Association Between Impaired Carbon Dioxide Reactivity and Ischemic Lesions in Arterial Border Zone Territories in Patients With Unilateral Internal Carotid Artery Occlusion

Robertus H. C. Bisschops, MD; Catharina J. M. Klijn, MD, PhD; L. Jaap Kappelle, MD, PhD; Alexander C. van Huffelen, MD, PhD; Jeroen van der Grond, PhD

Context: Ischemic lesions in patients with internal carotid artery (ICA) steno-occlusive disease can be categorized on the basis of their location and presumed cause: external border zone infarcts, internal border zone infarcts, cortical infarcts, lacunar infarcts, and periventricular lesions.

Objective: To evaluate the association between the prevalence and size of ischemic lesions and cerebral vasomotor reactivity in patients with unilateral occlusion of the ICA.

Design: Cross-sectional study.

Setting: Referral center.

Patients: Seventy consecutive patients were included in this study. All patients had a transient or minor disabling retinal or cerebral ischemia that was associated with unilateral occlusion of the ICA. Ischemic lesions on magnetic resonance imaging were identified on hard copies, and volume measurements were obtained by a magnetic resonance workstation. Vasomotor reactivity was assessed with transcranial Doppler ultrasonography with carbon dioxide challenge.

Main Outcome Measures: Prevalence and size of ischemic lesions.

Results: In the hemisphere ipsilateral to the ICA occlusion, we found an increased prevalence of internal border zone infarcts ($P = .01$), external borders zone infarcts ($P < .001$), and territorial infarcts ($P = .02$) compared with the contralateral hemisphere. Hemispheres with a carbon dioxide reactivity less than or equal to 18% demonstrated a significant increase in prevalence ($P = .007$) and volume ($P = .003$) of internal border zone infarcts compared with hemispheres with a carbon dioxide reactivity greater than or equal to 19%. No association between carbon dioxide reactivity and any other type of ischemic lesion was found.

Conclusion: In patients with an ICA occlusion, only internal border zone infarcts demonstrate a significant association with diminished cerebral hemodynamics.

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PATIENTS WITH obstructive disease of the internal carotid artery (ICA) can have a wide variety of ischemic brain lesions. These ischemic lesions can be identified on magnetic resonance imaging (MRI) of the brain and can be categorized on the basis of their location and presumed cause: external border zone infarcts, internal border zone infarcts, territorial cortical infarcts, lacunar infarcts, and periventricular lesions (PVLs). It has been suggested that different types of ischemic lesions are associated with different causes. Moreover, the most common cause of cerebral infarction in patients with an occlusion of the ICA is still unknown. Both embolic and hemodynamic causes have been suggested.

