Outcome of Patients With Negative CT Angiography Results for Arterial Occlusion Treated With Intravenous Thrombolysis

Robert Mikulik, MD, PhD; David Goldemund, MD; Michal Reif, MD; Petr Aulicky, MD; Petr Krupa, MD

Background and Purpose—Stroke patients without evidence of arterial occlusion may not be suitable candidates for thrombolytic therapy. In our study, we investigated the outcomes of patients with negative CT angiography results for arterial occlusion.

Methods—The study included patients treated within 3 hours after symptom onset with intravenous thrombolysis for significant neurological deficit between August 2003 and June 2007. All of the patients were documented with negative CT angiography results for arterial occlusion by independent reviews. Outcome measurements included modified Rankin score at 3 months, incidence of intracranial hemorrhage, and infarction volume on control CT. The predictors of unfavorable outcome (modified Rankin score, 2–6) were identified by multivariate logistic regression.

Results—Altogether, 173 patients received intravenous thrombolysis; of those, 138 underwent CT angiography. The CT angiography results were negative for arterial occlusion in 39 (28%) of the patients: mean age, 71 ± 10 years; 16 (41%) female; median baseline NIHSS, 11. At 3 months, modified Rankin score of 0 to 1 was achieved in 18 (46%) of the patients; 6 (15%) died; and 3 (8%) had symptomatic parenchymal hemorrhage. The median infarct volume was 1.5 cm³. The independent predictors of unfavorable clinical outcome were higher age (OR, 1.1; 95% CI, 1.01–1.27), and baseline NIHSS (OR, 18.8; 95% CI, 1.4 to 261). One patient had encephalitis diagnosed.

Conclusions—Negative baseline CT angiography is not uncommon. The risk of intracerebral hemorrhage after thrombolytic therapy for patients without evidence of arterial occlusion is similar to the risk carried in an unselected patient population. Given the prognosis, thrombolytic therapy seems justified; however, etiology other than stroke should be considered. (Stroke. 2009;40:868-872.)

Key Words: CT angiography ■ outcome ■ stroke care ■ thrombolysis

Treatment with an intravenous tissue plasminogen activator (tPA) within 3 hours of symptom onset is the first effective treatment of ischemic stroke aiming to achieve early recanalization.1 It has been argued, however, that tPA should be administered only to patients who have proven occlusive thromboemboli in brain arteries, because it is a potentially dangerous drug.2 The occlusive thromboembolic lesion can be diagnosed by several vascular imaging methods, such as transcranial Doppler, CT, or MR angiography. CT angiography is the most available tool, because it can be performed on any CT scanner with spiral capability as part of the baseline CT examination. It has been shown that CT angiography is accurate for the detection of large-vessel intracranial occlusion and therefore may be valuable in the rapid triage of acute stroke patients to thrombolytic treatment.3-5 CT angiography has also identified patients with autolyzed thrombi, and it has been suggested that CT angiography may represent a tool by which to exclude patients from thrombolytic therapy.6 Data on the risk and benefit of tPA treatment in patients who have negative CT angiography results for arterial occlusion are, however, lacking.

Thus, the goal of our study was to investigate the clinical outcome of patients treated with intravenous tPA who had normal baseline CT angiography results for arterial occlusion. Given the increasing use of and reliance on advanced imaging technologies, such findings could have a significant impact on the physician’s chosen method to treat stroke.

Patients and Methods

Study Design and Patient Selection
We reviewed a prospectively collected database of stroke patients treated with intravenous tPA within 3 hours from stroke onset beginning in August 2003 through June 2007. Every patient received intravenous tPA for significant neurological deficit according to the National Institute of Neurological Disorders and Stroke trial criteria.1 All patients had baseline noncontrast CT of the brain and CT angiography of intracranial vessels before administration of tPA. The CT angiographies were read by 2 independent readers (a board-
certified radiologist and a neurologist). In case of disagreement, a third reader (a board-certified neurologist) was consulted. Patients who had 2-reader-assessed CT angiography with negative baseline results for arterial occlusion were further analyzed. An independent reading by a single reader was also obtained to assess the presence and type of hemorrhagic transformation on control noncontrast CT, which was performed 22 to 36 hours after treatment.

