Nonocclusion and Spontaneous Recanalization Rates in Acute Ischemic Stroke

A Review of Cerebral Angiography Studies

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Background: Spontaneous recanalization is an understudied phenomenon in stroke. It is often overestimated by nonocclusion rates. The heterogeneity of the causes and manifestations of stroke and of the studies assessing vascular patency has created difficulties in assigning accurate rates of its incidence.

Methods: Systematic review of published articles about cerebral angiography in stroke.

Results: Lack of anticipated occlusions (nonocclusion rates) was noted in 28% of patients in suspected vessels 6 hours after stroke onset, whereas documented occlusions were noted in 17% of patients who underwent spontaneous lysis at 6 to 8 hours. At 3 to 4 days, the nonocclusion rate was 50% of studied vessels.

Conclusions: In the first 6 to 8 hours from stroke onset, spontaneous recanalization occurs in approximately 17% of patients, whereas nonocclusion exists in about 28% of patients and up to 50% by 4 days after stroke.

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S PONTANEOUS recanalization (SR) is an intriguing phenomenon in acute ischemic stroke. Cerebral angiographic and autopsy studies have clearly documented its occurrence. Assigning accurate rates of SR has been hindered by several factors, including the complexity of stroke as a disease process and the heterogeneity of available studies.

Concerning the study of arterial patency, several factors that are inherent to stroke affect the detection of occlusions. For instance, involvement of different major arterial distributions can cause similar symptoms and signs. Hence, an occlusion may be missed if the study does not include all the cerebral vessels. Moreover, occlusions that involve small arteries can be beyond the resolution of available radiologic studies and as such can also contribute to false rates.

Studies evaluating the phenomenon of SR differed at the level of several factors, such as the time of angiographic assessment from stroke onset, the presumed stroke location, and the presumed stroke mechanism. Each of these factors is known to exert an influence on the likelihood of recanalization. For example, a clot of embolic origin is known to recanalize spontaneously more often than occlusion caused by a local thrombosis.

Similarly, middle cerebral artery (MCA) clots are more prone to resolve spontaneously than internal carotid artery clots.

Is it possible to accurately estimate the incidence of SR? Ideally, such a task requires the documentation, by a reliable technique, of an occlusion that resolves spontaneously as noted using the same technique. Such studies are rare in neurology if cerebral angiography is chosen as the gold standard to evaluate arterial patency. As such, a need arises to derive SR rates from the baseline or screening angiogram assuming a visible clot is or was present in the studied vascular distribution, acknowledging the limitations.

As an attempt to answer the question, a MEDLINE search was conducted looking at all studies that were found by combining the medical subject heading of Cerebral Angiography and the keyword “stroke.” Studies selected involved patients thought clinically to have stroke in various distributions (as specified herein), with well-documented stroke onset, angiographic timing, and angiographic findings. Where available, details of study design (eg, randomization, blinding) were presented. These studies
are summarized in the “Report of Cases” section based on the interval during which angiography was performed after stroke onset.

**REPORT OF CASES**

### 4 HOURS

The EMS Bridging Trial was a prospective trial that randomized patients seen within 3 hours of stroke onset to receive either intravenous tissue plasminogen activator (tPA) or placebo followed by cerebral angiography, with the intent to administer intra-arterial tPA in case a clot was visualized. Angiography was performed within 4 hours of stroke onset on the vessel that was thought to be involved. Derex et al. analyzed the subset of patients who had stroke onset on the vessel that was thought to be involved. Derex et al analyzed the subset of patients who had no angiographic occlusion. Of 18 patients who received placebo, angiography did not reveal occlusions in 7 patients. Two patients had eventuial parenchymal lesions in the vertebrobasilar system but had only the carotid distribution evaluated by angiography. Patients without clots tended to have small lesion volume by brain imaging.

### 5 HOURS

In an attempt to correlate clinical to early radiologic findings, Horowitz et al. described 50 consecutive patients seen within 3 hours of stroke onset who underwent brain computed tomography (CT) and angiography. Patients included in the study had evidence of hemispheric dysfunction with hemiparesis. Patients who were excluded had transient ischemic attacks (TIAs), coma, and brainstem signs. Patients did not receive thrombolysis. Of the 35 angiographic studies performed within 5 hours of stroke onset, 15 did not show occlusion. The posterior circulation was not studied angiographically. Lack of intracranial occlusion correlated with negative results on early and follow-up CT scans and with a smaller infarct size. Eight of 9 patients with hemorrhagic infarction on follow-up CT had occluded vessels on initial angiograms.

