Patterns of Perfusion-Weighted Imaging in Patients With Carotid Artery Occlusive Disease

Claudia J. Chaves, MD; Irina Staroselskaya, MD; Italo Linfante, MD; Rafael Llinas, MD; Louis R. Caplan, MD; Steven Warach, MD, PhD

Background: The importance of hemodynamic factors in the pathophysiology of stroke and transient ischemic attacks in patients with internal carotid artery (ICA) stenosis or occlusion remains controversial.

Objective: To investigate whether perfusion-weighted imaging (PWI) could identify pathophysiologically meaningful categories in patients with symptomatic and asymptomatic ICA occlusive disease.

Methods: Thirty-eight consecutive patients with occlusion (22 patients) or severe stenosis (16 patients) of the ICA, determined by ultrasonography or magnetic resonance angiography, were identified from the Beth Israel Deaconess Medical Center Stroke Database, Boston, Mass. Thirty-five patients were symptomatic (29 who had strokes and 6 who had transient ischemic attacks) and 3 were asymptomatic. All symptomatic patients underwent PWI within the first 24 hours after symptom onset. The patterns of PWI were analyzed according to the degree of ICA stenosis and the clinical presentation.

Results: Three patterns of perfusion abnormalities were identified: extensive hypoperfusion involving the middle cerebral arterial and/or anterior cerebral arterial territories (25 patients), localized perfusion deficits involving predominantly the ipsilateral border zone areas (8 patients), and normal perfusion (5 patients). All 3 patterns were found whether or not the ICA was occluded. Patients who had acute stroke most frequently had extensive perfusion deficits involving 1 or 2 territories while patients who had transient ischemic attacks often had hypoperfusion affecting the border zone regions. All asymptomatic patients had normal perfusion.

Conclusions: In our sample the pattern of PWI related to the clinical presentation but not to the degree of ICA disease (occlusive vs severe stenosis). Our study findings add further support to the hypothesis that hypoperfusion is a major contributing factor in the pathophysiology of carotid artery occlusive disease.

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CAROTID ARTERY stenosis or occlusion is responsible for a significant proportion of transient ischemic attacks (TIAs) and strokes. The relative importance of hemodynamic factors as opposed to embolic mechanisms in the pathogenesis of TIAs and strokes in these patients remains unresolved. Hypoperfusion was the most common explanation for brain ischemia 50 years ago. In the last 2 decades, emphasis has switched to embolism as the main mechanism of brain infarcts not only in anterior but also in posterior circulation.1 More recently, Caplan and Hennerici2 have posited the idea that both mechanisms often coexist and are complementary in patients who had an ischemic stroke.

The precise determination of stroke mechanism has considerable relevance for both patient care and clinical research. Treatment with thrombolytic agents or anticoagulants is unlikely to prevent a hemodynamic stroke. However, surgical procedures such as external carotid artery–middle cerebral artery bypass to improve cerebral blood flow may be of no value in reducing embolic strokes. Therefore, a better understanding of stroke pathophysiology is essential to guide the optimal treatment and provide better outcomes for these patients.

Most of the studies that have investigated the role of hypoperfusion in patients with carotid artery occlusive disease have used positron emission tomography or single photon emission computed tomographic techniques; the vast majority within weeks after onset of the symptoms.3-5 With the advent of perfusion-weighted imaging (PWI), a rapid determination of cerebral perfusion in different vascular territories has become possible and is easily done in the short-term setting.6,7 We investigated the patterns of perfusion abnormalities detected by PWI in patients with symptomatic and asymptomatic severe internal carotid artery (ICA) occlusive disease.

METHODS

PATIENTS

We retrospectively identified 80 patients with severe ICA disease selected from a total of 648
patients in the Beth Israel Deaconess Medical Center Stroke Database collected from July 1, 1998, to April 1, 2000. Severity of disease was divided into 2 categories: occlusion or severe stenosis (≥80% luminal narrowing).

From the 80 patients, 38 (23 men and 15 women) met the following inclusion criteria:

- Detailed clinical information and neurologic examination findings.
- Magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) and PWI within the first 24 hours of the onset of symptoms.
- Eighty percent or more stenosis or occlusion of the intracranial or extracranial portions of the ICA detected by magnetic resonance angiography (MRA) and/or ultrasonography (carotid duplex or transcranial Doppler imaging).

These 38 patients ranged in age from 35 to 91 years (median age, 69 years). Thirty-four patients were white, 3 were black, and 1 was Asian. Twenty-nine patients had acute strokes, 6 patients had TIAs, and 3 patients were asymptomatic. The 3 asymptomatic patients were initially evaluated because of TIAs or strokes in the territory of the contralateral ICA.

