Mechanism of Ischemic Infarct in Spontaneous Carotid Dissection

D.H. Benninger, MD; D. Georgiadis, MD; C. Kremer, MD; A. Studer, MD; K. Nedeltchev, MD; R.W. Baumgartner, MD

Background and Purpose—It is unclear whether stroke in patients with spontaneous dissection of the cervical internal carotid artery (ICAD) is due to thromboembolism or impaired hemodynamics. This study investigated the mechanism of stroke in ICAD by examining brain imaging and cerebrovascular findings of such patients.

Methods—We retrospectively evaluated the prospectively collected brain CT, MR, and ultrasound findings of 143 ICADs causing ischemic stroke. Eleven patients were not included because they had an inappropriate temporal bone window (n=6) or were treated with thrombolysis (n=5). Thus, the data of 130 patients (76 men, 54 women) with 131 ICADs were analyzed.

Results—All patients had territorial infarcts; 6 patients (5%) also had border-zone infarct patterns. Territorial infarcts affected the middle cerebral artery (MCA) in 130 of 131 cases (99%) and the anterior cerebral artery (ACA) in 1 case (1%). Additional vascular territories were affected in 8 patients with MCA infarcts (ACA, n=5 [4%]; posterior cerebral artery, n=3 [2%]). The pattern (hemodynamic versus thromboembolic) and extent of infarction were not influenced by vascular findings (MCA stenosis or occlusion, ACA occlusion, degree of obstruction in the dissected ICA, pattern of cross-flow in 115 patients with >80% ICA stenosis or occlusion).

Conclusions—This study suggests that thromboembolism, not hemodynamic infarction, is the essential stroke mechanism in ICAD. (Stroke. 2004;35:482-485.)

Key Words: diagnostic imaging ■ carotid artery, internal, dissection ■ stroke ■ ultrasonography

Spontaneous dissection of the cervical internal carotid artery (ICAD) is a frequent cause of ischemic stroke in young adults.1,2 Some authors suggested that arterioarterial embolism causing territorial infarction is the main mechanism of stroke,3-5 whereas others assume that hemodynamic mechanisms play a crucial role.6

The objective of this study was to identify the mechanism of stroke in ICAD by investigating brain imaging and cerebrovascular findings of such patients.

Methods
We retrospectively analyzed all prospectively investigated consecutive adult patients presenting with ICAD who had suffered an ischemic stroke in the University Hospitals of Zürich and Bern since 1985, as reported recently.7 ICADs were classified as spontaneous when occurring spontaneously or secondary to a minor trauma.8 ICADs occurring after an obvious head or neck trauma were classified as traumatic and excluded from the study.

Baseline Investigations
All patients underwent physical and neurological examinations, routine blood tests, a 12-lead ECG, extracranial, transorbital, and transcranial ultrasound studies of the cerebral arteries, MRI of the neck with or without 3-dimensional time of flight MR angiography or intra-arterial digital subtraction angiography, cranial CT, MRI, or both. Furthermore, risk factors for ischemic stroke (Table 1), connective disorders associated with ICAD, and family history of ICAD were assessed.

