Infarct patterns, collaterals and likely causative mechanisms of stroke in symptomatic intracranial atherosclerosis

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INFARCT PATTERNS, COLLATERALS AND LIKELY CAUSATIVE MECHANISMS OF STROKE IN SYMPTOMATIC INTRACRANIAL ATHEROSCLEROSIS

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Abstract

Background—There are limited data on specific mechanisms of stroke in patients with intracranial arterial stenosis (ICAS). We undertook this study to describe infarct patterns and likely mechanisms of stroke in a large cohort of patients with ICAS, and to evaluate the relationship of infarct patterns with angiographic features (collaterals, stenosis location and stenosis severity).

Methods—We evaluated infarct patterns in the territory of a stenotic intracranial artery on neuroimaging performed at baseline and during follow-up if a recurrent stroke occurred in patients enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) study. We defined the likely mechanism of stroke (artery-to-artery embolism, perforator occlusive, hypoperfusion, or mixed) according to the site of ICAS and based on infarct patterns on neuroimaging. Collaterals were assessed using ASITN/SIR grades and stenosis severity using WASID measurement.

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*See the supplemental file for a list of WASID investigators.
technique. We evaluated association of infarct patterns with angiographic features using chi square tests.

Results—The likely mechanisms of stroke based on infarct patterns at baseline in 136 patients were: 69 artery-to-artery embolism (50.7%), 34 perforator occlusive (25%), 12 hypoperfusion (8.8%) and 21 mixed (15.5%). Perforator occlusive infarcts were more frequent in posterior circulation and mixed patterns were more prevalent in anterior circulation (both p<0.01). Most of the mixed patterns in the anterior circulation combined small pial or scattered multiple cortical infarcts with infarcts in borderzone regions, especially in cortical borderzone regions. Isolated borderzone infarcts were not significantly associated with poor collaterals or severity of stenosis. Among 47 patients with a recurrent infarct during follow-up, infarct patterns suggested an embolic artery-to-artery mechanism in 29 (61.7%).

Conclusions—Artery-to-artery embolism is probably the most common mechanism of stroke in both the anterior and posterior circulations in patients with ICAS. Extension of intracranial atherosclerosis at the site of stenosis into adjacent perforators also appears to be a common mechanism of stroke, particularly in the posterior circulation, whereas hypoperfusion as the sole mechanism is relatively uncommon. Further research to accurately establish the specific mechanisms of stroke in patients with ICAS is important since preliminary data suggest that the underlying mechanism of stroke is an important determinant of prognosis.

Introduction

Possible mechanisms of stroke associated with large artery intracranial atherosclerosis stenosis (ICAS) include artery-to-artery embolism, hypoperfusion, branch occlusive disease, or combination of these mechanisms (1–3). Establishing the specific mechanism of stroke in individual patients and the overall frequency of each mechanism in ICAS patients are potentially important because different mechanisms of stroke could be associated with different prognoses and responses to medical or endovascular treatment (4–6).

One way to try to establish mechanisms of stroke is to use infarct patterns on brain imaging to infer the underlying stroke mechanism. Previous studies have done this in patients without ICAS (5, 7–12) but there is a paucity of data on this subject in patients with ICAS. Additionally, there are limited data on the association between infarct patterns and angiographic features such as collateral circulation and severity of stenosis. We undertook this study to describe infarct patterns and likely mechanisms of stroke, as well as the association between infarct patterns and angiographic features, in a large cohort of patients with ICAS enrolled in the Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial.

Patients and Methods

Study design and Subjects

WASID was a double-blind, randomized, prospective, multicenter trial conducted at 59 sites in North America to compare aspirin with warfarin for preventing stroke in patients with symptomatic intracranial arterial stenosis (13). Details of the design of WASID and the baseline characteristics of patients in the trial have been published previously (13, 14). All 569
patients enrolled in WASID had a transient ischemic attack or nondisabling stroke within 90 days prior to enrollment that was attributable to angiographically verified 50% to 99% stenosis of a major intracranial artery (carotid, middle cerebral, vertebral or basilar). Patients with tandem extracranial stenosis and a cardiac source of embolism were excluded.