Infarcts in the border zones between the supply territories of the main intracerebral arteries have been associated with an impaired hemodynamic status of the brain, such as that found in patients with an occlusion of the ICA. However, the exact location of these so-called "external" cortical border zone infarcts in individual patients is still subject to debate because of the presumed variability of the supply territories of the different intracerebral arteries. Another area in the brain that is vulnerable to reduced cerebral perfusion pressure is the border zone between the superficial and deep branches of the middle cerebral artery (MCA), also known as the internal border zone. It is suggested that lesions in this area are sensitive and specific for the presence and severity of hemodynamic compromise in patients with steno-occlusive disease. Lesions adjacent to the ventricular wall, the PVLs, can have a he-
Magnetic resonance imaging was performed by a Philips Gyroscan ACS-NT 15 whole-body system (Philips Medical Systems, Best, the Netherlands) operating at 1.5 T. The MRI examination consisted of 19 sagittal T1-weighted scout images (repetition time [TR], 324 milliseconds; echo time [TE], 10 milliseconds), and 15 transversal/oblique T2-weighted images (TR, 2462 milliseconds; TE, 30 milliseconds; slice thickness, 4 mm; slice gap, 10 mm), and 15 transversal/oblique proton density–weighted images (TR, 2462 milliseconds; TE, 24 milliseconds; slice thickness, 6.0 mm; slice gap, 10 mm), and 15 transversal/oblique T2-weighted images (TR, 2462 milliseconds; TE, 100 milliseconds; slice thickness, 6.0 mm; slice gap, 1.0 mm). Infarcts were identified as hypointense lesions on T2-weighted MRI and were classified as (1) infarcts in the territory of the MCA, or in the posterior cortical border zone between the supply territory of the MCA and the posterior cerebral artery (Figure, A and B); (2) internal border zone infarcts (lesions located between the deep and superficial arterial system of the MCA in the corona radiata or centrum semiovale; (3) cortical territorial infarcts (cortical lesions not assigned as external border zone infarcts); (4) lacunar infarcts (diameter ≤10 mm), lesions located in the brainstem, the basal ganglia, thalamus, internal capsule, corona radiata, or centrum semiovale; and (5) PVLs, hyperintense lesions adjacent to the ventricular wall (Figure 1D). Proton-density scans were used to distinguish infarcts from dilated perivascular spaces. All scans were reviewed independently by 2 investigators (C.J.M.K. and L.J.K.). Discrepancies between the 2 readers were reevaluated in a consensus meeting.

Table 1. Baseline Characteristics of 70 Patients With Unilateral Occlusion of the Internal Carotid Artery

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Age, mean (range), y</th>
<th>Male sex</th>
<th>Hypertension</th>
<th>Diabetes mellitus</th>
<th>Hypercholesterolemia</th>
<th>Smoking</th>
<th>Myocardial infarction</th>
<th>Peripheral vascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), y</td>
<td>59 (35-71)</td>
<td>51 (73)</td>
<td>32 (46)</td>
<td>11 (16)</td>
<td>30 (43)</td>
<td>49 (70)</td>
<td>12 (17)</td>
<td>17 (24)</td>
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*Data are given as number (percentage) of patients unless otherwise indicated.

TCD WITH CARBON DIOXIDE REACTIVITY MEASUREMENT

Transcranial Doppler ultrasonography with carbon dioxide reactivity measurement was performed with a Multi-Dop X device (DWL, Sipplingen, Germany) with two 2-MHz pulsed Doppler probes for measurements in cerebral vessels. The investigators were blinded to the clinical data. To assess cerebrovascular reactivity, the change in blood flow velocity in the MCA in response to carbon dioxide inhalation was monitored. Although the change in blood flow in the MCA only reflects the cerebrovascular reactivity of the deep perforating MCA branches and not all vascular territories, it is thought that the cerebrovascular reactivity assessed with TCD with a carbon dioxide challenge is useful for characterizing the hemodynamic changes that occur in various types of ischemic cerebrovascular disease.

The blood flow velocities in both MCAs were assessed simultaneously while the patient was lying in the supine position with closed eyes. After a 2-minute baseline period, the patient inhaled a gas mixture of 5% carbon dioxide and 95% oxygen (Carbogene) for 2 minutes. Carbon dioxide reactivity was determined as the relative change in blood flow velocity in the MCA after 1.5 minutes of Carbogene inhalation. In 3 patients, carbon dioxide reactivity could not be measured on one or both sides because no adequate Doppler signal could be obtained, probably owing to temporal window insufficiency.

To obtain normal values, we investigated 30 control subjects (25 men; age 59±10 years [range, 40-78 years]) without cerebrovascular disease, who were scheduled for implantation of an internal cardioverter defibrillator. The mean±SD carbon dioxide reactivity for the controls was 52±17%. To define patients with poor carbon dioxide reactivity, we used a cutoff point of 18% (mean−2×SD of the carbon dioxide reactivity in controls).

