 1, only few collaterals with slow blood flow; or 2, many leptomeningeal collaterals from the anterior and posterior cerebral arteries. In patients with complete ICA occlusion, the contralateral common carotid artery was studied as well.

Patterns of cerebral infarcts were assessed by repeated CT or magnetic resonance imaging (MRI) 2 days, 10 days, and 4 weeks after treatment. The extent of the ischemic infarct was graded as small (<50% of the presumed MCA territory), large (50–90%), or total (90–100%). The presence of hemorrhage was defined as hemorrhagic infarction or parenchymal hematoma according to criteria described by Pessin et al.

All patients were monitored and treated on the Neurological Critical Care Unit for at least 3 days. Clinical outcome was defined as good when the patient recovered from the initial deficit (NINDS stroke scale score of <13) so that he was able to walk without assistance at discharge from the hospital or poor when no apparent improvement was seen 4 weeks after the stroke (NINDS stroke scale score of >12) compared with the presenting deficits. Death rates were assessed separately.

Results

The clinical, CT, angiographic, and outcome features of all patients entered into this study are given in Table 1. There were 13 women and 19 men aged 28–70 (median 60, mean±SD 58±11) years. All patients suffered from severe hemiparesis, conjugate ocular deviation, and impaired consciousness when admitted to the hospital. In 24 patients cardiac disease or arrhythmia suggested cardiac embolism; in the other eight patients MCA occlusion was associated with cervical arteriosclerotic ICA stenosis. One patient (case 11) had an isolated distal ICA occlusion with an open M1 segment. In 10 patients intracranial ICA occlusion was associated with ipsilateral MCA occlusion. Two additional patients (cases 8 and 18) had severe extracranial ICA stenosis associated with MCA occlusion. An isolated M1 segment occlusion was documented in 18 patients, while an M2 occlusion at the level of the MCA trifurcation was observed in three patients.

Prior to rt-PA infusion, the collateral blood supply through leptomeningeal anastomoses from the anterior and/or posterior cerebral artery was grade 0 or 1 in 17 patients and grade 2 in 15, irrespective of whether the occlusion was embolic.

The interval from the onset of symptoms to the start of rt-PA infusion was 226±68 (range 105–360) minutes (Table 1). Immediately after the rt-PA infusion, complete recanalization occurred in two patients with an MCA (M1 or M2 segment) occlusion and in one patient with an isolated distal ICA occlusion. Partial recanalization was seen in eight patients. Overall, early grade 2 or 3 recanalization was observed in 11 patients (34%).

Angiography (n=2) and TCD (n=5) performed 12–24 hours after symptom onset demonstrated partial recanalization of the MCA in a further seven patients. Despite systemic heparinization and with aPTTs of >120 seconds, postmortem examination 2 days after the stroke revealed reocclusion of the MCA in one patient (case 6). Hence, grade 2 or 3 arterial recanalization was seen in 17 of the 32 patients (53%) at 24 hours. In two patients (cases 12 and 13) the ICA remained occluded whereas the MCA had undergone partial recanalization.

Table 2 compares the characteristics of patients who did and did not demonstrate recanalization. No differences were observed in age, sex ratio, etiology, and interval from symptom onset to therapy onset. No patient with combined ICA/MCA occlusion demonstrated early recanalization. The incidence of early recanalization of combined ICA/MCA occlusion was significantly lower than in isolated M1 segment occlusion (p<0.01). All three M2 occlusions recanalized. Recanalization was significantly more frequent in patients with a grade 2 collateral circulation (p<0.05).

