Acute Stroke Patterns in Patients With Internal Carotid Artery Disease
A Diffusion-Weighted Magnetic Resonance Imaging Study

Kristina Szabo, MD; Rolf Kern, MD; Achim Gass, MD; Jochen Hirsch, PhD; Michael Hennerici, MD

Background and Purpose—Diffusion-weighted (DW) MRI is a sensitive method that facilitates early stroke pattern identification. There are limited data about the influence of stenosis grade on the development of particular stroke patterns in internal carotid artery (ICA) disease. We therefore investigated the lesion patterns on DW MRI in acute stroke patients with ICA disease.

Methods—DW MRI was analyzed in 102 consecutive acute stroke patients with different degrees of ipsilateral ICA disease. Patients were assigned to 1 of 5 observed lesion patterns: (1) territorial ischemia, (2) subcortical ischemia without or (3) with embolus fragmentation, (4) disseminated lesions in distal cortical regions, and (5) multiple lesions in hemodynamic risk zones. In addition, perfusion-weighted (PW) MRI and MR angiography information was included in the assessment.

Results—All patterns were observed in the different stages of ICA disease. Half of the patients with high-grade or subtotal stenosis had lesions in hemodynamic risk zones. Territorial stroke occurred in 47.6% of patients with ICA occlusion. Statistical analysis showed a significant relationship between the degree of stenosis and the observed stroke pattern ($P=0.001$). In 77.8% of patients exhibiting high-grade ICA stenosis, subtotal stenosis, or occlusion, the perfusion lesion was larger than the diffusion lesion (PW/DW mismatch).

Conclusions—Although in the individual patient any of the infarct patterns may occur, in statistical terms the incidence of a particular stroke pattern is clearly dependent on the degree of stenosis. (Stroke. 2001;32:1323-1329.)

Key Words: carotid artery diseases ■ magnetic resonance imaging, diffusion-weighted ■ stroke, acute

Atherosclerotic narrowing of the extracranial vessels is a well-recognized cause of cerebral ischemia. The annual stroke risk for patients with asymptomatic internal carotid artery (ICA) stenosis amounts to approximately 1% to 2%.1,2 Both embolic and hemodynamic mechanisms are assumed to be the cause of stroke in ICA disease.3 Neuroimaging studies have been performed in an attempt to improve the understanding of the underlying stroke mechanism as a basis for the identification of patients at high risk and for the best possible therapeutic rationale. Studies based on CT have suggested that hemodynamically significant stenoses or obstructions of the extracranial ICA may cause hemodynamic changes in the distal regions of the hemispheric blood supply, the so-called border zones between major vascular territories, while embolism from ICA stenosis is believed to disproportionately affect the middle cerebral artery (MCA) stem and distal branches producing territorial infarction, often including the deep lenticulostriate territory.4 The coexistence of hypoperfusion and arterial embolism in patients with border zone stroke and ICA disease has recently been postulated.5 Since the concept of border zone ischemia as a cause of stroke in patients with severe ICA stenosis has also been challenged,6,7 uncertainty still remains regarding the occurrence and mechanism of ICA disease-related stroke.

Diffusion-weighted (DW) MRI is exquisitely sensitive to detect areas of acute ischemic tissue change.8,9 The results of recent studies using DW and perfusion-weighted (PW) MRI in acute stroke patients support the hypothesis that the detection of the acute lesion and the delineation of the area of hemodynamic compromise (by PW MRI) can improve the understanding of pathophysiological mechanisms leading to cerebral ischemia in patients with ICA disease. We used DW MRI in acute stroke patients with symptomatic, unilateral ICA disease associated with a stenosis of $>50\%$ to analyze differences in stroke patterns considering lesion size, localization, and distribution and to gather information on the pathomechanism of stroke.