Hemorrhagic transformation was classified according to the European Cooperative Acute Stroke Study criteria as hemorrhagic infarction and parenchymal hemorrhage types I and II (PH1 and PH2).7,8 Symptomatic intracranial hemorrhage was defined as blood at any site in the brain on the control CT scan and a decrease in the National Institutes of Health Stroke Scale (NIHSS) score of ≥4 points.7,8

All patients were treated and monitored in an intensive neurological care unit with automated control of arterial pressure, pulse rate, respiratory rate, oxygen saturation, and surveillance of clinical state every hour for at least 3 days. Our ethics committee approved the protocol.

Data Collection
We prospectively documented demographic data, blood work-up, stroke risk factors, and neurological status. We examined the following baseline variables: age, sex, history of coronary heart disease, arterial hypertension, diabetes mellitus, hyperlipidemia, current cigarette smoking, presence of atrial fibrillation, previous stroke, aspirin use before thrombolysis, admission systolic blood pressure and diastolic blood pressure, blood glucose, fibrinogen, symptom onset-to-treatment time, etiology of stroke based on the Trial of ORG 10172 in Acute Stroke Treatment criteria,9 the NIHSS symptom onset-to-treatment time, etiology of stroke based on the European Cooperative Acute Stroke Study criteria as hemorrhagic infarction and parenchymal hemorrhage types I and II (PH1 and PH2).7,8 Symptomatic intracranial hemorrhage was defined as blood at any site in the brain on the control CT scan and a decrease in the National Institutes of Health Stroke Scale (NIHSS) score of ≥4 points.7,8

CT
CTs were performed on Philips MX 8000 4-detector CT scanner. For nonenhanced scans, 1.3-mm slice thickness was used. Spiral CT angiography used 1.3-mm collimation; table speed-pitch 0.875: and 0.6-mm reconstruction intervals. Other parameters were 120 kV, 200 mAs, 360 reconstruction algorithm, and scanning angle 0°; and field of view 200. Producing 167 to 200 source images (10–12 cm coverage), the scanning started at the atlas vertebra level and ended approximately at the top of lateral ventricles. The scanning delay after intravenous administration of the nonionic contrast agent (Iomeron, Ultravist, Scanlux, and Xenetix) ranged from 15 to 25 seconds according to the 20-mL test bolus. The average dose of contrast agent was 120 mL. Scanning time ranged from 20 to 30 seconds. Contrast medium was injected into an antecubital vein (intra muscular canulla >18 gauge) at an injection rate of 3.5 to 5 mL/sec with a mechanical injection pump (Medrad–Envision CT Injector).

All source images were transferred to an independent MX View workstation (Philips) to create the 3-dimensional reconstruction of the main brain arterial tree. The total time of the procedure did not exceed 20 minutes. Both source images and their 3-dimensional reconstructions were used to diagnose vessel occlusion.

Detailed CT Volumetric Analysis Methodology
On control CT, lesion volume was calculated from the cross-sectional area of the lesion on each slice multiplied by slice thickness.10–12 The lesion was manually traced on each slice of the CT scan. Two independent operators traced and calculated the lesion volume and the average from 2 measurements was taken for other calculations. Any area of parenchymal hemorrhage shown on the CT scans was included in the measurement of the lesion volume.10

Statistical Analysis
Analyses were performed with NCSS software version 2007. The baseline and outcome measures are presented as mean and SD for continuous variables, medians for categorical variables, and percentage for nominal variables. Interobserver agreement was calculated by kappa statistic for categorical variables (CT angiography) and intraclss correlation coefficients for continuous variables (infarct volume).13 Levels of clinical significance for intraclass correlation coefficients were defined according to conventional criteria (≥0.74, excellent; 0.60–0.74, good; 0.40–0.59, fair; <0.40, poor).