Hemorrhagic transformation was not more frequent with early recanalization or a better collateral circulation. In patients with hemorrhagic transformation the mean±SD interval from symptom onset to rt-PA infusion thrombolysis was 249±57 minutes. In nine patients...
TABLE 1. Clinical, Angiographic, and Outcome Features of 32 Patients With Middle Cerebral Artery Stroke Undergoing Intravenous Alteplase Therapy

<table>
<thead>
<tr>
<th>Case/age/sex</th>
<th>Cause</th>
<th>Site of occlusion</th>
<th>Collaterals (grade)</th>
<th>Interval (min)</th>
<th>Recanalization</th>
<th>Outcome</th>
<th>Infarct</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/64/M</td>
<td>N</td>
<td>M1</td>
<td>1</td>
<td>135</td>
<td>0  2</td>
<td>Poor</td>
<td>Large</td>
<td>HI</td>
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<tr>
<td>2/64/M</td>
<td>C</td>
<td>ICA/M1</td>
<td>1</td>
<td>300</td>
<td>0  0</td>
<td>Dead</td>
<td>Total</td>
<td>None</td>
</tr>
<tr>
<td>3/57/F</td>
<td>C</td>
<td>M2</td>
<td>2</td>
<td>210</td>
<td>3  3</td>
<td>Good</td>
<td>Small</td>
<td>HI</td>
</tr>
<tr>
<td>4/63/M</td>
<td>N</td>
<td>M1</td>
<td>1</td>
<td>280</td>
<td>2  2</td>
<td>Poor</td>
<td>Large</td>
<td>HI</td>
</tr>
<tr>
<td>5/68/M</td>
<td>N</td>
<td>ICA/M1</td>
<td>0</td>
<td>270</td>
<td>0  0</td>
<td>Dead</td>
<td>Total</td>
<td>PH</td>
</tr>
<tr>
<td>6/68/M</td>
<td>N</td>
<td>M1</td>
<td>2</td>
<td>150</td>
<td>2  2</td>
<td>Dead</td>
<td>Large</td>
<td>None</td>
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<tr>
<td>7/60/F</td>
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<td>M2</td>
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<tr>
<td>8/55/M</td>
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<td>M1*</td>
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<td>130</td>
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<tr>
<td>9/51/F</td>
<td>C</td>
<td>M1</td>
<td>2</td>
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<td>Good</td>
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<td>None</td>
</tr>
<tr>
<td>10/60/F</td>
<td>C</td>
<td>M2</td>
<td>1</td>
<td>165</td>
<td>2  2</td>
<td>Dead</td>
<td>Large</td>
<td>PH</td>
</tr>
<tr>
<td>11/49/F</td>
<td>C</td>
<td>ICA</td>
<td>2</td>
<td>150</td>
<td>3  3</td>
<td>Good</td>
<td>Small</td>
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<tr>
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<td>N</td>
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<td>2</td>
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<td>1  2†</td>
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<tr>
<td>13/65/M</td>
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<td>ICA/M1</td>
<td>2</td>
<td>270</td>
<td>0  2†</td>
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<td>Small</td>
<td>HI</td>
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<tr>
<td>14/50/M</td>
<td>C</td>
<td>M1</td>
<td>2</td>
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<td>2  2</td>
<td>Good</td>
<td>Small</td>
<td>HI</td>
</tr>
<tr>
<td>15/59/F</td>
<td>C</td>
<td>M1</td>
<td>1</td>
<td>240</td>
<td>0  0</td>
<td>Poor</td>
<td>Large</td>
<td>HI</td>
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<tr>
<td>16/48/F</td>
<td>C</td>
<td>M1</td>
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<td>290</td>
<td>2  2</td>
<td>Good</td>
<td>Small</td>
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<tr>
<td>17/70/F</td>
<td>C</td>
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<td>0  0</td>
<td>Poor</td>
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</tr>
<tr>
<td>18/59/M</td>
<td>N</td>
<td>M1*</td>
<td>0</td>
<td>180</td>
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<td>Poor</td>
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<td>19/48/F</td>
<td>C</td>
<td>ICA/M1</td>
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<td>120</td>
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<tr>
<td>20/62/F</td>
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<td>ICA/M1</td>
<td>1</td>
<td>150</td>
<td>0  0</td>
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<td>Total</td>
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<tr>
<td>21/68/M</td>
<td>C</td>
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<tr>
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<td>M1</td>
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<td>330</td>
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<td>Good</td>
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<td>HI</td>
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<tr>
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<td>Small</td>
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<td>C</td>
<td>ICA/M1</td>
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<td>Dead</td>
<td>Total</td>
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</tr>
<tr>
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<td>M1</td>
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<td>210</td>
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<td>Poor</td>
<td>Large</td>
<td>None</td>
</tr>
<tr>
<td>26/62/M</td>
<td>C</td>
<td>M1</td>
<td>2</td>
<td>300</td>
<td>0  0</td>
<td>Good</td>
<td>Small</td>
<td>None</td>
</tr>
<tr>
<td>27/69/F</td>
<td>C</td>
<td>M1</td>
<td>2</td>
<td>240</td>
<td>0  2</td>
<td>Poor</td>
<td>Large</td>
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<tr>
<td>28/56/M</td>
<td>C</td>
<td>M1</td>
<td>1</td>
<td>287</td>
<td>1  1</td>
<td>Poor</td>
<td>Total</td>
<td>HI</td>
</tr>
<tr>
<td>29/67/F</td>
<td>C</td>
<td>M1</td>
<td>2</td>
<td>240</td>
<td>0  2</td>
<td>Good</td>
<td>Small</td>
<td>HI</td>
</tr>
<tr>
<td>30/48/M</td>
<td>C</td>
<td>ICA/M1</td>
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<td>285</td>
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<td>Dead</td>
<td>Total</td>
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<tr>
<td>31/66/M</td>
<td>C</td>
<td>ICA/M1</td>
<td>1</td>
<td>315</td>
<td>0  0</td>
<td>Dead</td>
<td>Total</td>
<td>PH</td>
</tr>
<tr>
<td>32/28/M</td>
<td>C</td>
<td>M1</td>
<td>2</td>
<td>240</td>
<td>3  3</td>
<td>Good</td>
<td>Small</td>
<td>None</td>
</tr>
</tbody>
</table>