Neuroradiological Studies
Cranial CT and/ or MR images were reviewed by an experienced neuroradiologist and the principal investigator blinded to patient identity. Cerebral infarcts were classified according to the affected vascular territory9 and the topographic distribution of the lesion as cortical, subcortical, and border-zone infarcts. Cortical middle (MCA), anterior (ACA), and posterior (PCA) cerebral artery lesions were located in the territory of the pial branches, which supply the cerebral hemisphere.10 Definition of subcortical infarct was based on the following criteria: (1) involvement of the basal ganglia, internal capsule, thalamus, or centrum semioccuva; (2) sparing of the cortex; and (3) no morphological and topographic distribution of border-zone infarcts. Subcortical MCA lesions were located in the extreme capsule, claustrum, putamen, lateral part of the pallidum, posterior part of the head, and total body of the caudate nucleus, and parts of the internal capsule. Subcortical PCA lesions were located in the thalamus or the lateral or medial midbrain.11 Furthermore, subcortical infarcts were subdivided according to size into large striatocap-
cular infarcts resulting from occlusion of multiple lenticulostriate arteries and lacunar infarcts of <15 mm diameter resulting from occlusion of a single perforating artery. Border-zone infarcts of the internal junctional zone located between the deep and superficial perforators of the MCA were defined according to the maps of Bladin and Chambers12; those located between the territories of the MCA and ACA or PCA were defined using the definition of Damasio.9 We considered cortical and large subcortical (ie, striato-capsular) infarcts to be of embolic origin. Furthermore, acute lacunar infarcts, whether single or multiple, were assumed to be of embolic origin if they were located in the territory of the ICAD and explained the neurological deficits. Border-zone infarcts were considered to be of hemodynamic origin.

Statistical Analysis
Statistical analysis was carried out with the Systat software package. Differences between ICADs causing territorial and border-zone infarcts and territorial infarcts affecting different vascular territories were compared by nonparametric analysis of variance using the Mann-Whitney U test. Two-sided values of P<0.05 were considered significant.

Results
A total of 141 consecutive patients with 143 ICADs causing ischemic stroke were identified. Eleven patients were not included because they had an insufficient temporal bone window (n=6), rendering hemodynamic assessment impossible, or had been treated with intravenous thrombolysis (n=5), influencing extent of ischemia. Thus, 130 patients (76 men, 54 women; mean age, 45±11 years) with 131 ICADs causing ischemic stroke were analyzed. ICADs were unilateral in 123 of 131 cases (94%) and accompanied by an asymptomatic dissection of the opposite ICA in 3 (3%) and of the vertebral artery in further 3 cases (3%). One patient suffered 2 consecutive strokes caused by dissection of the left followed by the right ICA. No patients showed clinical signs or symptoms of collagen disease. No patient in this series had aortic root dilation at transesophageal echocardiography, which was performed in 9 cases. Two patients had a family history of arterial dissection.

Cerebral ischemic strokes caused by ICAD were studied by both MRI and CT in 94 (72%), MRI in 11 (8%), and CT in 26 cases (20%). CT and MRI were done after a median latency of 0 and 4 days (range, 0 to 14 and 0 to 33 days), respectively. Territorial infarcts were found in all, and additional border-zone infarcts were seen in 6 patients (5%) (Table 2). Territorial infarcts affected the MCA in 130 of 131 cases (99%) and all patients who were excluded. Additional vascular territories were affected in 8 patients with MCA infarcts (ACA, n=5 [4%]; PCA, n=3 [2%]). One patient had an isolated ACA territory infarct. Of 130 patients, 79 had subcortical infarcts in the territory of the MCA that was supplied by the dissected ICA but not in watershed areas or another vascular territory. Sixty-two of 79 patients with subcortical infarcts (lacunar, striatocapsular, or both) had also cortical infarcts in the same MCA territory, whereas the remaining 17 patients had subcortical infarcts. Subcortical infarcts were of the striatocapsular type in 11 of 17 cases and of the lacunar type in the remaining 6 cases. All lacunar infarcts were located in the territory of the MCA and were related to acute neurological deficits; therefore, they were considered recent. No patient showed signs of chronic infarct at brain imaging.

The pattern of cross-flow in 115 patients with >80% ICA stenosis or occlusion (Table 3), degree of ICA stenosis, and the number of MCA (n=41) and ACA (n=6) occlusions and MCA stenoses (n=3; Table 4) at presentation did not differ between ICADs causing territorial and border-zone infarcts and ICADs solely causing territorial infarcts. The median time interval between the onset of stroke symptoms and ultrasound studies was 1 day (range, 0 to 12 days) and did not differ between ICADs causing solely territorial and those causing both territorial and border-zone infarcts. No or minimal atherosclerosis was documented in the craniocephalic arteries and ascending aorta. Catheter angiography of both internal carotid and vertebral arteries was performed in 53 of 130 patients (41%) after a median latency of 6 days (range, 0 to 116 days; mean, 16±26 days); fibromuscular dysplasia was diagnosed in 3 of these patients.

