Time Course of Vascular Reactivity Using Repeated Phase-Contrast MR Angiography in Patients With Carotid Artery Stenosis

Nolan S. Hartkamp, MD, MSc; Jeroen Hendrikse, MD, PhD; H. Bart van der Worp, MD, PhD; Gert J. de Borst, MD, PhD; Reinoud P.H. Bokkers, MD, PhD

Background and Purpose—Cerebral vascular reactivity assessment is typically performed with 2 perfusion measurements before and after a vasodilatory challenge. The aim of this study was to assess the time course of the vasodilatory effect in the brain-feeding arteries after a challenge with acetazolamide in patients with a stenosis of the internal carotid artery (ICA).

Methods—Twenty-one patients with a symptomatic ICA stenosis and 18 healthy control subjects underwent 2-dimensional phase-contrast MR angiography to repeatedly measure the blood flow (mL/min) in both ICAs at baseline and in 5-minute intervals for 30 minutes after intravenous administration of acetazolamide.

Results—At baseline, the blood flow was significantly lower in the stenosed ICAs of patients (155 ± 110 mL/min) than in the contralateral ICAs (237 ± 15 mL/min, P < 0.05) and the ICAs of healthy control subjects (249 ± 15 mL/min, P < 0.05) and remained lower throughout the time course. The maximum vasodilatory effect in the stenosed ICAs was observed after 15.3 ± 0.9 minutes, which was significantly later than in the contralateral ICAs (within 12.9 ± 0.7 minutes, P < 0.05) and healthy ICAs (within 12.8 ± 0.8 minutes, P < 0.05).

Conclusions—The onset of the maximum vasodilatory effect after administration of acetazolamide is delayed in patients with a symptomatic ICA stenosis. (Stroke. 2012;43:553-556.)

Key Words: blood flow ■ carotid artery stenosis ■ cerebral hemodynamics ■ magnetic resonance imaging ■ stroke

Impairment of the cerebral autoregulation is an important predictor of stroke recurrence in patients with a symptomatic stenosis of the internal carotid artery (ICA). One of the most frequently used vasodilatory challenges to assess cerebrovascular reactivity is the intravenous administration of acetazolamide. The maximum vasodilatory effect of acetazolamide in healthy volunteers is in excess of 12 minutes after administration. The time course of the vasodilatory effect in patients with ICA stenosis is however unclear. Two-dimensional phase-contrast MR angiography is a noninvasive method for measuring blood flow in the brain-feeding arteries. By adding a vasodilatory challenge, 2-dimensional phase-contrast MR angiography can accurately assess cerebrovascular reactivity when compared with perfusion MRI. The short measurement time of 2-dimensional phase-contrast MR angiography (<1 minute) allows for repeated measurements to assess reactivity over time after a vasodilatory challenge.

The aim of the present study was to assess the time course of the vasodilatory effect in the brain-feeding arteries after a challenge with acetazolamide in patients with an ICA stenosis and compare the hemodynamic change in these patients with that of healthy subjects.

Materials and Methods

The study was approved by the Institutional Ethical Review Board and written informed consent was obtained from all participants.

Subjects

Twenty-one patients with an unilateral symptomatic ICA stenosis > 50% and 18 age- and sex-matched healthy control subjects were prospectively included in this study (Table). All patients had had a transient ischemic attack, amaurosis fugax, or nondisabling ischemic stroke ipsilateral to the ICA stenosis and were referred to the Department of Radiology. Grading was performed on the basis of peak systolic velocities assessed with duplex ultrasonography and confirmed with CT angiography. Patients were excluded with diabetes mellitus, severe renal or liver dysfunction, or disabling stroke, defined as a score of 3 to 5 on the modified Rankin Scale. General risk factors for atherosclerotic disease were recorded. The healthy control subjects were recruited through local media advertisements; all were without a history of neurological disease and vascular pathology on MRI or MRA of the brain.
Imaging protocol with 2 consecutive 2-dimensional phase-contrast quantitative volume flow (mL/min) measurements according to a previously published protocol12 before and in 5-minute intervals after intravenous administration of 14 mg/kg acetazolamide (Goldshield Pharmaceuticals, Croydon Surrey, UK) with a maximum dose of 1200 mg. Collateral circulation in the circle of Willis was determined according to a previously published protocol110. The collateral circulation in the circle of Willis could not be visualized in any of the patients or control subjects. Differ- ences of the vasodilatory effect in patients associated with retrograde collateral blood flow in the precommunicating segment of the anterior cerebral artery ipsilateral to the ICA stenosis. One patient showed a unilateral fetal-type posterior communicating artery ipsilateral to the ICA stenosis. No significant difference was found in blood flow and vascular reactivity between these patients.