M, male; F, female; N, noncardiac; C, cardiac; M1, middle cerebral artery (MCA) trunk; ICA, internal carotid artery; M2, MCA branch; Interval, time between stroke and start of alteplase infusion; Recanalization: 0, no reperfusion; 1, minimal reperfusion; 2, partial reperfusion; 3, complete reperfusion; HI, hemorrhagic infarction; PH, parenchymal hematoma.

*In conjunction with severe ICA stenosis.

†ICA still occluded.

(28%) hemorrhagic infarction of the cortical or subcortical gray matter was detected by CT or MRI 2 days (n=4), 10 days (n=4), or 4 weeks (n=1) after the stroke. Four of these patients demonstrated recanalization immediately after completion of the rt-PA infusion, and an additional three patients displayed recanalization at 24 hours. Five of the nine patients with hemorrhagic infarction had a good outcome, and no patient deteriorated. Hemorrhagic infarction was associated with small infarcts in five patients and large infarcts in four.

Fatal parenchymal hematoma occurred in three of the 32 patients (cases 5, 10, and 31) (9%). The aPTT, prothrombin time (PT), and platelet count were normal in all three patients before rt-PA infusion. In one patient (case 5) with combined ICA/MCA occlusion, the MCA did not recanalize. A medium-sized white matter hemorrhage in the center of a complete MCA territory infarct was seen 9 hours after symptom onset. The patient died 13 hours later due to edema and subsequent herniation. A second patient (case 10) suffered a stroke during coronary artery angiography. This patient was pretreated with an intravenous bolus of 1 g aspirin. Slight local brain swelling and cortical hypodensity was already visible 100 minutes after symptom onset on the initial CT scan. Recanalization of an MCA occlusion occurred immediately after rt-PA infusion. Eighteen hours after symptom onset, multifocal parenchymal hemorrhages within the ipsilateral MCA territory and the contralateral frontal lobe, subdural and subarachnoid spaces, and fourth ventricle were documented. The patient died 4 days after her stroke. A third patient (case 31) suffered from cardioembolic occlusion of the distal carotid artery following a myocardial infarction. Partial reperfusion of the anterior
cerebral artery and persistent occlusion of the M1 segment were seen after rt-PA infusion. Twenty-three hours later, CT revealed a hypodensity of the entire MCA territory and a parenchymal hemorrhage in the basal ganglia. This patient died 3 days after his stroke due to space-occupying edema. In all three patients the aPTT and PT were >120 seconds after alteplase and heparin discontinued. In patients 10 and 31 the aPTT and PT normalized after the hemorrhage was detected and the heparin infusion. This patient displayed recanalization and the remaining patient had a grade 2 collateral supply. Additionally, two patients developed puncture site hematomas not requiring blood transfusion.