We included two overlapping groups of patients from the WASID trial for the present study: 1) Group 1: 136 patients who had an infarct in the territory of the stenotic artery on brain imaging as the qualifying event for WASID and who had complete anterior and posterior circulation angiographic information on the state of collaterals (flow chart in supplemental eFigure 1), and 2) Group 2: 47 patients who had a recurrent infarct in the territory of the stenotic artery confirmed by brain imaging during follow-up in the trial (flow chart in supplemental eFigure 2).

**Angiography Data**

All conventional angiograms that qualified patients for WASID were centrally adjudicated for the degree of the luminal arterial according to the WASID measurement technique\(^{15}\). Stenoses were classified as moderate (50–69%) or severe (70–99%). Evaluation of collateral circulation was performed by one of the co-authors (D.S.L)\(^{16}\). Collaterals were assessed with the American Society of Interventional and Therapeutic Neuroradiology (ASITN)/ Society of Interventional Radiology (SIR) Collateral Flow Grading System\(^{17}\). This system categorizes collaterals into five grades (0–4) varying between 0 indicating no collaterals visible and 4 indicating complete and rapid collateral blood flow to the territory distal to the stenosis. For this analysis, collaterals were categorized as absent (grade 0), poor (grades 1 and 2), or good (grades 3 or 4). All angiographic readings were done blinded to the results of neuroimaging and patient outcomes.

**Infarct Patterns on Neuroimaging and likely mechanisms of stroke**

All brain CT and MRI studies were reviewed by two investigators (E.L.C, M.G.M) blinded to clinical and angiography data. A third reader’s (M.C) opinion was obtained in cases of disagreement. Topography of ischemic infarcts by vascular territories was determined with references to published templates\(^{18, 19}\).

Infarct patterns were classified as follows: **Perforator pattern** in the presence of subcortical lesions in the distribution of perforating vessels that originate at the site of stenosis; **Territorial pattern** in the presence of one or more lesions located distal to the stenotic vessel (cortical, subcortical or both) that were restricted to the territory supplied by a single intracranial artery; **Borderzone pattern** in the presence of one or more lesions in the internal borderzone region (corona radiata or centrum semiovale) and/or in the cortical borderzone region (between middle cerebral artery and anterior cerebral artery or middle cerebral artery and posterior cerebral artery); **Mixed pattern** when a combination of any of the previous patterns was present.

We defined the likely mechanism of stroke related to ICAS as follows: perforator occlusive for a perforator pattern of infarct, artery-to-artery embolism for a territorial pattern of
Results

Patterns of Baseline Infarcts and Association with Angiographic Features

The neuroimaging studies used to evaluate the 136 patients with baseline infarcts (72 in posterior circulation and 64 in anterior circulation) were CT in 14 patients, DWI-MRI in 89 patients, and FLAIR-MRI in 33 patients. The following infarct patterns were found in these 136 patients: 69 territorial (50.7%), 34 perforator (25%), 12 borderzone (8.8%) and 21 mixed (15.5%). The most frequent infarct pattern in both anterior and posterior circulation was territorial (embolic artery-to-artery mechanism, Figure 1). Perforator occlusive infarcts were more frequent in posterior circulation and mixed patterns were more prevalent in anterior circulation (both p<0.01, Figure 1). All isolated borderzone patterns in anterior circulation (n=12) involved the internal borderzone region and in seven of them the cortical borderzone regions (anterior or posterior) were also affected. Most of the mixed patterns in the anterior circulation (14/17=82.3%) combined small pial or scattered multiple cortical infarcts with infarcts in borderzone regions, especially in cortical borderzone regions.

Analyses correlating stroke patterns with angiographic features showed no statistically significant differences between infarct patterns and severity of stenosis or collateral patterns (Table 1). Of note, borderzone infarcts were not associated with impaired collaterals or severe stenosis. Regarding location of stenosis, borderzone pattern occurred more frequently with MCA (23.4%) than with ICA stenosis (5%), and territorial pattern (embolic) occurred more frequently with vertebral (75.9%) than with basilar stenosis (41.4%) (Table 1).

