Intra-arterial Thrombolysis of Acute Iatrogenic Intracranial Arterial Occlusion Attributable to Neuroendovascular Procedures or Coronary Angiography

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Background and Purpose—For selected stroke patients, intra-arterial thrombolysis (IAT) has been shown to be an effective treatment option. However, knowledge of safety and efficacy of IAT in patients with acute stroke as a complication of arterial catheter interventions is limited.

Methods—We analyzed clinical radiological findings and functional outcomes in consecutive patients 3 months after treatment with IAT for peri-procedural strokes occurring during neuroendovascular or cardiac catheter interventions. To measure outcome, the modified Rankin scale score was used.

Results—Of a total of 432 patients treated with IAT, 12 (4 women and 8 men; mean age, 60 years) were treated because of an ischemic stroke after a neuroendovascular procedure (n=6) or coronary angiography (n=6). The median baseline National Institutes of Health Stroke Scale score was 15. Recanalization was complete (thrombolysis in myocardial infarction grade 3) in 6, partial (thrombolysis in myocardial infarction 2) in 5, and minimal (thrombolysis in myocardial infarction 1) in 1. Nine patients (75%) had a favorable outcome (modified Rankin scale score, 0 to 2), and 3 had a poor outcome (modified Rankin scale score, 3 or 4). All patients with complete recanalization had a favorable outcome, whereas only 3 of 6 patients with partial or minimal recanalization (P=0.18) had a favorable outcome. Follow-up brain imaging was normal in 2 and showed new ischemic lesions in 10 patients. Two patients (17%) had a symptomatic intracerebral hemorrhage.

Conclusion—In acute stroke attributable to arterial catheter interventions, IAT is feasible and has the potential to improve outcome in these patients. A high recanalization rate could be achieved. (Stroke, 2008;39:1491-1495.)

Key Words: angiography ■ outcome ■ thrombolysis ■ urokinase

Ischemic stroke is a rare but serious complication of neuroendovascular catheter interventions and coronary angiography. Direct arterial injury, air embolism, thrombus formation in the catheter or on its surface, or dislocation of pre-existing atherosclerotic or thrombotic material are potential mechanisms.1

A randomized trial showed significant clinical benefit of intra-arterial thrombolysis (IAT) in acute noniatrogenic stroke patients with M1 or M2 segment occlusion of the middle cerebral artery (MCA) up to 6 hours from symptom onset.2 IAT restored vessel patency, at least partially in two-thirds of the patients with MCA occlusion. This therapeutic approach may also be beneficial in acute stroke attributable to arterial catheter interventions. However, until now data for such patients were rare. Therefore, we report our experience of IAT in acute iatrogenic stroke attributable to neuroendovascular procedures or coronary angiography.

Subjects and Methods
Patients were recruited from a prospective IAT for acute ischemic stroke database. From January 1998 to December 2006, 432 consecutive patients were treated with IAT in our institution. The indications and contraindications for IAT at our institution have been previously published.3 In brief, IAT was performed if: (1) a clear diagnosis of ischemic stroke was established; (2) baseline NIHSS score was ≥4 points or isolated hemianopia or aphasia were present; (3) the onset of symptoms time was clearly defined; (4) treatment could be initiated within 6 hours from symptom onset; and (5) the patient or family consented to arteriography and possible thrombolysis.

Patients were included if acute stroke symptoms were detected: (1) during or immediately after coronary angiography (n=6); or (2) during or immediately after neuroendovascular procedures (n=6). Patients in whom an intracranial occlusion occurred during coiling of an intracranial aneurysm (n=4) were treated with intra-arterial abciximab and additional mechanical recanalization techniques. These patients were not included because the GP IIb/IIIa antagonist abciximab has a different mechanism of action, and because all these
patients were treated under general anesthesia; therefore, a clinical examination was not possible.