Subjects and Methods

Patients
In a prospective design, 102 consecutive patients (35 women, 67 men; mean age 66.2 years) admitted to the stroke unit of our hospital...
<table>
<thead>
<tr>
<th>Pattern</th>
<th>Description</th>
<th>Conventional Imaging Term</th>
<th>Example (DW MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Large lesion involving the cortex</td>
<td>Territorial infarction</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Subcortical lesion with or without additional smaller lesion(s)</td>
<td>Subcortical infarction</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Large lesion involving the cortex with additional smaller lesion(s)</td>
<td>Territorial infarction with fragmentation</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Several disseminated small lesions</td>
<td>...</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Small lesions in hemodynamic risk zones</td>
<td>Border zone infarction</td>
<td></td>
</tr>
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with acute ischemia distal to ipsilateral extracranial ICA disease with atherosclerotic narrowing >50% were analyzed. According to a standardized acute stroke care protocol, the following examinations were performed in all patients: detailed physical and neurological examination, assessment of cardiovascular risk factors, Doppler and duplex sonography of the extracranial vessels, transcranial Doppler sonography, transthoracic or transesophageal echocardiography, 24-hour ECG monitoring, and MRI. A total of 58 patients with stenosis of the MCA (n = 3), infratentorial stroke (n = 5), cardiac source of embolism (n = 23), dissection of the ICA (n = 8), or contralateral ICA disease with a stenosis degree >50% (n = 19) were excluded from the study. Informed consent was obtained from all patients in writing before MRI was performed. The study had been approved by the local ethics committee.

**Doppler Studies**

Obstructive lesions of the ICA with a reduction in diameter of >50% were diagnosed by noninvasive carotid studies with the use of continuous-wave Doppler (Multi Dop T1, DWL) and duplex sonography with frequency-based and power-based color coding (HDI 5000, ATL).

The degree of ICA stenosis was classified as low grade in the case of slight to moderate increase in local flow (with or without pulsatility loss or systolic deceleration) in the continuous-wave Doppler study and a 50% to 70% diameter reduction in duplex imaging. Stenoses with >70% diameter reduction in the duplex scan and with a strong local flow increase (>8 kHz), systolic deceleration, and poststenotic decrease of systolic flow velocity in the continuous-wave Doppler examination were classified as high grade. Subtotal stenosis was defined as a very narrow stenosis with abnormally low flow velocities at the site of maximum narrowing. Obstructions with no detectable ICA flow information in color-coded duplex ultrasound after the application of an echo contrast agent (Levovist, Schering) were classified as occlusion.10–12 Doppler-diagnosed occlusion was confirmed in every case by conventional angiography or extracranial MR angiography (MRA) of the neck.

**MRI Studies**

MRI was performed on a 1.5-T MR system (Magnetom Vision, Siemens Medical Systems) with the following standardized protocol: (1) transverse, coronal, and sagittal localizing sequences followed by transverse oblique contiguous images (slice thickness 5 mm, field of view 240 mm²) aligned with the inferior borders of the corpus callosum (applied on sequences 2 to 5); (2) T2-weighted images (turbo spin echo, repetition time [TR] 2620 ms/echo time [TE] 85 ms, 16 slices, 256x256 matrix); (3) T1-weighted images (TR 530 ms/TE 10 ms, 12 slices, 192x256 matrix); (4) DW echo-planar (EP) images (TR 4000 ms/TE 100 ms, b = 0/60/160/360/640/1000 s/mm², 96x128 matrix, sequential application of 3 separate diffusion-sensitizing gradients in perpendicular directions); (5) perfusion-weighted free induction decay–EP sequence following the first pass of a contrast bolus through the brain (2000/65/flip angle 90°, 11 slices, 40 acquisitions, 2-second interval, 128x128 matrix), contrast agent (15 mL Omnisecan, Nycomed) injected manually through a large-gauge venous cannula into the antecubital vein); and (6) 3-dimensional time-of-flight MRA sequence of the circle of Willis (flip angle 20°, 165x512 matrix, slice thickness 2 mm).