### Table 1. Presenting Cerebrovascular Risk Factors in 130 Patients With 131 ICADs

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>% (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smokers</td>
<td>45 (59)</td>
</tr>
<tr>
<td>Current/former*</td>
<td>33 (43/12 (16)</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>29 (38)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hypercholesterolemia (&gt;5 mmol/L)</td>
<td>35 (46)</td>
</tr>
<tr>
<td>History of migraine</td>
<td>21 (27)</td>
</tr>
<tr>
<td>History of migraine with aura</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Peripheral artery disease</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Aortic, cardiac, or paradox source of embolism†</td>
<td>0 (1)</td>
</tr>
</tbody>
</table>

*Current smokers were defined as actual smoking or in the last 5 years; former smokers, as smoking >5 years ago.
†An ECG was done in all; transthoracic echocardiography, in 20; and transesophageal echocardiography, in 9 patients.

### Table 2. Territorial and Border-Zone Infarcts in 131 ICADs

<table>
<thead>
<tr>
<th>Type</th>
<th>Brain Infarct, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Territorial</td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Additional MCA</td>
<td>4 (5)</td>
</tr>
<tr>
<td>MCA</td>
<td>99 (130)</td>
</tr>
<tr>
<td>Cortical</td>
<td>85 (111)</td>
</tr>
<tr>
<td>Subcortical</td>
<td>60 (79)</td>
</tr>
<tr>
<td>Lacunar only</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Cortical and subcortical</td>
<td>47 (62)</td>
</tr>
<tr>
<td>PCA*</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Border zone</td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>5 (6)</td>
</tr>
<tr>
<td>MCA</td>
<td>2 (2)</td>
</tr>
<tr>
<td>ACA-MCA</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>

*All infarcts were cortical and occurred in the presence of an additional MCA territory infarct.
TABLE 3. Presenting Intracranial Cross-Flow Pattern in 115 ICADs With >80% Stenosis or Occlusion Causing 115 Territorial and 6 Border-Zone Brain Infarcts

<table>
<thead>
<tr>
<th>Cross-Flow in &gt;80% Stenosis or Occlusion, % (n)</th>
<th>OphA (n=59)</th>
<th>ACoA (n=92)</th>
<th>PCoA (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Territorial infarct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA (n=4)</td>
<td>25 (1)</td>
<td>25 (1)</td>
<td>100 (4)</td>
</tr>
<tr>
<td>MCA (n=114)</td>
<td>52 (59)</td>
<td>81 (92)</td>
<td>46 (53)</td>
</tr>
<tr>
<td>PCA (n=3)*</td>
<td>67 (2)</td>
<td>67 (2)</td>
<td>33 (1)</td>
</tr>
<tr>
<td>Border zone (n=6)*</td>
<td>67 (4)</td>
<td>67 (4)</td>
<td>50 (3)</td>
</tr>
</tbody>
</table>

OphA indicates ophthalmic artery; ACoA, anterior communicating artery; and PCoA, posterior communicating artery.

*All patients with border-zone infarcts also had territorial infarcts.

Recurrent ischemic events were observed in 3 patients during the first 2 weeks and consisted of transient ischemic attacks in all cases. Two of these patients were treated with heparin; 1 was treated with aspirin.