During the same period a total of 28,787 coronary angiographies, 14,770 with percutaneous transluminal coronary angioplasty and 11,613 with coronary stent implantation, were performed at our hospital. In 3 patients with acute focal neurological deficits during coronary angiography IAT was not performed because of rapid spontaneous improvement of the clinical symptoms; additionally, these patients had no arterial occlusion on cerebral arteriography. One of the 3 had a minor stroke and 2 had TIA. A total of 5,400 patients underwent neuroendovascular procedures. Diagnostic 4-vessel digital subtraction angiography was performed in 4,754 patients, endovascular coiling in 2,477, endovascular stent implantation in 381 (197 internal carotid artery, 35 common carotid artery, 4 external carotid artery, 2 vertebral artery, 16 innominate artery, 83 subclavian artery, and 25 intracranial arteries), and balloon occlusion test of the carotid artery in 18.

Patient history and clinical examination before the interventional procedure was performed in all patients by a cardiologist or a neurologist and documented in the medical charts. None of the 12 patients treated with IAT for iatrogenic stroke had previous neurological deficits. The prethrombolysis neurological status was assessed immediately after detection of the first stroke symptoms using the NIHSS score by different neurologists.\(^6\) The 6 patients in whom stroke occurred during cardiac procedures underwent CT scans before IAT to exclude intracranial hemorrhage.

Arteriography was performed by a transfemoral approach. The femoral artery sheath was still in place in all patients. Patients received a diagnostic 4-vessel angiogram to assess the complete vessel status and collateral circulation if present. No heparin bolus was given in the neuroradiologic patients and in patients with diagnostic coronary angiography. In patients with an acute coronary syndrome, we administer a bolus of 100 IE unfractionated heparin per kg body weight before coronary intervention. When additional glycoprotein IIb/IIIa receptor antagonists are used, a dose of 70 IE unfractionated heparin per kg body weight is given. Urokinase in a mean dose of 792,000 U (range, 500,000 to 1,000,000) was infused directly into or near the proximal end of the occluding thrombus over 60 to 90 minutes. In 2 patients, in addition to pharmacological thrombolysis, mechanical thrombus disruption (patient 3) or thrombus aspiration (patient 4) was performed. Time to treatment was defined as the time from the last documented normal patient examination to the administration of intra-arterial thrombolytic therapy. Recanalization was analyzed by an arteriogram immediately after IAT and classified according to thrombolysis in myocardial infarction (TIMI) grades as follows: no recanalization, TIMI grade 0; minimal recanalization, TIMI grade 1; partial recanalization, TIMI grade 2; and complete recanalization, TIMI grade 3.\(^5\) Eight patients received aspirin 250 to 500 mg and 1 patient received clopidogrel 75 mg in the first hours after thrombolysis. The other 3 patients were treated with a combination of clopidogrel 75 mg and aspirin 100 mg.

A control CT (n = 4) or MRI (n = 8) scan was performed 1 to 3 days after IAT. CT or MRI lesions were classified similar to the criteria published by Mead et al\(^6\) as follows: (1) large cortical MCA infarct (more than half of the MCA territory); (2) medium or small cortical anterior circulation infarct (less than half of the MCA territory, or any of the anterior cerebral artery territory); (3) large (>1.5 cm) subcortical infarct (striatocapsular); (4) lacunar (<1.5 cm) anterior circulation infarct; (5) lacunar (<1.5 cm) posterior circulation infarct; and (6) nonlacunar posterior circulation infarct.

All patients were examined with MRA (n = 8) or CTA (n = 3) and transcranial ultrasound (n = 6) within 72 hours of treatment. Outcome was assessed 3 months after stroke by different neurologists performing a clinical examination using the modified Rankin scale (mRS).\(^7\)

### Statistical Analyses

Statistical analysis was performed with the SPSS 10 for Macintosh statistical software. For comparison of outcome, patients were divided into 2 groups with either a favorable (mRS 0 to 2) or a poor outcome (mRS 3 to 6).