**Analysis of Infarct Patterns**

As suggested by earlier studies, 5 patterns of ischemic lesions were differentiatied on DW MRI on the basis of lesion size, distribution, and localization.3–13 Patients were assigned to one of these patterns by 2 expert readers (A.G., R.K.) unaware of the clinical data. The definition of stroke patterns is summarized with examples in Table 1. Pattern 1 is defined as a large ischemic lesion involving the cerebral cortex and subcortical structures in 1 or more major cerebral artery territories, referred to as "territorial infarction." An example of pattern 1 is given in Figure 1. This stroke subtype is assumed to be a partial MCA infarction if a distal MCA branch is occluded, a large MCA infarction in the case of a proximal occlusion at the level of the bifurcation or trifurcation paired with the absence of an efficient collateral system,14 or a complete anterior cerebral artery (ACA) and MCA territory infarction in the case of a distal ICA embolism. Pattern 2 is defined as "subcortical infarction" in the territory of deep perforating branches originating from the distal ICA or the MCA trunk. This pattern has been explained by the occlusion of the MCA in the presence of patent collaterals, where the occlusion is either due to the embolization into the MCA, resulting in a large striatocapsular lesion, or due to the occlusion of a deep perforating artery of the carotid system, leading to a subcortical lesion.15,16 Pattern 3 ("territorial infarction with fragmentation") represents a large ischemic lesion, as in pattern 1, with additional smaller lesions either in cortical or in subcortical regions, probably due to partial fragmentation of the embolus.17 In pattern 4, several disseminated small lesions are sprinkled in random fashion in the distal territory of the MCA, involving mainly cortical regions. The possible cause of this pattern may be a fragmented embolus or multiple microemboli in smaller vessels.18 Pattern 5 ("border zone infarction") denotes lesions either completely or predominantly located in regions considered to be one of the hemodynamic risk zones between major cerebrovascular territories:9 the superficial or cortical border zones wedged between the ACA and MCA or between the MCA and posterior cerebral artery (PCA), and the deep or subcortical border zone located in the vascular territory between deep and superficial arterial systems.20–22 Figure 2 shows an example of a patient with pattern 5 stroke.

**Morphology of the Circle of Willis and the MCA**

In an attempt to identify possible confounding factors for the infarct patterns, the morphology and anatomic variability of the vessels of the circle of Willis were analyzed. For this purpose, coronal and transverse views of 3-dimensional MRA reconstruction were rec-
Evaluation of PW MRI
To obtain information about hemodynamic alterations caused by vascular pathology, calculated time-to-peak (TTP) images demonstrating the delay of the contrast agent arrival in the brain parenchyma were used for semiquantitative analysis. The average TTP value obtained in the contralateral MCA territory as reference tissue was subtracted from the bolus arrival time of the affected hemisphere. According to Neumann-Haefelin et al, a TTP delay >4 seconds was considered an indicator of a clinically relevant perfusion deficit. In conformity with these findings, PW MRI studies were classified as (1) normal, (2) perfusion deficit equal to the DW MRI lesion, or (3) perfusion deficit larger than the DW MRI lesion.

Statistical Analysis
The $\chi^2$ test was used to analyze observed proportions and to determine the presence of a relationship between the following: degree of ICA stenosis and incidence of stroke patterns; patency of the circle of Willis and incidence of stroke patterns; degree of ICA stenosis and patency of the circle of Willis; extent of the ipsilateral MCA signal and incidence of stroke patterns; and degree of ICA stenosis and degree of perfusion abnormality. A value of $P<0.05$ was considered statistically significant.

Results
DW MRI lesions of the MCA territory were identified in all patients. Large territorial infarction (pattern 1) was observed in 30 cases; in 5 of these patients, additional acute lesions were noted in the ACA territory, suggesting complete carotid artery territory infarction. Four patients with direct blood supply of the PCA from the ICA had additional lesions in the PCA territory. Pattern 2 was noted in 13 patients and pattern 3 in 11 patients. Fifteen patients exhibited pattern 4 with small disseminated lesions not involving hemodynamic risk zones. Small disseminated lesions in the hemodynamic risk zones (pattern 5) were detected in 33 cases, of which the cortical risk zones were affected in 18, the subcortical regions in 8, and both the cortical and the subcortical regions in 7. In 3 patients, the readers’ initial conclusions regarding pattern classification were different because of disagreement about lesion location. After reviewing the data together, the readers agreed on pattern 5 (as opposed to pattern 4) in all cases.

Stroke Patterns in Relation to Stenosis Grade
Low-grade ICA stenosis was present in 19 patients (18.6%), high-grade stenosis was observed in 31 cases (30.4%), 10 cases showed subtotal stenosis (9.8%), and 42 patients had ICA occlusion (41.2%). Table 2 summarizes the distribution of stroke patterns in the subgroups with different ICA stenosis grade. In patients with low-grade ICA stenosis, no clear-cut preference for a particular pattern was observed. In contrast, 51.6% of patients with high-grade and 50% of patients with subtotal stenosis had lesions in hemodynamic risk zones (pattern 5). Territorial infarction (pattern 1) was observed in 47.6% of the patients with ICA occlusion. Figure 3 shows the cumulative frequency distribution of stroke patterns in each of the 4 groups. The $\chi^2$ analysis of the stroke pattern proportions over the 4 stenosis grades defined above revealed a statistically significant difference ($P=0.001$), indicating the dependency of the stroke pattern distribution on the degree of stenosis.
Stroke Pattern Relationship to Patency of the Circle of Willis and the MCA Signal