Infarct Patterns and Likely Mechanisms of Recurrent Stroke

Of the 569 patients enrolled in WASID, 77 had a recurrent stroke in the territory during a mean follow-up of 1.8 years. Of these patients, 47 had a definite recurrent infarct in the territory on available images, 26 in the anterior circulation and 21 in the posterior circulation. Of these 47 patients, 8 did not have an infarct on baseline imaging (qualifying event was either a TIA or imaging negative stroke). Based on our a priori rules as defined above, the mechanisms of recurrent stroke in the 47 patients were artery-to-artery embolism in 29 (61.7%), perforator occlusive in 11 (23.4%), hypoperfusion in 2 (4.2%) and mixed in 5 patients (10.7%). In the 39 patients with both baseline and follow-up infarcts on neuroimaging, the majority of patients with an embolic appearing infarct on follow-up imaging had also an embolic pattern at baseline (75%). Out of the 47 patients with a recurrent infarct in the territory, 26 underwent follow-up vascular imaging, which showed that the intracranial stenosis had progressed to occlusion in only 5 patients. In these 5 patients, the patterns of the recurrent stroke on brain imaging suggested an embolic mechanism in 4 patients and a mixed pattern in 1 patient.

Discussion

Although there are multiple possible mechanisms of stroke in patients with ICAS, the infarct patterns on brain imaging in this study strongly suggests that artery-to-artery embolism is
the most common. Ulceration, plaque rupture, or shear stress from high-grade stenosis likely induces platelet-fibrin deposition which may embolize downstream to distal vessels. Microembolic signals detected by transcranial Doppler that can be associated with multiple infarcts on DWI sequences supports this hypothesis\(^{(2)}\). Additionally, other reports have shown that multiple acute infarcts, especially small scattered ones, are frequently related to large artery atherosclerosis, presumably from artery-to-artery embolism \(^{(3, 7, 10, 20, 21)}\).

The risk of recurrent stroke in WASID was virtually the same on warfarin or aspirin suggesting that neither was particularly effective for preventing the most common mechanism of stroke, artery-to-artery embolism. However, the recently published final results of SAMMPRIS \(^{(22)}\) are encouraging in this respect since the risk of recurrent stroke in the medical arm, both at 30 days and 1 year, were approximately half of the rates in those WASID patients who had similar entrance criteria to the SAMMPRIS patients. This suggests that high-dose statins, better blood pressure control and the combination of aspirin and clopidogrel may be effective for lowering the risk of artery-to-artery embolism in ICAS patients. Indeed, combination antiplatelet therapy has been shown to decrease microemboli detected by transcranial Doppler in patients with ICAS compared with aspirin alone\(^{(23)}\), and aggressive statin and antihypertensive therapy may decrease the risk of artery-to-artery embolism by stabilizing atherosclerotic plaque in extracranial carotid plaques \(^{(24, 25)}\).

Internal borderzone infarcts, which have been associated with hypoperfusion, did not correlate with the absence of collaterals assessed by ASTIN/SIR grades in this study. Conversely, borderzone infarcts were more frequently present among patients with any grade of collaterals than in those with no collaterals (table 1). Other studies have also failed to demonstrate a clear association between borderzone infarcts and an impaired collateralization via the circle of Willis\(^{(26)}\).

We also found that majority of mixed patterns in the anterior circulation included infarcts in cortical distal areas together with lesions in the borderzone region, especially in the cortical borderzone region. This finding supports the hypothesis that a combined embolic-hypoperfusion mechanism may be responsible for these multiple infarcts involving a borderzone region\(^{(12)}\). Support for this is provided by data from an animal model of embolic stroke\(^{(27)}\). Others have also shown that borderzone infarcts, especially cortical borderzone ones, usually coexist with infarcts in other locations\(^{(28)}\). Of interest, isolated internal borderzone infarcts were more frequently associated with MCA lesions than with intracranial carotid stenoses in our study, supporting the findings in other studies that internal borderzone infarcts are more frequent with MCA than extracranial ICA stenosis\(^{(9, 29)}\). Internal borderzone infarcts in patients with MCA stenosis have been associated with neurological worsening in a recent study\(^{(30)}\).