### Results

#### Baseline Data, Recanalization, Complications, and Outcome

Among 432 patients treated with IAT, we identified 12 patients (4 women and 8 men; mean age, 60 years) who were treated because of an ischemic stroke after coronary angiog-
raphy (n = 6) or a neuroendovascular intervention (n = 6). Neuroendovascular procedures included carotid stent implantation in 2 patients, presurgical embolization of a falx meningioma in 1, balloon occlusion test of the carotid artery in 1 patient, and planned subclavian stent implantation in 2 patients. Baseline characteristics and risk factors did not differ significantly between the IAT cohort of noniatrogenic strokes (n = 420) and the 12 iatrogenic stroke patients (mean age, 61 [SD = 13] vs 60 years [SD = 9]; percentage of women [43% vs 33%]; hypertension [58% vs 58%], smoking [23% vs 17%], hypercholesterolemia [43% vs 33%], diabetes mellitus [14% vs 17%], previous stroke or TIA [10% vs 25%]; \( P > 0.05 \) for all variables) except for a shorter average time to treatment (95 vs 273 minutes; \( P = 0.0001 \)) in iatrogenic strokes.

The occlusion was located in the M1 segment of the MCA in 5 patients, in the M2 segment of the MCA in 4, in the intracranial internal carotid artery in 2, and in the anterior cerebral artery in 1 patient.

The average time from symptom onset to treatment was 95 (SD = 71) minutes. Complete recanalization (TIMI grade 3, Figure) was achieved in 6 patients, partial recanalization (TIMI 2) in 5, and minimal recanalization (TIMI 1) in 1.

No reocclusion was observed on MRA (n = 8), CTA (n = 3), or transcranial ultrasound (n = 6) within 72 hours of treatment. Two patients (17%) had a symptomatic intracranial hemorrhage. No extracranial hemorrhages were observed.

On follow-up brain imaging, 2 patients had a large anterior circulation infarct, 3 had a small anterior circulation infarct, and 2 had a striato-capsular infarct. In 2 patients a follow-up MRI (n = 1) or CT (n = 1) did not show any ischemic lesion.

Nine patients (75%) had a favorable outcome (mRS 0 to 2) and 3 had a poor (mRS 3 or 4) outcome after 3 months.

Baseline data, clinical and radiological findings, and outcome of each patient are summarized in Table 1.

### Predictors of Outcome and Recanalization

The average time from symptom onset to treatment tended to be shorter in patients with complete recanalization than in those with partial or minimal recanalization (71 vs 118 minutes; \( P = 0.423 \)). All 6 patients with complete recanaliza-

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**Table 1. Baseline Data, Clinical and Radiological Findings, and Outcome of 12 Patients With Acute Iatrogenic Intracranial Vessel Occlusion Attributable to Coronary Angiography or Neuroendovascular Procedures**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (yr), Sex</th>
<th>Type of Catheter Intervention</th>
<th>Initial NIHSS</th>
<th>Onset to Angiography, min</th>
<th>Location of Occlusion</th>
<th>Recanalization</th>
<th>Type of Infarction on CT/MRI After Stroke</th>
<th>mRS, 3 mon After Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72, M</td>
<td>Diagnostic coronary angiography</td>
<td>20</td>
<td>195</td>
<td>MCA, M1</td>
<td>Partial</td>
<td>Large anterior circulation cortical infarct (MCA territory)</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>55, M</td>
<td>Diagnostic coronary angiography</td>
<td>16</td>
<td>110</td>
<td>MCA, M1</td>
<td>Complete</td>
<td>Striato-capsular infarct</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>62, F</td>
<td>Diagnostic coronary angiography</td>
<td>16</td>
<td>125</td>
<td>MCA, M2</td>
<td>Complete</td>
<td>No lesion on CT</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>58, M</td>
<td>Diagnostic coronary angiography</td>
<td>17</td>
<td>240</td>
<td>ICA intracranial</td>
<td>Partial</td>
<td>Small anterior circulation cortical infarct (MCA territory)</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>65, M</td>
<td>Diagnostic coronary angiography</td>
<td>8</td>
<td>150</td>
<td>MCA, M2</td>
<td>Minimal</td>
<td>Small anterior circulation cortical infarct (MCA territory)</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>51, M</td>
<td>Diagnostic coronary angiography</td>
<td>22</td>
<td>105</td>
<td>MCA, M2</td>
<td>Complete</td>
<td>Large anterior circulation cortical infarcts (MCA territory)</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>39, F</td>
<td>Angiography before subclavian stent</td>
<td>15</td>
<td>15</td>
<td>ICA intracranial</td>
<td>Partial</td>
<td>Small anterior circulation cortical infarct (MCA territory)</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>62, F</td>
<td>Angiography before embolization of falx meningioma</td>
<td>5</td>
<td>18</td>
<td>MCA, M1</td>
<td>Complete</td>
<td>No lesion on MRI</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>53, M</td>
<td>Angiography before balloon occlusion test</td>
<td>14</td>
<td>55</td>
<td>MCA, M1</td>
<td>Complete</td>
<td>Multiple small anterior circulation cortical infarcts (MCA territory)</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>70, F</td>
<td>During carotid dilatation prior to stent placement</td>
<td>12</td>
<td>19</td>
<td>MCA, M1</td>
<td>Partial</td>
<td>Striato-capsular infarct</td>
<td>4</td>
</tr>
<tr>
<td>11</td>
<td>72, M</td>
<td>During carotid stent placement</td>
<td>6</td>
<td>16</td>
<td>MCA, M2</td>
<td>Complete</td>
<td>Multiple small anterior circulation cortical infarcts (MCA territory)</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>62, M</td>
<td>Angiography before subclavian stent</td>
<td>12</td>
<td>90</td>
<td>ACA, A2</td>
<td>Partial</td>
<td>Multiple small anterior circulation cortical infarcts (ACA territory)</td>
<td>0</td>
</tr>
</tbody>
</table>
tion had a favorable outcome after 3 months, whereas of the 6 patients with partial or minimal recanalization the outcome was favorable only in 3 (P=0.18). There was no association with vessel recanalization or clinical outcome based on, age, sex, vascular risk factors, baseline NIHSS score, urokinase dose, location of vessel occlusion, or the type of catheter used (Tables 2 and 3).