Three-dimensional reconstruction from MRA sequences of the intracranial arteries was available in 84 patients; in all other cases MRA could not be acquired in satisfactory quality because of movement artifacts. In 14 cases (16.6%), the circle of Willis was complete on the symptomatic side. Hypoplastic or absent vessel segments of the ipsilateral circle of Willis were noted in 35 patients each (41.7%). In contrast to the findings regarding the degree of ICA stenosis, χ² analysis based on a 3×5 contingency table (normal, hypoplastic, or absent ipsilateral circle of Willis versus the 5 stroke patterns) failed to demonstrate a statistically significant relationship between the patency of vessel segments in the ipsilateral circle of Willis and the occurrence of a particular stroke pattern (P=0.879). In addition, the analysis of the relationship between ICA stenosis grade and circle of Willis patency did not show a statistically significant relationship between these parameters in our study population (P=0.594).

Twenty-four patients (28.6%) exhibited an absence of blood signal in the MCA, while 37 patients (44.0%) showed substantial signal reduction. In 23 cases (27.4%), MCA signal appeared normal. In patients with MCA occlusion, territorial infarction (pattern 1) was present in 58.3% (n=14), while in patients with normal signal stroke pattern 1 was seen in only 13% (n=3). A statistically significant association was found between MCA signal and stroke pattern distribution (P<0.001). The findings of the MCA signal evaluation are summarized in Table 3.

Relationship Between PW MRI Abnormality and Degree of ICA Stenosis

Perfusion data were acquired in 43 patients. Normal perfusion was seen in 6 cases (13.9%), PW and DW MRI lesions were of the same size in 7 cases (16.3%), and the PW MRI lesion was larger than the DW MRI lesion in 30 patients (69.8%). In the patients with PW-DW mismatch, 93.3% had ICA stenosis from high grade to occlusion, while in patients without PW MRI lesion, low-grade ICA stenosis was observed in 57.1%. The association between PW MRI abnormality and the degree of underlying ICA stenosis was statistically significant (P=0.025). Findings of the PW MRI evaluation are summarized in Table 4.

Discussion

The analysis of ischemic lesions on DW MRI demonstrates that stroke in patients with ICA occlusive disease is heterogeneous. The 5 stroke patterns, representing different characteristics from small embolic lesions to large territorial ischemia, were seen in all groups regardless of the degree of ICA stenosis. However, statistical analysis demonstrated that the degree of ICA obstruction may favor certain stroke patterns, indicating a preferred pathomechanism in the different ICA stenosis subgroups.

In the postmortem arteriographic and pathological study by Rodda and Path,24 massive infarcts involving 2 major cerebral artery territories were associated with distal ICA occlusion, MCA territory infarcts were seen when the ICA was occluded or stenosed, and border zone infarcts were characterized by ICA disease and limited circle of Willis anastomosis. In other studies, small border zone infarcts were seen as marker for high-grade ICA stenosis and occlusion,25,26 while this association was denied in a larger trial.3 Multiple acute lesions (pattern 4) have been recognized in recent publications as a new stroke pattern in distal and proximal stenosis,18 and they are thought to be caused by multiple emboli or the breakup of an embolus.17

In contrast to previous CT-based studies, DW MRI offers a better chance of detecting not only gross abnormalities but also very subtle acute ischemic lesions. This is the likely explanation of the discrepancy between our results and previous CT studies that suggested an association of large lesions with high-grade ICA stenosis.3 In our study 61.7% of the acute strokes in patients with some degree of ICA stenosis and 26.2% in patients with ICA occlusion presented with disseminated small acute lesions (pattern 4 and pattern 5), which may have been missed with conventional imaging. In keeping with the current concept of the hemodynamic relevance of ICA stenosis, our data show that in patients with high-grade stenosis the highest frequency of lesions occurs in the hemodynamic risk zones. PW MRI data suggest that in high-grade ICA stenosis the complete MCA territory may be

TABLE 2. Contingency Table for Analysis of ICA Stenosis Grade and Stroke Pattern Proportions