**IMAGING STUDIES**

The MRI stroke protocol used in our institution includes the following: DWI, proton density; fluid-attenuated inversion recovery; T2*-weighted, T1-weighted, T2-weighted imaging; PWI; and MRA of the intracranial vessels. All of these imaging techniques were performed using a 1.5-T whole-body system (Siemens Medical Systems, Erlangen, Germany) with echo-planar imaging capability. The extracranial carotid artery was studied by 2-dimensional and 3-dimensional time of flight MRA and/or duplex imaging of the carotid arteries. The degree of extracranial and intracranial carotid artery stenosis by MRA was calculated using the North American Symptomatic Carotid Endarterectomy Trial and Warfarin-Aspirin Symptomatic Intracranial Disease Study for Stroke criteria. When carotid ultrasonography was used, 80% or more stenosis was defined as a systolic ICA–common carotid artery ratio great than 4.0 and diastolic velocities greater than 100 cm/s. Absence of signal in the ICA with externalization of the common carotid artery was the criterion used to define carotid occlusion.

Diffusion-weighted imaging was performed according to the protocol described elsewhere. The PWI was performed through a dynamic first-pass bolus tracking of gadolinium-labeled diethylenetriamine pentaacetic acid (0.1 mg/kg) with an echo-planar gradient echo with an echo time of 60 milliseconds and repetition time of 2 seconds. The dynamic perfusion series were processed on a pixel-by-pixel basis to produce maps reflecting the relative mean transit time (rMTT), relative cerebral blood volume (rCBV), and relative cerebral blood flow (rCBF). The rMTT was calculated from the first moment to the peak in the concentration-time curve. The rCBV was calculated as the area under the concentration-time curve up to the time of maximal susceptibility effect in the contralateral control region. This index, also called the “initial CBV,” was used instead of the total CBV because it provides better differentiation between a region operationally defined as the ischemic penumbra and the ischemic core. The rCBF was obtained by the ratio between the rCBV and rMTT.

A qualitatively visual analysis of the rMTT, rCBV, and rCBF maps was performed blinded to the severity of carotid artery disease and clinical symptoms. In this study, we used the term “hypoperfusion” when one of, or a combination of, reduced rCBF, reduced rCBV, and prolonged rMTT was detected in the perfusion maps. The patterns of PWI were then analyzed according to the degree of carotid stenosis or occlusion and the clinical presentation: stroke, TIAs, or no related symptoms.

**STATISTICAL ANALYSIS**

Data analysis was performed using an SPSS statistical package (SPSS Inc, Chicago, Ill). The frequencies and distribution of the study population characteristics were evaluated using descriptive statistics procedure. Relationships between the perfusion maps and other variables such as clinical presentation and whether ICA stenosis or occlusion were tested using the χ² statistic.

We studied 38 patients. Twenty-two patients had ICA occlusion and 16 patients had 80% or more ICA stenosis (11 involving the extracranial carotid artery and 5 the carotid siphon). Six patients had bilateral ICA disease—5 patients had contralateral carotid stenosis (>70%) and 1 had contralateral carotid occlusion.

From the 22 patients with ICA occlusion (Table 1), 18 patients had acute strokes, 3 patients had TIAs, and 1 patient was asymptomatic. Among the 16 patients with ICA stenosis (Table 2), 11 patients had acute strokes, 3 patients had TIAs, and 2 patients were asymptomatic.

Three patterns of perfusion abnormalities were detected in these patients: pattern I, extensive hypoperfusion with prolonged rMTT, decreased rCBV, and rCBF involving the entire ipsilateral middle cerebral artery (MCA) and/or anterior cerebral artery (ACA) territories (25 patients); II, limited hypoperfusion involving predominantly the ipsilateral borderzone regions (8 patients); and III, normal perfusion maps (5 patients).

**PATTERN I: EXTENSIVE HYPERPERFUSION WITH PROLONGED rMTT, DECREASEd rCBV, AND rCBF INVOLVING THE ENTIRE IPSILATERAL MCA AND/OR ACA TERRITORIES (25 PATIENTS)**

All 25 patients in this group had strokes—17 secondary to ICA occlusion (Figure 1) and 8 due to ICA stenosis (Figure 2). In 22 of these 25 patients the hypoperfusion involved only the ipsilateral MCA territory, while in the other 3 patients the ACA territory was also affected. Only 1 of these 3 patients had an ICA occlusion; the other 2 had high-grade ICA stenosis in the neck. None of the asymptomatic patients or those who presented with a TIA had this pattern, despite the presence of carotid stenosis or occlusion.