A third mechanism of stroke in intracranial atherosclerosis is perforator occlusive disease, as the atherosclerotic plaque can protrude into the orifice of perforators and occlude the lumen, causing a subcortical infarct\(^{(31)}\). We found this pattern more represented in posterior circulation, especially in basilar stenosis, and it was not associated with severity of stenosis (table 1). High-resolution-MR studies have shown that atherosclerotic plaques in basilar...
artery can lead to paramedian and deep small pontine infarctions, regardless of the severity of stenosis of the parent vessel\(^{[32]}\).

This study has some important limitations: infarct patterns on structural brain imaging can only be used to infer and not prove the mechanism of stroke. Studies using functional imaging (flow studies, collateral perfusion, embolus detection) were not performed in this study and could add important data establishing the specific stroke mechanisms; the results may not be extrapolated to all patients with ICAS as our study population was derived from a clinical trial, e.g., patients with large disabling infarcts were excluded from the trial; not all participants had DWI MRI sequences; finally, the inherent limitations of a post-hoc analysis.

Despite these limitations, this study provides unique data on the relationships between infarct patterns on brain imaging, angiographic features, and likely mechanisms of stroke in a large cohort of patients with ICAS. Further research to accurately establish the specific mechanisms of stroke in patients with ICAS is important since preliminary data suggest that the underlying mechanism of stroke is an important determinant of prognosis\(^{(4)}\), and it is likely that the entrance criteria for future trials for ICAS will be based on the underlying pathophysiologic mechanism of the presenting stroke.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References**


Figure 1.
Bars represent percentage of each infarct pattern in anterior and posterior circulation.
## Table 1

Baseline infarct patterns and angiographic features.

<table>
<thead>
<tr>
<th>BASELINE INFARCT PATTERNS</th>
<th>Perforator</th>
<th>Territorial (embolic a-to-a)</th>
<th>Borderzone</th>
<th>Mixed</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stenosis severity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- 50–70% (n=74)</td>
<td>18 (24.3%)</td>
<td>35 (47.3%)</td>
<td>8 (10.8%)</td>
<td>13 (17.6%)</td>
<td>0.65</td>
</tr>
<tr>
<td>- ≥70% (n=62)</td>
<td>16 (25.8%)</td>
<td>34 (54.8%)</td>
<td>4 (6.4%)</td>
<td>8 (13%)</td>
<td></td>
</tr>
<tr>
<td><strong>Collaterals (ASITN/SIR)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- None (0) (n=82)</td>
<td>22 (26.8%)</td>
<td>42 (51.2%)</td>
<td>5 (6.1%)</td>
<td>13 (15.9%)</td>
<td>0.56</td>
</tr>
<tr>
<td>- Poor (1–2) (n=35)</td>
<td>7 (20%)</td>
<td>18 (51.4%)</td>
<td>5 (14.3%)</td>
<td>5 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>- Good (3–4) (n=19)</td>
<td>5 (26.3%)</td>
<td>9 (47.4%)</td>
<td>2 (10.5%)</td>
<td>3 (15.8%)</td>
<td></td>
</tr>
<tr>
<td><strong>Stenosis location</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>- ICA (n=20)</td>
<td>1 (5%)</td>
<td>13 (65%)</td>
<td>1 (5%)</td>
<td>5 (25%)</td>
<td></td>
</tr>
<tr>
<td>- MCA (n=47)</td>
<td>9 (19.1%)</td>
<td>17 (36.2%)</td>
<td>11 (23.4%)</td>
<td>10 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>- Vertebral (n=29)</td>
<td>7 (24.1%)</td>
<td>22 (75.9%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>- Basilar (a=29)</td>
<td>13 (44.8%)</td>
<td>12 (41.4%)</td>
<td>0</td>
<td>4 (13.8%)</td>
<td></td>
</tr>
<tr>
<td>- Tandem (n=11)</td>
<td>4 (36.4%)</td>
<td>5 (45.4%)</td>
<td>0</td>
<td>2 (18.2%)</td>
<td></td>
</tr>
</tbody>
</table>

In brackets, percentage of each stroke pattern according to each angiographic category. Location of stenosis: ICA: internal carotid artery; MCA: middle cerebral artery; VA: vertebral artery; BA: basilar artery; Tandem: ICA+MCA or VA+BA concomitant stenoses.

* Chi-Square test for comparisons among any of the subgroups