STATISTICAL ANALYSIS

We used a χ² test that was corrected for continuity or a Fischer exact test (when appropriate) to compare the prevalence of PVLs, territorial infarcts, lacunar infarcts, external border zone infarcts, and internal border zone infarcts between the hemispheres ipsilateral and contralateral to the unilateral occlusion of the ICA and between hemispheres with low and normal
those with a relatively high carbon dioxide reactivity, and patients with a high carbon dioxide reactivity had significantly larger mean volume of internal border zone infarcts compared with the contralateral hemisphere. Differences in lesion volume between hemispheres ipsilateral and contralateral to the ICA occlusion were found for any of the other types of lesions.

For the cerebral lesions with a putative hemodynamic cause, ie, internal border zone infarcts, external border zone infarcts, and PVLs, we also determined differences in lesion volume between hemispheres ipsilateral and contralateral to the ICA occlusion (Table 4) and between hemispheres with a carbon dioxide reactivity less than or equal to 18% and a carbon dioxide reactivity greater than 19% (Table 5). In the hemisphere ipsilateral to the ICA occlusion, we found a significantly larger mean volume of internal border zone infarcts compared with the contralateral hemisphere (mean±SD, 1.00±0.33 mL vs 0.08±0.04 mL; P=.004). Hemispheres with a carbon dioxide reactivity less than or equal to 18% also demonstrated a significantly larger mean volume of internal border zone infarcts compared with the contralateral hemisphere (mean±SD, 1.00±0.33 mL vs 0.08±0.04 mL; P=.004). Hemispheres with a carbon dioxide reactivity greater than 19% (mean±SD, 1.18±0.47 mL vs 0.24±0.11 mL; P=.003). No differences in volume were found for the external border zone infarcts and PVLs in the hemispheres ipsilateral and contralateral to the ICA occlusion or hemispheres with a low or normal carbon dioxide reactivity.

In Table 2, the prevalence of PVLs, territorial infarcts, lacunar infarcts, and external and internal border zone infarcts in the hemisphere ipsilateral and contralateral to the side of the ICA occlusion are presented. We found territorial infarcts (23% vs 7%; P=.02), external border zone infarcts (24% vs 2%; P<.001), and internal border zone infarcts (21% vs 6%; P=.02) more often in the hemisphere ipsilateral to the ICA occlusion than in the contralateral hemisphere. No differences were found in the prevalence of PVLs or lacunar infarcts. The prevalence of ischemic lesions in the different regions in hemispheres with a relatively low carbon dioxide reactivity (≤18%) compared with those with a relatively high carbon dioxide reactivity (>19%) is presented in Table 3. We found an increased prevalence of internal border zone infarcts (27% vs 8%; P=.007) in hemispheres with a carbon dioxide reactivity

<table>
<thead>
<tr>
<th>Table 2. Prevalence of Ischemic Brain Lesions in the Hemisphere Ipsilateral and Contralateral to the Unilateral Occlusion of the Internal Carotid Artery*</th>
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<td>Ipsilateral Hemisphere</td>
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<tr>
<td>Periventricular lesions</td>
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<td>Frontal horn</td>
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<td>Lateral ventricular wall</td>
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<td>Occipital horn</td>
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<td>Territorial infarcts</td>
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<tr>
<td>Lacunar infarcts</td>
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<tr>
<td>External border zone infarcts</td>
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<td>Internal border zone infarcts</td>
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<table>
<thead>
<tr>
<th>Table 3. Prevalence of Ischemic Brain Lesions in Hemispheres With a Carbon Dioxide (CO₂) Reactivity ≤18% vs ≥19% in 70 Patients With Unilateral Internal Carotid Artery Occlusion*</th>
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<tbody>
<tr>
<td>CO₂ Reactivity ≤18%</td>
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<tr>
<td>-----------------------</td>
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RESULTS