The predictors of unfavorable outcome (defined as mRS 2–6) were identified by logistic regression analysis. The OR with 95% CI limits was estimated and tested by the Wald χ² test. Parameters with a potential discrimination power with P≤0.05 in univariate regression were entered into multivariate analysis. For the final model, statistical significance was set at P≤0.05.

Results
Altogether, 173 patients received intravenous thrombolysis between August 2003 and June 2007. Thirty-two patients were excluded from the study because they did not have any CT angiography performed for the following reasons: agitation (n=8); physician’s discretion (for patients with dense middle cerebral artery sign on unenhanced brain CT and severe neurological deficit; median NIHSS, 19; min, 15; max, 23; n=9); history of allergy to contrast agent (n=7); referral from other hospital that had not used CT angiography (n=6), baseline MRI instead of CT (n=1); or technical reasons (n=1). Three patients were further excluded because of low-quality CT angiography. Of the remaining 138 patients, 98 (71%) had occlusion diagnosed on CT angiography (baseline NIHSS median, 15; min, 5; max, 36; 68% had unfavorable outcome at 3 months; 37% died), and 40 (29%) had unfavorable outcome at 3 months; 37% died), and 40 (29%)
had negative CT angiography results for arterial occlusion based on 2 independent assessments. One patient was excluded because of a missing control CT at follow-up. Therefore, 39 patients were used for a final analysis. Interobserver agreement for reading CT angiograms was kappa = 0.71 (disagreement occurred in 17 cases; based on the third-reviewer opinion, occlusion was missed in 7 cases by the radiologist and 4 cases by the neurologist, and patency was misdiagnosed as occlusion in 3 cases both by the radiologist and the neurologist).

The baseline demographic parameters of patients with negative CT angiography results for arterial occlusion are in Table 1. At 3 months after treatment, the mRS of 0 to 1 and 0 to 2 were achieved in 18 (46%) and 23 (59%) patients, respectively. In subgroups with lacunar and large-vessel stroke, the mRS of 0 to 1 was achieved in 5 (45%) and 16 (59%) patients, respectively (P = 0.44). Six patients (15%) died—2 because of recurrent stroke, 2 because of PH2 hematoma, and 2 because of cardiac or pulmonary complications. Three patients (8%) had PH2 hematoma (1 with atherothrombotic, 1 with cardioembolic, and 1 with lacunar stroke), which was remote in 2 cases (Figure). All PH2 hematomas were asymptomatic and led to death in 2 cases. Two patients (5%) had asymptomatic small hematoma type I. One patient (3%) had hemorrhagic infarction type II.

Fourteen patients (36%), 5 with initial clinical symptoms of small-vessel stroke (lacunar syndromes) and 9 with large-vessel stroke (presence of cortical clinical symptoms), did not have any new infarction on control CT. In the remaining 25 patients, 1 had encephalitis diagnosed. The others developed infarction on control CT in the following territories: lacunar, 7; M1 segment of middle cerebral artery, 3; M2 segment of middle cerebral artery, 6; M3 segment of middle cerebral artery, 1; P2 segment of posterior cerebral artery, 2; P3 segment of posterior cerebral artery, 3; anterior inferior cerebellar artery, 1; and superior cerebellar artery, 1 (Figure).

The median infarct volumes measured on control CT and their comparison with infarct volumes of tPA-treated patients in National Institute of Neurological Disorders and Stroke trial are shown in Table 2. Interobserver agreement was excellent for the measurement of the infarction volume (intraclass correlation coefficients = 0.95; 95% CI, 0.91–0.98).