### 6 HOURS

In 1989, Fieschi et al. studied radiographic and clinical findings in 80 consecutive stroke patients. Patients included in the study were seen within 4 hours of symptom onset; patients with infratentorial signs or TIA or who were comatose were excluded. Computed tomography, carotid angiography, and transcranial Doppler (TCD) studies were performed on all patients. Nineteen percent had no occlusions on angiography; these patients tended to have lesser neurologic deficits at presentation and at follow-up. Of 15 patients with MCA occlusions followed with angiography or TCD, 11 (73%) had reperfusion 1 week after stroke onset.

In 1998, del Zoppo et al. published the PROACT I (Prolyse in Acute Cerebral Thromboembolism) study data on patients with MCA distribution stroke symptoms within 6 hours of stroke onset. Patients were randomized to receive in a double-blinded fashion placebo or intra-arterial prourokinase if angiograms revealed TIMP flow grades 0 or 1, corresponding to no or minimal contrast penetration, respectively. Patients included in the study had a minimum National Institutes of Health Stroke Scale (NIHSS) score of 4 or higher (unless they had isolated aphasia or hemianopsia). Patients were excluded if they had an NIHSS score greater than 30, coma, or minimal neurologic stroke symptoms or lacunar syndromes. Of 105 patients screened with angiography, 25 had no occlusion. Patients with occlusion of the horizontal M1 segment or the M2 division of MCA were enrolled. Of 14 randomized patients receiving placebo, 2 (14%) had evidence of recanalization (8 hours after stroke onset). Of note, placebo patients also received heparin at high or low doses, although none of the patients receiving the high dose had any improvement in vessel patency. This study was open label.

In the sequel to the latter study, Furlan et al. reported the PROACT II data. This open-label study was also randomized and controlled, and enrollment criteria were similar to those of phase II except that patients having sulcal effacement in more than one third of the MCA territory were excluded. Of 474 patients screened with angiography, 142 had no occlusion. Of 50 randomized patients receiving placebo, 9 (18%) had evidence of reperfusion 8 hours after stroke onset.

In 1999, Suarez et al. published a prospective series of patients seen within 6 hours of stroke onset who underwent intra-arterial thrombolysis with the intent of administering intra-arterial urokinase. Patients included in the study had carotid territory deficits, with a minimum NIHSS score of 4, and were not improving clinically. Patients with edema causing mass effect on brain CT were excluded. Of the 62 patients who underwent baseline angiography, 8 had no visible clots, and 7 had partial stenosis.

### 8 HOURS

In an earlier trial, del Zoppo et al. enrolled patients in a dose escalation trial using tPA. Patients with strokes involving the anterior or posterior circulation were eligible. Patients were excluded if they had major deficits (eg, a combination of hemiplegia, decreased consciousness, and forced gaze deviation), minimal or transient deficits, and notable mass effect on brain CT. Of 139 patients who underwent angiography, 27 had no occlusions; these patients also did not undergo thrombolysis.

Toriyama et al. studied a retrospective but consecutive series of patients who underwent radiologic testing with dynamic CT testing (similar to CT perfusion) and angiography within 8 hours of stroke onset. Patients also received urokinase if internal carotid artery or MCA occlusions were seen. Patients were included in the study if they had hemispheric deficits with hemiparesis and no or minor CT hypodensity. Nineteen of 57 patients had no vessel occlusion on initial angiography; these patients had less incidence of hypodensity on early CT scan and lesser baseline neurologic deficits.

### 3 DAYS

In 1969 (pre-CT), Fieschi and Bozzao published an article describing angiographic findings in 96 patients with
presumed acute stroke. Patients were included if they had a clinical diagnosis of major cerebrovascular accident affecting the hemisphere and lacked signs of increased intracranial pressure. Additional studies included lumbar punctures. Of the 96 patients, 86 were thought to have ischemic strokes, of which 37 had no occlusions by angiography.

### 4 DAYS

To investigate the cause of cerebral infarction and correlate it with size and location of infarcts, Olsen et al published in 1985 angiographic data on 73 consecutive patients with carotid territory symptoms. Patients were included if they had deficits persisting for at least 24 hours and possible lacunar strokes. Patients with evidence of brainstem involvement were excluded. Only the carotid artery on the presumed affected hemisphere was studied by angiography. Thirty-eight patients had no occlusions. Of 8 patients with documented MCA occlusion who were studied post mortem (up to 34 months after stroke), all except 1 patient (whose autopsy was performed 1 week after stroke) had a patent MCA.

A summary of these studies is presented in the Table.

