Infarct Patterns, Collaterals and Likely Causative Mechanisms of Stroke in Symptomatic Intracranial Atherosclerosis

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Key Words

Infarct patterns · Intracranial atherosclerotic stenosis · Collaterals · Stenosis location · Warfarin-Aspirin Symptomatic Intracranial Disease study

Abstract

Background: There are limited data on the specific mechanisms of stroke in patients with intracranial atherosclerotic 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 these infarct patterns to 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) trial. We defined the likely mechanism of stroke (artery-to-artery embolism, perforator occlusion, hypoperfusion or mixed) according to the site of ICAS and based on the infarct patterns on neuroimaging. Collaterals were assessed using American Society of Interventional and Therapeutic Neuroradiology/Society of Interventional Radiology (ASITN/SIR) grades, and stenosis severity using the WASID trial's measurement technique. We evaluated the association of infarct patterns with angiographic features using χ^2 tests. **Results:** The likely mechanisms of stroke based on the infarct patterns at baseline in the 136 patients included in the study were artery-to-artery embolism ($n = 69$; 50.7%), perforator occlusion ($n = 34$; 25%), hypoperfusion ($n = 12$; 8.8%) and mixed ($n = 21$; 15.5%). Perforator-occlusive infarcts were

See the online supplementary file for a list of WASID trial investigators.

more frequent in the posterior circulation, and mixed patterns were more prevalent in the 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 border-zone regions, especially the cortical ones. Isolated border-zone infarcts were not significantly associated with a poor grading for collaterals or the severity of stenosis. Among 47 patients with a recurrent infarct during follow-up, the infarct patterns suggested an artery-to-artery embolic mechanism in 29 (61.7%). **Conclusions:** Artery-to-artery embolism is probably the most common mechanism of stroke in both the anterior and the posterior circulations in patients with ICAS. An 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 is important to accurately establish the specific mechanisms of stroke in patients with ICAS, since preliminary data suggest that the underlying mechanism of stroke is an important determinant of prognosis.

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Introduction

Possible mechanisms of stroke associated with large-artery intracranial atherosclerotic stenosis (ICAS) include artery-to-artery embolism, hypoperfusion, branch occlusive disease and a 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 is 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, 7–11], 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

The WASID trial 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 ICAS [12]. Details on the design of this trial and the baseline characteristics of the patients included have been published previously [12, 13]. All 569 patients enrolled in the WASID trial had a transient ischemic attack or nondisabling stroke within 90 days prior to enrollment that was attributable to angiographically verified 50–99% 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: group 1 consisted of 136 patients who had an infarct in the territory of the stenotic artery on brain imaging as the qualifying event and who had complete angiographic information on the state of collaterals in the anterior and posterior circulation (flow chart in online suppl. fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000362922), and group 2 comprised 47 patients who had a recurrent infarct in the territory of the stenotic artery confirmed by brain imaging during the follow-up of the trial (flow chart in online suppl. fig. 2).

Angiographic Data

All conventional angiograms that qualified patients for the WASID trial were centrally adjudicated for the degree of arterial luminal narrowing according to the WASID measurement technique [14]. Stenoses were classified as moderate (50–69%) or severe (70–99%). Evaluations of the collateral circulation were performed by one of the coauthors (D.S.L.) [15]. Collaterals were assessed with the American Society of Interventional and Therapeutic Neuroradiology (ASITN)/Society of Interventional Radiology (SIR) collateral flow grading system [16]. This system categorizes collaterals into 5 grades (0–4) varying from 0 (no collaterals visible) to 4 (complete and rapid collateral blood flow to the territory distal to the stenosis). For this analysis, the collaterals were categorized as absent (grade 0), poor (grades 1 and 2) or good (grades 3 and 4). All angiographic readings were conducted blinded to the results of the 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. and M.G.M.) blinded to the clinical and angiographic data. A third reader's (M.I.C.) opinion was sought in cases of disagreement. The topography of the ischemic infarcts by vascular territories was determined with reference to published templates [17, 18].