**PATTERN II: LIMITED HYPERPERFUSION INVOLVING PREDOMINANTLY THE IPSILATERAL BORDER ZONE REGIONS (8 PATIENTS)**

Four patients in this group had strokes, secondary to ICA occlusion in 1 (Figure 3) and stenosis in 3. All 4 patients had contralateral ICA stenosis (3 patients) or occlusion (1 patient). The remaining 4 patients had TIAs, due to an ICA occlusion in 2 and stenosis in the other 2.

In 4 of these 8 patients, hypoperfusion was detected only on the rMTT map. Two of them had ICA stenosis and stroke and the other 2, ICA occlusion and TIAs.
PATTERN III: NORMAL PERFUSION MAPPING
(5 PATIENTS)

This pattern was present in 2 patients with TIAs; one had an ICA occlusion (Figure 4), and the other had ICA stenosis. All 3 asymptomatic patients had this pattern regardless of the presence or absence of carotid occlusion (Figure 5).

Patients with stroke referable to the diseased carotid artery had a different frequency of patterns than patients with TIA or who were asymptomatic ($P < .001$). They were more likely to have pattern I than either of the other 2 patterns. Patients without stroke in this sample never displayed pattern I. There was no significant difference in the proportions of patterns between the occlusion and stenosis groups ($P < .65$).

In all patients with stroke, there was a large mismatch between perfusion and diffusion acutely, with the hypoperfused region being much greater than the area with restricted diffusion. Ten of these patients had follow-up studies performed 3 to 14 days after symptoms onset (mean, 5 days; median, 4 days). In 7 patients the

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<th>Table 1. Patterns of Perfusion-Weighted Imaging in 22 Patients With Internal Carotid Artery Occlusion</th>
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<td><strong>Perfusion Findings</strong></td>
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<td><strong>Pattern I (n = 17)</strong></td>
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<td><strong>Pattern II (n = 3)</strong></td>
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<td>Abnormal rMTT, rCBV, and rCBF BDZ territory</td>
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Abbreviations: BDZ, border zone; rCBF, relative cerebral blood flow; rCBV, relative cerebral blood volume; rMTT, relative mean transit time; TIAs, transient ischemic attacks.

*Pattern I is extensive hypoperfusion with prolonged rMTT, decreased rCBV, and rCBF involving the entire ipsilateral middle cerebral artery and/or anterior cerebral artery territories; pattern II, limited hypoperfusion involving predominantly the ipsilateral BDZ regions; and pattern III, normal perfusion maps.

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<th>Table 2. Patterns of Perfusion-Weighted Imaging in 16 Patients With Internal Carotid Artery Stenosis</th>
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<td><strong>Perfusion Findings</strong></td>
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Figure 1. Imaging studies of a 61-year-old man who had expressive aphasia and mild right-sided hemiparesis. Diffusion-weighted imaging (DWI) showed a left frontal stroke. Perfusion-weighted imaging showed prolonged relative mean transit time (rMTT), decreased relative cerebral blood volume (rCBV), and relative cerebral blood flow (rCBF) involving the entire left middle cerebral artery territory. Magnetic resonance angiography (MRA) of the head showed no flow in the left internal carotid artery and decreased flow in the left middle cerebral artery. A complete occlusion of the left internal carotid artery was detected by ultrasonography.
mismatch persisted while in the remaining 3 patients, there was an increase in the size of the stroke involving the entire hypoperfused territory.

**COMMENT**

The role of hemodynamic factors in the pathophysiology of stroke and TIAs in patients with ICA occlusive disease is controversial. Most studies have used positron emission tomography and/or single photon emission computed tomographic techniques, usually performed within a few days or weeks of stroke onset. The advent of PWI has allowed identification of perfusion abnormalities within hours of the symptom onset and is easily done in the short-term setting. The precise determination of stroke mechanism acutely is important to guide patient management.

We found 3 patterns of PWI in our patients with ICA occlusive disease: pattern I, extensive hypoperfusion involving the entire right internal carotid artery territory. Magnetic resonance angiography (MRA) of the head showed severe decreased flow in the right siphon and internal carotid artery. Carotid ultrasound showed a 90% stenosis in the right internal carotid artery.
volving the entire ipsilateral MCA and/or ACA territories; II, limited hypoperfusion involving predominantly the ipsilateral border zone regions; and III, normal perfusion mapping.