### Table

<table>
<thead>
<tr>
<th>Study, y</th>
<th>Time, h</th>
<th>Stroke Location</th>
<th>Nonocclusion Rate, No./Total No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derec et al, 2001</td>
<td>4</td>
<td>Nonspecific</td>
<td>5/16 (31)</td>
</tr>
<tr>
<td>Horowitz et al, 1991</td>
<td>5</td>
<td>Hemispheric</td>
<td>15/38 (32)</td>
</tr>
<tr>
<td>Fieschi et al, 1989</td>
<td>6</td>
<td>MCA territory</td>
<td>19/80 (24)</td>
</tr>
<tr>
<td>del Zoppo et al, 1997</td>
<td>6</td>
<td>MCA territory</td>
<td>25/105 (24)</td>
</tr>
<tr>
<td>Furlan et al, 1999</td>
<td>6</td>
<td>MCA territory</td>
<td>142/474 (30)</td>
</tr>
<tr>
<td>Suarez et al, 1999</td>
<td>6</td>
<td>Carotid territory</td>
<td>15/62 (24)</td>
</tr>
<tr>
<td>Torigawa et al, 1993</td>
<td>8</td>
<td>Hemispheric</td>
<td>19/57 (33)</td>
</tr>
<tr>
<td>del Zoppo et al, 1992</td>
<td>8</td>
<td>Nonspecific</td>
<td>27/139 (19)</td>
</tr>
<tr>
<td>Fieschi and Bozza, 1969</td>
<td>3 Days</td>
<td>Hemispheric</td>
<td>37/86 (47)</td>
</tr>
<tr>
<td>Olsen et al, 1985</td>
<td>4 Days</td>
<td>Carotid territory</td>
<td>38/73 (52)</td>
</tr>
</tbody>
</table>

*MCA indicates middle cerebral artery.

Spontaneous recanalization in stroke is a difficult entity to characterize with accuracy. Assigning a precise estimate of its occurrence requires large studies with homogeneous patient characteristics and radiographic techniques. Historically, enrolling large numbers of stroke patients with homogeneous characteristics has been difficult to achieve in stroke trials.

Numerous factors can result in false assignment of SR rates. One major factor is falsely attributing a stroke syndrome to a particular vascular distribution, since studies tended to perform angiography on 1 major arterial distribution (eg, carotid or vertebrobasilar). Still, with angiography, it is possible to miss small arterial and/or perforator occlusions. A recent study classifying acute stroke patients using the Oxfordshire Community Stroke Project (OCSP) classification found that of all the patients categorized clinically to have partial or total anterior circulation strokes, 7% had an infarct in the posterior circulation and another 7% had small subcortical (lacunar) strokes as seen by CT or magnetic resonance imaging.

Other pitfalls exist, such as the occurrence of stroke mimickers (multiple sclerosis, seizures, migraines, hyperglycemia, hypertensive encephalopathy, etc). Venous thrombosis can be missed if unsuspected.

Having mentioned these variables, it may be more appropriate to label the lack of angiographic occlusion as nonocclusion rates. Nonocclusion rates are likely to overestimate the SR rate. Using these studies, most of which assessed anterior circulation strokes, nonocclusion rates occur at an average of 25% to 30% in the first 6 hours (mean, 28%; PROACT II being the main contributor regarding number of patients) and about 50% in the first 3 to 4 days. Similar results (27.5%) were found by magnetic resonance angiography in 40 patients who underwent imaging studies within 6 hours of stroke onset. If one subtracts the percentages of false localization and small arterial occlusions (using percentages from the OCSP study) from the mean SR at 6 hours, the yield would be a rate of approximately 14%. If only documented occlusions followed by SR are considered, the 2 PROACT studies yield an SR of 17% from their placebo arm. Another small, angiography-based, placebo-controlled study of intravenous tPA administered within 6 hours from carotid territory stroke onset found that 2 (17%) of 12 patients given placebo experienced SR. A similar rate (18.8%) of MCA recanalization at 6 hours was noted using TCD in 50 patients. Accordingly, the true SR rate at 6 to 8 hours lies somewhere between 14% and 28%, likely closer to 17%.

The studies described herein tend to exclude patients with resolved or resolving symptoms (ie, patients who may be classified as having a TIA). Patients without documented occlusions still developed infarcts, so SR did not necessarily correlate with a TIA clinically. Still, patients with no documented acute occlusion tended to have better outcomes overall.

Knowledge of SR can result in several important consequences. Patients may be withdrawn from thrombolytic trials and hence avoid hazardous medications. As such, incorporating a noninvasive imaging technique to assess SR may improve patient selection. In addition, patients with strokes and no documented angiographic occlusions may receive a more appropriate stroke workup, such as a more diligent workup of embolic sources. As far as stroke trials are concerned, these rates may have to be considered in planning, such as sample size calculations, if recanalization is taken as an end point.

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script for important intellectual content (Dr Graffagnino); administrative, technical, and material support (Dr Kassem-Moussa); study supervision (Dr Graffagnino).

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REFERENCES