The characteristics of patients with poor or good outcome are shown in Table 3. Significant differences were found between the groups with respect to collateral circulation, recanalization at 8 and 24 hours, and extent of infarction. In three patients (cases 4, 6, and 10) outcome was poor or death although thrombolysis resulted in partial recanalization within 6 hours after symptom onset. Two of these patients (cases 4 and 10), however, had poor collateral flow, and in patient 6 postmortem examination revealed MCA reocclusion.

Six patients (cases 8, 12, 13, 23, 26, and 29) had good outcome despite the absence of early recanalization. These patients had recanalization 12–24 hours after rt-PA infusion and/or grade 2 collaterals. Good outcome correlated with both partial or complete recanalization ($p<0.05$) and with a grade 2 collateral blood supply ($p<0.01$). When recanalization at 24 hours was considered, one patient died due to a large infarct and parenchymal hematoma and two patients (12%) had poor outcome with a grade 1 collateral supply. In contrast, eight of 15 patients who did not display recanalization within 24 hours died and poor outcome occurred in six. Two of these 14 patients had a grade 2 collateral supply. All 18 patients with a large or total infarct had a poor or fatal outcome. Among the 14 patients with a small infarct and good outcome, 13 displayed recanalization and the remaining patient had a grade 2 collateral supply.

### Discussion

Thirty-two acute stroke patients were treated with 100 mg single-chain rt-PA (alteplase) in a regimen identical to that in a study of myocardial infarction early after symptom onset in a safety, recanalization efficacy, and clinical outcome study. Heparin anticoagulation was instituted with the rt-PA infusion. This patient group differs from those in previous reports in that it was homogeneous with respect to the site of occlusion and severity of the stroke syndrome, and it is the largest stroke cohort treated with rt-PA at doses recommended for myocardial infarction. 22

There is little reported experience in acute stroke with rt-PA and concomitant heparin at these dose rates. The incidence of intracerebral hemorrhagic events in our series (38%) was not higher than that reported from pathology series or selected CT studies on nonanticoagulated patients. 27-28 Hemorrhagic infarction was more frequent than in a recent nonangiographic rt-PA study and the findings of Yamaguchi et al and was as
TABLE 3. Potential Outcome Predictors

<table>
<thead>
<tr>
<th>Cause</th>
<th>No.</th>
<th>Sex ratio (M/F)</th>
<th>Grade 0 or 1</th>
<th>At 8 hr</th>
<th>At 24 hr</th>
<th>Hemorrhage</th>
<th>Infarct extent</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>650</td>
<td>12/6</td>
<td>15</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>Poor/death</td>
</tr>
<tr>
<td>Noncardiac</td>
<td>58</td>
<td>3</td>
<td>15</td>
<td>8</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>Good</td>
</tr>
</tbody>
</table>

M, male; F, female; ICA, internal carotid artery; M1, middle cerebral artery (MCA) trunk; M2, MCA branch; Recanalization, reperfusion grade 2 or 3; HI, hemorrhagic infarction; PH, parenchymal hematoma.

*pStudent's two-tailed t test.
†Fisher's exact probability test.

The outcome for patients with recanalization was significantly better than that of patients without MCA reperfusion. The outcome seems to be better than that of patients with MCA occlusion and very severe stroke syndromes receiving standard therapy or acute embolectomy. In our study, patients with nonrecanalized combined ICA/MCA occlusion and a poor collateral blood supply contributed to mortality. Seven of eight patients with this occlusion pattern died, and the single survivor was severely disabled. This might explain why the outcome of the no-recanalization group was worse than that suggested by the literature.