The infarct patterns were classified as follows:

- (1) Perforator pattern – subcortical lesions in the distribution of perforating vessels that originate at the site of stenosis
- (2) Territorial pattern – 1 or more lesions located distal to the stenotic vessel (cortical, subcortical or both) that are restricted to the territory supplied by a single intracranial artery
- (3) Border-zone pattern – 1 or more lesions in the internal (corona radiata or centrum semiovale) and/or the cortical border-zone region (between the middle cerebral artery and the anterior ce-

Table 1. Baseline infarct patterns and angiographic features

	Perforator	Territorial ^a	Border zone	Mixed	p ^b
Stenosis severity					0.65
50–70% (n = 74)	18 (24.3%)	35 (47.3%)	8 (10.8%)	13 (17.6%)	
≥70% (n = 62)	16 (25.8%)	34 (54.8%)	4 (6.4%)	8 (13%)	
Collaterals – ASITN/SIR grade					0.56
None – 0 (n = 82)	22 (26.8%)	42 (51.2%)	5 (6.1%)	13 (15.9%)	
Poor – 1 or 2 (n = 35)	7 (20%)	18 (51.4%)	5 (14.3%)	5 (14.3%)	
Good – 3 or 4 (n = 19)	5 (26.3%)	9 (47.4%)	2 (10.5%)	3 (15.8%)	
Stenosis location					<0.01
ICA (n = 20)	1 (5%)	13 (65%)	1 (5%)	5 (25%)	
MCA (n = 47)	9 (19.1%)	17 (36.2%)	11 (23.4%)	10 (21.3%)	
VA (n = 29)	7 (24.1%)	22 (75.9%)	0	0	
BA (n = 29)	13 (44.8%)	12 (41.4%)	0	4 (13.8%)	
Tandem (n = 11)	4 (36.4%)	5 (45.4%)	0	2 (18.2%)	

Percentages of each stroke pattern according to each angiographic category are given in parentheses. ICA = Internal carotid artery; VA = vertebral artery; BA = basilar artery; tandem = ICA + MCA or VA + BA concomitant stenoses.

^a Artery-to-artery embolism.

^b χ^2 test for comparisons between any of the subgroups.

rebral artery or the middle cerebral artery and the posterior cerebral artery)

(4) Mixed pattern – a combination of any of the previous patterns

We defined the likely mechanism of stroke related to ICAS as follows: perforator occlusion for a perforator pattern, artery-to-artery embolism for a territorial pattern, hypoperfusion for a border-zone pattern and a mixed mechanism for a mixed pattern of infarct.

Results

Patterns of Baseline Infarcts and Association with Angiographic Features

The neuroimaging studies used to evaluate the 136 patients with baseline infarcts (72 in the posterior circulation and 64 in the anterior circulation) were CT in 14 cases, diffusion-weighted imaging (DWI) MRI in 89 cases and FLAIR MRI in 33 cases. The following infarct patterns were found in these 136 patients: territorial (n = 69; 50.7%), perforator (n = 34; 25%), border zone (n = 12; 8.8%) and mixed (n = 21; 15.5%). The most frequent infarct pattern in both the anterior and the posterior circulation was territorial (artery-to-artery embolism; fig. 1). Perforator-occlusive infarcts were more frequent in the posterior circulation, and mixed patterns were more prevalent in the anterior circulation (both $p < 0.01$; fig. 1). All isolated border-zone patterns in the anterior circulation (n = 12) involved the internal border-zone region, and in

Fig. 1. Prevalence of each infarct pattern in the anterior and the posterior circulations in percent.

7 of them, the cortical border-zone 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 the border-zone regions, especially the cortical ones.

The analyses correlating stroke patterns with angiographic features showed no statistically significant differences between the infarct patterns with regard to the severity of stenosis or collateral patterns (table 1). Of note, border-zone infarcts were not associated with a poor grading for collaterals or severe stenosis. Regarding the location of stenosis, the border-zone pattern occurred more frequently with middle cerebral artery (MCA) stenosis (23.4%) than with ICAS (5%), and the territorial pattern (artery-to-artery embolism) occurred more frequently with vertebral (75.9%) than with basilar artery stenosis (41.4%; table 1).