In Table 2, the prevalence of PVLs, territorial infarcts, lacunar infarcts, and external and internal border zone infarcts in the hemisphere ipsilateral and contralateral to the side of the ICA occlusion are presented. We found territorial infarcts (23% vs 7%; P=.02), external border zone infarcts (24% vs 2%; P<.001), and internal border zone infarcts (21% vs 6%; P=.02) more often in the hemisphere ipsilateral to the ICA occlusion than in the contralateral hemisphere. No differences were found in the prevalence of PVLs or lacunar infarcts. The prevalence of ischemic lesions in the different regions in hemispheres with a relatively low carbon dioxide reactivity (≤18%) compared with those with a relatively high carbon dioxide reactivity (>19%) is presented in Table 3. We found an increased prevalence of internal border zone infarcts (27% vs 8%; P=.007) in hemispheres with a carbon dioxide reactivity less than or equal to 18% than in those with a carbon dioxide reactivity greater than 19%. No significant differences were found for any of the other types of lesions.

For the cerebral lesions with a putative hemodynamic cause, ie, internal border zone infarcts, external border zone infarcts, and PVLs, we also determined differences in lesion volume between hemispheres ipsilateral and contralateral to the ICA occlusion (Table 4) and between hemispheres with a carbon dioxide reactivity less than or equal to 18% and a carbon dioxide reactivity greater than 19% (Table 5). In the hemisphere ipsilateral to the ICA occlusion, we found a significantly larger mean volume of internal border zone infarcts compared with the contralateral hemisphere (mean±SD, 1.00±0.33 mL vs 0.08±0.04 mL; P=.004). Hemispheres with a carbon dioxide reactivity less than or equal to 18% also demonstrated a significantly larger mean volume of internal border zone infarcts compared with hemispheres with a carbon dioxide reactivity greater than 19% (mean±SD, 1.18±0.47 mL vs 0.24±0.11 mL; P=.003). No differences in volume were found for the external border zone infarcts and PVLs in the hemispheres ipsilateral and contralateral to the ICA occlusion or hemispheres with a low or normal carbon dioxide reactivity.
When we analyzed carbon dioxide reactivity as a continuous variable, we found a significant correlation ($r = -0.171; P = .04$) between internal border zone lesion volume and carbon dioxide reactivity. For the PVLs ($r = 0.122; P = .161$) and the external border zone infarcts ($r = -0.015; P = .91$), such an association was not found.

Patients with unilateral occlusion of the ICA have an increased prevalence of internal border zone infarcts, external border zone infarcts, and territorial infarcts in the hemisphere ipsilateral to the ICA occlusion compared with contralateral hemispheres. No differences were found for PVLs and lacunar infarcts. Internal border zone infarcts were more common in hemispheres with a carbon dioxide reactivity less than or equal to 18%. Of the ischemic lesions with a possible hemodynamic cause, there was a significant increase in internal border zone infarct volume in the hemisphere ipsilateral to the ICA occlusion compared with the contralateral hemisphere. Moreover, in the hemispheres with a carbon dioxide reactivity less than or equal to 18%, there was a significant increase in internal border zone infarct volume compared with hemispheres with a carbon dioxide reactivity greater than 19%. No difference in volume was found for external border zone infarcts and PVLs between the hemispheres ipsilateral and contralateral to the occlusion and between hemispheres with carbon dioxide reactivity less than or equal to 18% and those with carbon dioxide reactivity greater than 19%.

We found a significant increase in prevalence and volume of internal border zone infarcts in the hemisphere ipsilateral to the ICA occlusion compared with the contralateral hemisphere. It is well recognized that a considerable portion of the deep white matter (centrum semiovale and corona radiata) is an arterial border zone that is vulnerable to hypoperfusion. The deep white matter is supplied by the medullary penetrators from the pial-MCA system and the deep perforating, lenticulostriate branches of the MCA. The area between these vascular territories represents the internal border zone. Several studies reported that an increase in prevalence of internal border zone infarcts is associated with the severity of the ICA lesion. Internal border zone infarction may result from intracranial MCA obstruction rather than hemodynamic alterations due to carotid artery disease. However, the association between lesions in the deep white matter and hemodynamic compromise in patients with unilateral occlusion of the ICA has been described before and it is even suggested that these lesions are specific and sensitive for the presence and severity of the hemodynamic compromise. The latter is in accordance with our results. We found a significant increase in prevalence and volume of internal border zone infarcts in the hemispheres with a low carbon dioxide reactivity. Moreover, we found a significant correlation between a decrease in carbon dioxide reactivity and internal border zone lesion volume. Both findings suggest that lesions in the deep white matter may have a hemodynamic origin.