### Discussion

Ischemic stroke is a rare but well-known complication of cardiac or neurovascular catheter interventions attributable mostly to embolism.\(^5\)–\(^\text{11}\) Possible pathomechanisms include direct arterial injury, air embolism, thrombus formation on the catheter or guide wire, and dislocation of pre-existing atherosclerotic plaques or thrombotic material, especially from the aortic arch.

In this study, we report our experience of treatment with IAT of patients who experienced stroke symptoms during or immediately after catheter interventions. The principal result of this study is the high percentage of patients with a favorable clinical outcome (75%) without any deaths. Our results compare well with a series of 22 stroke patients as a favorable outcome (75%) without any deaths. Our study reported favorable outcomes in 48% of patients, 19% case fatalities, and 66.7% of complete or partial recanalization rates in 21 peri-coronary angiography stroke patients treated with intra-arterial recombinant tissue plasminogen activator or urokinase.\(^\text{14}\) In the PROACT II study, the largest randomized intra-arterial thrombolysis trial in noniatrogenic stroke patients with MCA, the percentage of favorable outcomes (mRS ≤2) was 40% in the IAT group and 25% in the control group.

We think the favorable results in our study are mainly attributable to the high recanalization rate (50% complete and 42% partial recanalization) and the shorter average time interval (95 min) from symptom onset to treatment.\(^\text{15}\) Nevertheless, a mean time interval of 95 minutes is still too long. Time to treatment was defined as the time from the last documented normal patient examination to the administration of IAT. This means that the true time from symptom onset to treatment may be shorter in several patients. Because all IATs were performed by a neuroradiologist in neuroangiography suite, time delay resulted from the transfer from the cardiological laboratory to the neuroangiography suite (≈15 minutes). However, there is a potential to further shorten the time delay because we performed CT scan before IAT in cardiac patients to exclude intracerebral hemorrhage. Immediate angiography may be more beneficial and a subsequent CT should probably only be performed if angiography does not reveal a vessel occlusion. After the analyses of our own

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### Table 2. Predictors of Vessel Recanalization Immediately After Thrombolysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Complete Recanalization, n (%)</th>
<th>Partial or Minimal Recanalization, n (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>6 (50)</td>
<td>6 (50)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>59 (8)</td>
<td>61 (12)</td>
<td>0.432</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>1.0</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>1 (17)</td>
<td>1 (17)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>3 (50)</td>
<td>4 (67)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>1 (17)</td>
<td>3 (50)</td>
<td>0.545</td>
</tr>
<tr>
<td>Mean time to treatment (SD), min</td>
<td>71 (48)</td>
<td>118 (93)</td>
<td>0.423</td>
</tr>
</tbody>
</table>