The frequency of the 3 patterns of PWI abnormalities did not correlate with the severity of the carotid artery occlusive disease (P<.05) in our patients, similar to the findings reported with positron emission tomographic imaging.12,14 The presence of collateral circulation has been implicated as the main reason for this discrepancy.12,14,16

In our study the perfusion abnormalities had a statistically significant correlation with the patient’s clinical presentation (P<.001). Extensive perfusion deficits involving the entire MCA or MCA-ACA territories (pattern I) was the most common abnormality in patients with stroke, occurring in 25 (86%) of 29 patients. In the remaining 4 patients with stroke, the area of hypoperfusion involved predominantly the ipsilateral border zone territory (pattern II). All 4 of these patients had a contralateral carotid stenosis3 or occlusion.4 A concern that this could represent a technical error, due to the presence of contralateral disease causing an underestimation of the area of hypoperfusion, was investigated by recreating the perfusion maps using areas outside the carotid distribution,
such as the posterior cerebral arteries and cerebellar hemispheres, as the area of comparison. Similar perfusion maps and concentration-time curves were obtained making this possibility less likely. Our patients with TIAs most often had localized hypoperfusion involving the ipsilateral border zone territories or no abnormalities. None of these patients had extensive perfusion abnormalities as seen in patients who had acute strokes. Normal perfusion maps were present in all asymptomatic patients.

Our findings differ from those described by Maeda et al.17 These authors studied 9 patients with qualitative PWI, 5 with ICA occlusion (2 bilateral), and 4 with ICA stenosis greater than 80%. From these 9 patients, 6 had TIAs, 2 had strokes, and 1 was asymptomatic. All 6 patients with TIAs and the 1 asymptomatic patient had prolonged rMTT maps involving the MCA and/or ACA territories. However, 5 (including the asymptomatic patient) had strokes documented by the T2-weighted imaging. Unfortunately, DWI was not performed in these patients; therefore, the age of the infarct and its relationship with the patient’s symptoms were unclear. The 2 patients with stroke had prolonged rMTT in the MCA and/or ACA territories, similar to our findings. The rCBV maps in all of these 9 patients varied from increased, decreased, or no abnormalities while in our study only decreased or normal rCBV was found. This difference is probably explained by the use of different rCBV indices between the 2 studies; Maeda et al17 used the total rCBV, calculated as the entire area under the concentration-time curve, while we used the initial rCBV, a more flow-weighted index.

A recent study in which quantitative PWI was used to evaluate 11 patients with carotid occlusion or stenosis greater than 70% found, as we did, different perfusion patterns in these patients, with normal hemodynamics in some and hypoperfusion in others.18 Unfortunately, data about their clinical presentation were unavailable. These authors found a positive correlation between quantitative MTT and the degree of carotid stenosis, but not with MTT when it was calculated as the normalized first moment of the delta R2 (t) curve nor with CBV and CBF. Whether quantitative MTT is a more accurate indicator of hemodynamic status than the other parameters is still unclear and needs further investigation.

Different perfusion patterns, as seen in our patients, have been reported before in patients with symptomatic and asymptomatic carotid artery occlusive disease studied using positron emission tomographic scanning.19 However, the occurrence of hypoperfusion involving predominantly the ipsilateral border zone regions as seen in most of our patients with TIAs has not been described before. The prognostic implication of this finding is unclear, but it suggests the increased vulnerability of these regions to situations of cerebral hypoperfusion.

The clinical importance of the persistent large mismatch (perfusion > diffusion) observed in follow-up studies in 7 of our 10 patients who had a stroke remains unclear. Future studies are necessary to clarify if these persistent hypoperfused areas represent an increased risk for future strokes or TIAs.

We found that in patients with carotid artery occlusion or severe stenosis, PWI varied according to the patient’s clinical presentation. Extensive hypoperfusion was the most common abnormality in patients with acute stroke while in patients with TIAs, the perfusion deficits were usually limited to the ipsilateral border zone territories. Asymptomatic patients had normal perfusion studies. These findings add further support to the hypothesis that hypoperfusion is a major contributing factor in the pathophysiology of symptomatic ICA occlusive disease.

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Author contributions: Study concept and design (Drs Chaves, Caplan, and Warach); acquisition of data (Drs Chaves, Staroselskaya, Llinfante, Llinas, and Warach); analysis and interpretation of data (Drs Chaves, Caplan, and Warach); drafting of the manuscript (Dr Chaves); critical revision of the manuscript for important intellectual content (Drs Staroselskaya, Llinfante, Llinas, and Warach); administrative, technical, and material support (Drs Staroselskaya, Llinas, and Warach); study supervision (Drs Chaves, Caplan, and Warach).

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