Poor clinical outcome despite early reperfusion was associated with reocclusion, parenchymal hemorrhage, and a poor collateral blood supply. Poor outcome despite the lack of MCA reperfusion within 8 hours after stroke onset may reflect the significance of collateral flow, as suggested by others.

frequent as reported by the rt-PA Stroke Study Group. Whereas hemorrhagic infarction did not appear to affect outcome, in this series hematoma was generally associated with clinical deterioration and death. The hematoma occurred within 24 hours after the stroke in all three patients. All had a poor collateral blood flow and a large or total MCA territory infarct. Two of the three displayed no recanalization. This suggests that neither reflow nor the collateral blood supply, but the extent of ischemia, supported parenchymal hemorrhage in these three patients. The incidence of hematoma in our series (9%) is lower than or as high as in selected historical control studies and other thrombolytic studies. From these observations we conclude that the intravenous infusion of rt-PA with heparin in this regimen does not increase the incidence of clinically significant intracerebral hemorrhage following acute stroke.

In this study there is no evidence that early reperfusion was associated with hemorrhagic transformation. However, seven of nine patients with hemorrhagic infarcts up to 4 weeks after stroke displayed recanalization at 24 hours. This trend for more and sometimes late hemorrhagic transformation in cases with delayed recanalization may indicate the higher vulnerability of the vessel's wall with prolonged ischemia.

Whether reperfusion after thromboembolic occlusion was due to thrombolysis or spontaneous recanalization cannot be decided by this study. Spontaneous recanalization was observed in 27–59% of patients by angiography during the first days after stroke. After intraarterial urokinase or streptokinase infusion, the frequency of recanalization of ICA occlusion was 13% and 53% and that of MCA occlusion was 42%, 65%, and 82%. After the intravenous infusion of two-chain rt-PA (duteplase) partial or complete recanalization was noted in 32 of 93 patients (34%), most consistently those with distal occlusions, and in 25 of 58 patients (43%) with carotid territory embolic stroke.

In our series the overall frequency of early recanalization (partial and complete) was similar (34%) to that found with duteplase. Recanalization of isolated MCA occlusion within 8 hours after stroke was as frequent (48%) as achieved by Mori and colleagues using intra-arterial urokinase. Early recanalization of MCA occlusion was more frequent following 100 mg rt-PA (alteplase) than 70 mg rt-PA (34% versus 25%), although the frequency of delayed recanalization did not differ (53% versus 50%). However, whether there is a dose-rate response has to be confirmed by a randomized study.

In agreement with other studies, reperfusion of MCA branch occlusion was more frequent than of M1 segment or ICA occlusion. This may result from more efficient thrombolysis of smaller distal thrombi. It is possible that large thrombi in larger vessels may require higher doses of rt-PA. The higher frequencies of reperfusion with a grade 2 collateral circulation in proximal occlusions may have been due to better access of rt-PA to the ischemic area. Our data, however, may be affected by spontaneous recanalization in smaller arteries, which may represent the natural history of MCA occlusion.

Reocclusion was documented in one patient by postmortem study. Whether heparin may prevent reocclusion in some patients after recanalization of arterial occlusions should be studied further.
hand, a good collateral flow did not prevent large infarcts and poor outcome in two patients in whom recanalization was not achieved within 24 hours after symptom onset. Good outcome despite a grade 0 or 1 collateral supply was observed in only one patient showing early reperfusion. These observations suggest that both reperfusion and collateral flow are important factors enabling parts of ischemic brain tissue to survive. Even very early reperfusion alone, however, cannot prevent infarcts in regions with a poor collateral blood supply (e.g., the basal ganglia). Delayed reperfusion may be a consequence of endogenous thrombolysis and spontaneous recanalization. More data on the rate of spontaneous reperfusion after acute thromboembolic occlusion are badly needed. They can be provided noninvasively by TCD or MRI angiography. Further investigations of the effects of arterial recanalization should take into account the significance of collaterals and the site and pathology of intracranial arterial occlusion.

In conclusion, it has been shown that rt-PA at a dose recommended for coronary artery reperfusion can be given intravenously together with heparin with acceptable safety. This study supports earlier reports of a positive correlation between recanalization and good clinical outcome.

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R von Kummer and W Hacke

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