### Table 3. Predictors of Functional Clinical Outcome 3 Months After Thrombolysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Favorable Outcome (mRS 0–2)</th>
<th>Poor Outcome (mRS 3–5)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N of patients</td>
<td>9 (75)</td>
<td>3 (25)</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>2 (22)</td>
<td>2 (67)</td>
<td>0.236</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>60 (7)</td>
<td>60 (19)</td>
<td>0.644</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>2 (22)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Current smoking, n (%)</td>
<td>2 (22)</td>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>5 (56)</td>
<td>2 (67)</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>4 (44)</td>
<td>0</td>
<td>0.491</td>
</tr>
<tr>
<td>Mean time to treatment (SD), min</td>
<td>101 (70)</td>
<td>76 (103)</td>
<td>0.518</td>
</tr>
</tbody>
</table>

P indicates difference between subgroups by Fisher exact test or Mann–Whitney test.
data and the data on IAT in iatrogenic stroke in the literature, we have changed our protocol accordingly. We will receive a new combined (hybrid) angiography-CT system within the next months. This combined technique will shorten the time delay if a CT scan is needed. Another alternative might be intravenous thrombolysis if the femoral artery sheath has been removed, which was not the case in our patients. However, rapid repuncture is possible in most patients and vessel recanalization is probably more likely in IAT. The high recanalization rate after IAT and the fact that only 2 patients needed both pharmacological and mechanical thrombolysis indicate that most vessels were occluded by thromboembolic material and not by cholesterol emboli. Similar high recanalization rates were achieved in other series using urokinase.9–11 However, in a study of 9 neuroendovascular patients treated with IAT using recombinant tissue plasminogen activator, partial or complete recanalization rates were lower (44%) than in those using urokinase.13 Thus, intra-arterial urokinase might be superior to recombinant tissue plasminogen activator in recanalizing occluded vessels attributable to arterial catheter interventions. However, because of different patient selections, catheter techniques, and doses of the thrombolytic agents, further studies are needed to compare the efficacy of urokinase and recombinant tissue plasminogen activator.

Despite the favorable outcome in most patients, 83% (10 of 12 patients) showed new cerebral infarctions on follow-up brain imaging. Three of them had multiple small lesions on MRI that were most likely embolic. These results are consistent with the results of another report of acute stroke attributable to cardiac catheter interventions, in which diffusion-weighted MRI often revealed multiple asymptomatic small ischemic lesions.12 IAT is an intervention with potentially serious complications. In our study the rate of symptomatic intracerebral hemorrhage was 17% (2/12 patients). This higher bleeding rate compared to other case series and randomized trials is most likely a chance observation caused by the small sample size.2,16

Our study has several limitations. This is a retrospective study. Not all patients undergoing coronary arteriography or neuroendovascular procedures were examined by a neuroradiologist immediately after the intervention. Therefore, some minor strokes may have been missed. However, data of all patients undergoing IAT were collected prospectively. Furthermore, the lack of significant predictors of recanalization or clinical outcome may be attributable to the small numbers in the study. The neurologists who performed post-treatment assessment were not blinded to the recanalization rates of the IAT. Finally, it is not possible to address the efficacy of IAT in the special setting of acute arterial catheter-induced strokes because of the heterogeneity of patients and the lack of a control group.

In conclusion, this study indicates that pharmacological thrombolysis with urokinase has the potential to at least partially recanalize occluded vessels and to improve clinical outcome in patients with acute peri-procedural stroke after neuroendovascular and cardiac catheter interventions. In selected cases mechanical disruption of the thrombus or tissue plasminogen activator may be necessary.

Because of the potential for serious complications, this therapeutic approach should be performed in experienced stroke centers. In the case of very long travel distances to a specialized stroke center, it might be an option that interventionists develop the required skills to perform intracranial IAT.

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Disclosures
None.

References
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