In univariate logistic regression analysis, the predictors of unfavorable clinical outcome were: higher age (OR, 1.1; 95% CI, 1.01–1.2), baseline NIHSS $>$ 12 (OR, 18.7; 95% CI, 2.1–167), and diabetes (OR, 5.5; 95% CI, 1.2–25). In a

Table 2. Comparison of the Outcome and Infarct Volume between CT Angiography Negative Patients and a tPA-Treated Cohort in NINDS Trial

<table>
<thead>
<tr>
<th></th>
<th>CT Angiography Negative</th>
<th>NINDS tPA-Treated Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRS 0–1</td>
<td>46%</td>
<td>39%</td>
</tr>
<tr>
<td>Mortality</td>
<td>15%</td>
<td>17%</td>
</tr>
<tr>
<td>Infarct volume at 24 h, cm³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (interquartile range)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.5 (0–37)</td>
<td>14 (1–68)</td>
</tr>
<tr>
<td>Large vessel</td>
<td>20 (0–60)</td>
<td>14 (2–61)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>28 (0–82)</td>
<td>27 (4–104)</td>
</tr>
<tr>
<td>Small vessel</td>
<td>0.3 (0–1.6)</td>
<td>2 (0–9)</td>
</tr>
<tr>
<td>Normal control CT</td>
<td>36%</td>
<td>57%*</td>
</tr>
</tbody>
</table>

*Assessed at 3 months.
multivariate model, only older age (OR, 1.1; 95% CI, 1.01–1.27) and baseline NIHSS >12 (OR, 18.8; 95% CI, 1.4–261) remained significant (see complete results of univariate and multivariate analysis in Table 3).

**Discussion**

Our study uses the largest cohort of patients to date to systematically address the outcome of stroke patients who had negative baseline CT angiography results for arterial occlusion and were treated with tPA. We identified negative baseline CT angiography results as a common finding, occurring in as much as 29% of all our patients admitted with ischemic stroke within 3 hours after symptom onset and meeting the criteria for tPA treatment. Our study showed that only approximately half of these patients achieved a favorable clinical outcome; 15% died. The size of brain parenchyma damage measured as infarction volume on control CT was substantial in our patients. Therefore, we could not demonstrate that normal arterial status or occult occlusion as shown by CT angiography before tPA treatment ensures a generally good prognosis. Our study could not confirm the findings of a previous smaller study that a majority of patients achieve independence if baseline CT angiography results are negative for arterial occlusion.16

The risk of symptomatic intracerebral hemorrhage (ICH) was 8% in our patients. We found that tPA treatment in patients with negative baseline CT angiography results for arterial occlusion carries a similar risk of symptomatic ICH as the risk carried in an unselected patient population.1,8 Our findings contrast with the previous study of 17 stroke patients with normal baseline CT angiography results before treatment with tPA, which showed zero risk of any ICH.16

Our study also cannot confirm the results of another study based on transcranial Doppler, which found 25% risk of symptomatic ICH in patients with negative transcranial Doppler and the presence of cortical symptoms.17 The difference in the risk of ICH in the latter study and our study, however, may be explained by the different properties of transcranial Doppler and CT angiography in diagnosing intracranial occlusion.

Incidentally, 1 of our patients had viral encephalitis diagnosed according to cerebrospinal fluid examination and MRI. He presented with "large-vessel stroke" symptoms and his baseline NIHSS was 19. Thrombolysis did not cause any complication in this patient, and antiviral therapy led to a complete resolution of neurological deficit. However, our data show that negative CT angiography results should lead physicians to consider other diagnoses than stroke, especially if the occlusion of a large vessel is to be expected from clinical presentation and yet is not confirmed by CT angiography.18

We argue that although patients with negative baseline CT angiography results are exposed to the risks of ICH, they still should be treated with tPA for several reasons. First, 12 of our patients had lacunar strokes, which can benefit from tPA treatment.1 Second, another 23 patients had occlusion of distal branches of the main brain arteries, based on clinical presentation and the size and location of infarctions on control CT. Previous studies have shown that distal branch occlusions are diagnosed less reliably on CT angiography.4,5 Third, in 3 patients, the extent of infarction indicated the

### Table 3. Predictors of Unfavorable Clinical Outcome in Patients with Negative CT Angiography Results for Arterial Occlusion