Discussion

The present study identified cerebral embolism as the underlying pathophysiological mechanism in the vast majority of ischemic lesions in patients with ICAD, encompassing cortical, striatocapsular, and lacunar infarcts, whereas accompanying hemodynamic infarct patterns were observed in merely 5% of cases. This observation is in accordance with the results of previous studies suggesting that thromboembolism is the most important mechanism of ischemic stroke in ICAD.1-5 Our observations challenge the results of Weiller and colleagues,6 who found infarcts located in the internal junctional zone in 5 of 11 patients with ICAD, suggesting an underlying hemodynamic mechanism. An abnormal vasomotor reactivity was diagnosed in these 5 patients in the acute stroke phase. Although the authors interpreted this finding as an impaired hemodynamic reserve, it could be due to the fact that vasomotor reactivity is impaired in the core region of an acute infarct and in the surrounding penumbra13 and not necessarily imply a hemodynamic stroke mechanism. Furthermore, it has recently been suggested that border-zone infarcts might result from both embolic and hemodynamic mechanisms by impaired clearance of emboli in hypoperfused regions.14

A limitation of this study is the variability of the MCA territory, particularly in patients with severe ICA stenosis or occlusion.15-17 Although this variability can render it impossible to categorize certain infarcts as hemodynamic, it does not affect the identification of territorial MCA infarcts, which were found in all patients in this study. Even supposing that some additional border-zone infarcts were missed because of this limitation, it does not alter the main finding of this study, which clearly indicates embolism as the main stroke mechanism in patients with ICAD.

The number of MCA and ACA occlusions and stenoses, the degree of ICA obstruction, and the pattern of cross-flow in cases with >80% ICA stenosis or occlusion did not differ between ICADs causing territorial infarcts and border-zone infarct patterns. These findings suggest that intracranial hemodynamics did not significantly differ between the 2 groups. Still, the small number of patients with border-zone infarcts prohibits any definitive statements on this issue. Although we recognize this limitation of the present study, it must be taken into account that the enrolled patients represent the total number of patients who presented over a period of 10 years in 2 university hospitals with a catchment area of ~2 million people.

The vast majority of the ischemic infarcts were located in the MCA territory (99%), also affecting the territories of the PCA and ACA in 6% of cases, whereas a single territorial infarction of the ACA was found. This confirms the nonrandom distribution of cerebral embolism, predominantly to the MCA territory, as documented in animal and human studies.18 Interestingly, 5% of patients had symptomatic lacunar infarcts in the territory of the ICAD, suggesting microembolism as underlying cause. Another intriguing finding of the present study was the total absence of chronic (asymptomatic) infarcts in brain imaging. Such infarcts were found in 29% of randomly selected patients <60 years of age19 and in 13.6% of patients <55 years of age in a population-based study.20 This observation, together with the absence of significant atherosclerosis in ultrasound studies of the brain-supplying arteries, adds weight to the hypothesis that ICAD is not an arterial disease of atherosclerotic origin.

In conclusion, our data support that thromboembolism, not hemodynamic infarction, is the essential stroke mechanism in ICAD, suggesting that prevention of arterioarterial embolism is the main therapeutic goal in these patients.

TABLE 4. Intracranial Stenosis and Occlusion and Degree of Stenosis or Occlusion of the Causative 131 ICADs Causing Territorial and Border-Zone Infarcts

<table>
<thead>
<tr>
<th>Brain Infarct</th>
<th>Intracranial Stenosis or Occlusion, % (n)</th>
<th>Degree of Stenosis or Occlusion of ICAD, % (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type</td>
<td>Vascular Territory, n</td>
<td>MCA Occlusion</td>
</tr>
<tr>
<td>Territorial</td>
<td>ACA, 6</td>
<td>50 (3)</td>
</tr>
<tr>
<td></td>
<td>MCA, 130</td>
<td>32 (41)</td>
</tr>
<tr>
<td></td>
<td>PCA, 3</td>
<td>0</td>
</tr>
<tr>
<td>Border zone*</td>
<td>6</td>
<td>50 (3)</td>
</tr>
</tbody>
</table>

*All patients with border-zone infarcts also had territorial infarcts.
References

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