We found a significant increase in the prevalence of infarcts in the external border zones in the hemisphere on the side of the ICA occlusion in comparison with the contralateral hemisphere. However, we did not find an association in the prevalence or size of these lesions between hemispheres with a carbon dioxide reactivity less than or equal to 18% and hemispheres with a carbon dioxide reactivity greater than 19%. This latter finding is in accordance with other studies in which no association was found between the level of hemodynamic impairment and the prevalence of cortical infarction in the possible external border zone regions. A decreased perfusion pressure in the ipsilateral hemisphere with an insufficient collateral supply could cause infarction in the external border zone areas in patients with stenosis or occlusion of the ICA. The anterior border zone, especially, may be selectively vulnerable to severe ICA stenosis or occlusion since the stenosed ICA supplies both the anterior cerebral artery and the MCA. In patients with severe ICA lesions, a regional impaired perfusion, lowered hemodynamic reserve, and a tendency toward a rising oxygen extraction fraction has been found in the anterior border zone region. However, the existence of selective external border zone hemodynamic impairment in patients with severe carotid artery diseases has also been denied. A possible explanation is that the interpretation of infarct patterns on brain scans of individual patients is likely to be hampered by the variability in intracranial arterial territory distributions. This may in particular play a role in the determination of the cortical wedge type of border zone infarction. Moreover, one should also realize that a TCD with carbon dioxide reactivity...
reactivity reflects only the changes in blood flow velocity in the core territory of the MCA. Although TCD is useful for characterizing the hemodynamic changes that occur in various types of ischemic cerebrovascular disease, the arteries that supply the territories of the anterior cerebral artery-MCA and MCA–posterior cerebral artery may not be fully represented by a TCD measurement.

We did not find any association between PVLs and vasomotor reactivity measured with TCD with carbon dioxide challenge or measured with single-creased cerebral vasomotor reactivity measured with TCD associated with a decreased cerebral blood flow or a decreased cerebral vasomotor reactivity measured with TCD with carbon dioxide challenge or measured with single-photon emission tomography and acetazolamide administration. The discrepancies between these studies and our results can be explained by the patients that we studied. We included patients with symptomatic unilateral occlusion of the ICA only, whereas others included patients from population-based studies of elderly persons. It is expected that cerebral hemodynamics in subjects from an elderly population–based study without ICA occlusion are within normal limits.

In conclusion, patients with unilateral occlusion of the ICA have a large load of ischemic brain lesions. Of lesions with a presumed hemodynamic cause, eg, internal border zone infarcts, external border zone infarcts, and PVLs, only the internal border zone infarcts demonstrate a significant increase in prevalence and volume in the hemispheres with a low carbon dioxide reactivity. No differences in prevalence and volume for the external border zone infarcts or PVLs were found between hemispheres with a low and normal carbon dioxide reactivity.

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Author contributions: Study concept and design (Drs Kappelle and van der Grond); acquisition of data (Drs Bisschops, Klijn, van Huffelen, and van der Grond); analysis and interpretation of data (Drs Bisschops, Klijn, Kappelle, and van der Grond); drafting of the manuscript (Drs Bisschops); critical revision of the manuscript for important intellectual content (Drs Klijn, Kappelle, van Huffelen, and van der Grond); administrative, technical, and material support (Drs Bisschops and Klijn); study supervision (Drs Kappelle, van Huffelen, and van der Grond).

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