Infarct Patterns and Likely Mechanisms of Recurrent Stroke

Of the 569 patients enrolled in the WASID trial, 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 (the 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 occlusion in 11 (23.4%), hypoperfusion in 2 (4.2%) and mixed in 5 patients (10.7%). Among 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 also had had an embolic pattern at baseline (75%). 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 pattern of the recurrent stroke on brain imaging suggested an embolic mechanism in 4 cases and a mixed pattern in 1 case.

Discussion

Although there are multiple possible mechanisms of stroke in patients with ICAS, the infarct patterns on brain imaging in this study strongly suggest 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 support 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, 19, 20].

The risk of recurrent stroke in the WASID trial was virtually the same whether patients were on warfarin or on aspirin, suggesting that neither was particularly effective in preventing the most common mechanism of stroke, *i.e.* artery-to-artery embolism. However, the recently published final results of SAMMPRIS [21] are encouraging in this respect, since the risk of recurrent stroke in the medical arm, both at 30 days and 1 year, was approximately half of that for the WASID trial patients who fulfilled en-

trance criteria similar to those of the SAMMPRIS patients. This suggests that high-dose statins, better blood pressure control and the combination of aspirin and clopidogrel may be effective in 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 [22], and aggressive statin and antihypertensive therapy may decrease the risk of artery-to-artery embolism by stabilizing atherosclerotic plaque in extracranial carotid plaques [23, 24].

Internal border-zone infarcts, which have been associated with hypoperfusion, did not correlate with the absence of collaterals as assessed by ASTIN/SIR grades in this study. Conversely, border-zone infarcts were more frequently present among patients with any grade of collaterals than in those with no collaterals (table 1). One other study has also failed to demonstrate a clear association between border-zone infarcts and impaired collateralization via the circle of Willis [25].

We also found that a majority of mixed patterns in the anterior circulation included infarcts in distal cortical areas together with lesions in the border-zone region, especially the cortical one. This finding supports the hypothesis that a combined embolism-hypoperfusion mechanism may be responsible for these multiple infarcts involving a border-zone region [11]. Support for this is provided by data from an animal model of embolic stroke [26]. Another study has also shown that border-zone infarcts, especially those in the cortical border zone, usually co-occur with infarcts in other locations [27]. Of interest, isolated internal border-zone infarcts were more frequently associated with MCA lesions than with ICAS in our study, supporting the findings in other studies that internal border-zone infarcts are more frequent with MCA stenosis than with extracranial ICAS [9, 28]. Internal border-zone infarcts in patients with MCA stenosis have been associated with neurological worsening in a recent study [29].

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 [30]. We found this pattern represented more often in the posterior circulation, especially in basilar stenosis, and it was not associated with the severity of stenosis (table 1). High-resolution MR studies have shown that atherosclerotic plaques in the basilar artery can lead to paramedian and small deep pontine infarctions, regardless of the severity of stenosis of the parent vessel [31].

This study has some significant limitations: infarct patterns on structural brain imaging can only be used to infer and not to prove the mechanism of stroke. Examinations using functional imaging (flow studies, collateral perfusion and embolus detection) were not performed in this study and could add important data when establishing specific stroke mechanisms. Furthermore, 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). Also, not all the participants had undergone DWI MRI. Finally, the inherent limitations of a post hoc analysis have to be mentioned.

Despite these limitations, this study provides unique data on the relationships between infarct patterns on brain imaging, angiographic features and likely mecha-

nisms of stroke in a large cohort of patients with ICAS. Further research is important to accurately establish the specific mechanisms of stroke in patients with ICAS, since preliminary data suggest that the underlying mechanism of stroke is an important determinant of prognosis [4] and it is likely that, in future trials, the entrance criteria for ICAS will be based on the underlying pathophysiologic mechanism of the presenting stroke.

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