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Analysis</th>
<th>Multivariate Analysis</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>1.1 (1.01–1.2)</td>
<td>1.13 (1.01–1.27)</td>
</tr>
<tr>
<td>Female</td>
<td>1.2 (0.33–4.25)</td>
<td>0.80</td>
</tr>
<tr>
<td>NIHSS baseline &gt;12</td>
<td>18.7 (2.1–167)</td>
<td>0.01</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>2.5 (0.68–9)</td>
<td>0.17</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3.2 (0.56–18)</td>
<td>0.19</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>0.3 (0.03–2.47)</td>
<td>0.24</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5.5 (1.2–25)</td>
<td>0.03</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.3 (0.4–4.7)</td>
<td>0.66</td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>0.5 (0.1–1.9)</td>
<td>0.31</td>
</tr>
<tr>
<td>Previous stroke</td>
<td>0.3 (0.05–1.6)</td>
<td>0.15</td>
</tr>
<tr>
<td>Previous acetyl salicylic acid</td>
<td>2.2 (0.6–8.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>Glucose level baseline</td>
<td>1.3 (0.9–1.8)</td>
<td>0.18</td>
</tr>
<tr>
<td>Fibrinogen baseline</td>
<td>1 (0.4–2.5)</td>
<td>0.99</td>
</tr>
<tr>
<td>Blood pressure systolic</td>
<td>1.03 (1.001–1.006)</td>
<td>0.054</td>
</tr>
<tr>
<td>Blood pressure diastolic</td>
<td>1.04 (0.99–1.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>Symptom onset-to-treatment time</td>
<td>0.99 (0.98–1.02)</td>
<td>0.97</td>
</tr>
<tr>
<td>Stroke etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>1.9 (0.38–10)</td>
<td>0.43</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>4.8 (0.68–34)</td>
<td>0.12</td>
</tr>
<tr>
<td>Lacunar</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
occlusion of the main stem of the middle cerebral artery. Because the artery was shown to be clearly open on baseline CT angiography, the most likely explanation for this apparent discrepancy is reocclusion, which has been shown to happen in 25% of patients who achieve spontaneous recanalization before tPA bolus.19 Last, the incidence of normal arterial status in acute stroke patients based on CT angiography results (29%) in our study as well as in other studies (36%)16 seems higher than in studies based on digital angiography or transcranial Doppler (17% to 24%),17 thus possibly underestimating the real clot burden.

More studies are needed to confirm the efficacy of tPA in patients with negative CT angiography results for arterial occlusion. In our study we identified age and baseline NIHSS as the only predictors of unfavorable clinical outcome. Therefore, until more data on patients with negative CT angiography results for arterial occlusion are available, it seems reasonable to rely on the severity of neurological deficit in deciding whether to treat the patients with tPA.

The primary limitation of our study is the fact that we used a 4-detector CT scanner. The quality of 3-dimensional reconstructions often allowed us to visualize only the major intracerebral vessel. Clots located distally may have been overlooked, although source images were used in all cases. The newer generation of CT scanners may overcome this issue. Also, we used the presence of infarction on the control CT as a marker of the presence of the clot at baseline. To distinguish between normal artery status and occult artery occlusion, CT angiography needs to be coupled with other vascular imaging modality. Finally, our study was not designed to compare the outcome of patients with positive and negative CT angiography results for occlusion, because such analysis cannot provide information on the response to tPA in either group. It would, however, be useful for a future study to test how findings on baseline CT angiography predict the outcome of patients treated with tPA.

In conclusion, nearly one-third of the patients included in our study did not have any evidence of an occlusive thromboembolic lesion at baseline, either because of previous recanalization or, more probably, because of the inability to detect large-vessel distal or lacunar occlusions with CT angiography. The risk of intracerebral hemorrhage after tPA treatment for patients who have negative CT angiography results for arterial occlusion is similar to risk for the unselected patient population. Our data could have a significant impact on a physician’s decision to treat stroke, because we argue that tPA treatment seems justified because only less than half of patients with negative CT angiography results achieve excellent outcomes. However, etiologies other than stroke should be considered.

Acknowledgments
The authors thank Anne Johnson for her editorial assistance.

Disclosures

None.

References


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Stroke. 2009;40:868-872; originally published online January 8, 2009;
doi: 10.1161/STROKEAHA.108.532572
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

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