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Pattern 1</th>
<th>Pattern 2</th>
<th>Pattern 3</th>
<th>Pattern 4</th>
<th>Pattern 5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-grade</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td>7</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>High-grade</td>
<td>7</td>
<td>1</td>
<td>2</td>
<td>5</td>
<td>16</td>
<td>31</td>
</tr>
<tr>
<td>Subtotal</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Occlusion</td>
<td>20</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>9</td>
<td>42</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>13</td>
<td>11</td>
<td>15</td>
<td>33</td>
<td>102</td>
</tr>
</tbody>
</table>

P=0.001 (χ² analysis).
hemodynamically altered despite the presence of only small acute lesions on DW MRI. Similar observations have been communicated in recent publications.\textsuperscript{27,28} While low-grade stenosis without obvious hemodynamic impairment appears to cause ischemic lesions suggestive of artery-to-artery embolism, in patients with a higher grade of ICA stenosis and obvious hemodynamic alterations, lesions were mostly seen in the arterial border zones.

In the present study 32.4\% of patients demonstrated pattern 5 stroke. Several authors have postulated an association between hemodynamic compromise and subsequent brain infarction in patients with critical carotid artery disease, especially under the conditions of limited collateral circulation.\textsuperscript{22,25} The role of severe arterial hypotension causing bilateral border zone strokes has also been described and confirmed by experimental studies.\textsuperscript{29,30} A recent report suggested the interaction of embolic and hemodynamic mechanisms in the development of border zone strokes.\textsuperscript{5} Some of these theories are based on the high prevalence of emboli documented by transcranial Doppler monitoring in symptomatic high-grade carotid artery disease or during cardiac surgery, providing a possible link to the concept of embolism in a hypoperfused region.\textsuperscript{31–33} Our data demonstrate the high probability of lesion development in hemodynamic risk zones; however, they do not allow unequivocal conclusions about the exact pathomechanism because emboli detection was not part of the study protocol.

Although we must emphasize that all stroke patterns have been observed in patients with ICA occlusion, the development of a large territorial ischemia is the most likely consequence. Accordingly, strokes associated with atherosclerotic ICA occlusion are most likely to be caused by the formation of a large embolus that leads to the subsequent impairment of blood flow in the ipsilateral MCA.

The circle of Willis is considered an important collateral pathway in maintaining adequate cerebral blood flow in patients with ICA obstruction,\textsuperscript{34} and a noncompetent circle of Willis has been regarded as a predisposing condition for border zone infarcts.\textsuperscript{19} MRA has been used by others for the assessment of vessel patency in the circle of Willis.\textsuperscript{35} A recent investigation found that patients with ICA obstruction but no or only minor neurological deficits have a higher prevalence of a complete circle of Willis, a favorable anatomic predisposition.\textsuperscript{36} As an explanation, the authors suggested the possibility of either preexistent or acquired morphology secondary to hemodynamic adaptation. In contrast, in our patient population MRA showed a very high percentage (83.4\%) of noncompetent circle of Willis vessels, and no association was found between circle of Willis patency and stroke pattern distribution or ICA stenosis grade. However, even high-resolution MRA has limitations because it provides no information on flow direction and on the existence of small communicating vessels that conventional angiography would identify. With these limitations in mind, we consider our observations as a measure of anatomic patency of collateral pathways, not a marker of functional collateralization.

On the other hand, our patients, who all suffered a complete stroke leading to some degree of disability, may represent a subgroup with a high prevalence of hypoplastic or aplastic circle of Willis, in which the cerebrovascular system is unable to adapt to reduced blood supply in an adequate manner. As a consequence, they are destined by morphological factors to develop severe stroke in the case of ICA disease. Further studies may clarify the relationship between anatomic predisposition, remodeling of collateral pathways, and stroke subtype.

In summary, we propose that the degree of ICA stenosis significantly influences the pattern of cerebral ischemia as seen on DW MRI. Our findings reflect a changing distribution of stroke patterns with increasing ICA stenosis. In high-grade ICA stenosis, multiple embolic lesions are a common feature of cerebral ischemia. The increasing degree of stenosis leads to additional hemodynamic alterations within subcortical and cortical border zone areas. The full interpretation of our study is limited both by the lack of transcranial emboli detection and by the lack of Doppler or angiographic data characterizing collateral blood supply; these methods might add clarification to the pathomechanism of stroke in ICA disease in future investigations.

**Acknowledgment**

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References


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