Magnetic Resonance Imaging
All patients were scanned on a clinical 3.0-Tesla whole-body system (Achieva; Philips Medical Systems) undergoing multiple 40-second 2-dimensional phase-contrast quantitative volume flow (mL/min) measurements according to a previously reported protocol12 before and in 5-minute intervals after intravenous administration of 14 mg/kg acetazolamide (Goldshield Pharmaceuticals, Croydon Surrey, UK) with a maximum dose of 1200 mg. Collateral circulation in the circle of Willis was determined according to a previously published imaging protocol with 2 consecutive 2-dimensional phase-contrast measurements, of which 1 was phase-encoded in the anteroposterior direction and 1 in the right–left direction.13

Blood Flow and Vascular Reactivity Measurements
The multiple sequential blood flow measurements were incorporated in a clinical reactivity examination. The measurements were performed at different time points for each subject and have therefore been binned in 5-minute intervals for group analysis. No differences were found in the blood flow between both ICAs of the healthy control subjects, for which reason these values were averaged for further analysis. To obtain a measure for the time to reach maximum vasodilatory effect of each vessel, the earliest time point per subject was chosen at which the blood flow was >90% of the maximum measured value. Vascular reactivity was defined as the percentage increase in blood flow between baseline and 15 minutes after the vasodilatory challenge (ie, the 15- to 20-minute interval) according to the referenced timing for reactivity measurements in most studies.3–6

Statistical Analysis
SPSS (SPSS Inc, Chicago, IL) for Windows, Version 15.0.1, was used for statistical analysis and differences were assessed using t tests. A probability value of <0.05 was considered to indicate statistical significance. Data are expressed as mean±SEM unless otherwise specified.

Results
The time course of individual blood flow values in the ICAs of healthy control subjects and patients after the vasodilatory challenge is shown in Figure 1. These data are shown for the healthy control subjects and patient groups at baseline and in 5-minute intervals in Figure 2. The blood flow in the stenosed ICAs was significantly lower in each interval than that in the contralateral ICAs of patients (P<0.05) or than that in both ICAs of healthy control subjects (P<0.05). There was, however, no significant difference in vascular reactivity after 15 minutes between the stenosed ICA (46.9%±6.7%) and contralateral ICA (56.0%±9.4%) of patients and the ICAs (58.2%±7.2%) of healthy control subjects.

Time to Reach Maximum Vascular Reactivity
The onset of the maximum vasodilatory effect in the stenosed ICAs (within 15.3±0.9 minutes) was significantly delayed when compared with the contralateral ICAs (within 12.9±0.7 minutes, P<0.05) of patients or the ICAs of healthy control subjects (within 12.8±0.8 minutes, P<0.05). The blood flow in the stenosed ICAs of patients in the 10- to 15-minute interval was lower than that of the 15- to 20-minute interval (difference 18.0±5.5 mL/min; P<0.01). The vascular reactivity in patients was also lower in the 10- to 15-minute interval in the stenosed ICAs (difference 10.2%±2.7%; P<0.01) when compared with the 15- to 20-minute interval. In the ICAs of healthy control subjects and in the contralateral ICA of the patients, there were no significant differences in the blood flow and the vascular reactivity between the 10- to 15- and 15- to 20-minute interval.

Collateral Circulation
Three patients demonstrated anterior collateral flow with retrograde blood flow in the precommunicating segment of the anterior cerebral artery ipsilateral to the ICA stenosis. One patient showed a unilateral fetal-type posterior communicating artery ipsilateral to the ICA stenosis. No significant difference was found in blood flow and vascular reactivity between these patients.

Discussion
The present study shows that the maximum vasodilatory effect of acetazolamide was reached later in the stenosed ICAs of patients than in the contralateral ICAs and the ICAs of healthy control subjects. Furthermore, the vascular reactivity in the stenosed ICAs of patients was lower but not significantly reduced when compared with the contralateral ICAs or with the ICAs of healthy control subjects. Differences of the vasodilatory effect in patients associated with collateral circulation in the circle of Willis could not be found. This might, however, be due to the small sample size.

The maximum vasodilatory effect in the stenosed ICAs was reached after 15 minutes, whereas in the contralateral

### Table. Demographic and Clinical Characteristics of the Study Population

<table>
<thead>
<tr>
<th></th>
<th>Healthy Control Subjects</th>
<th>Stenosis Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>12 (67%)</td>
<td>14 (67%)</td>
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<tr>
<td>Age, y, mean±SD</td>
<td>68.4±5.9</td>
<td>68.6±7.9</td>
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<td>Degree of ICA stenosis, no.</td>
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<td></td>
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<td>0%–49%</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>50%–69%</td>
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<td>2</td>
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<tr>
<td>70%–99%</td>
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<td>Occluded</td>
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<td>0</td>
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<tr>
<td>Presenting events, no.</td>
<td></td>
<td></td>
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<tr>
<td>Transient ischemic attack</td>
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<td>13</td>
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<tr>
<td>Transient monocular blindness</td>
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<td>3</td>
</tr>
<tr>
<td>Ischemic stroke</td>
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<td>5</td>
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<tr>
<td>Presenting events, no.</td>
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<td></td>
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<tr>
<td>Previous myocardial infarction</td>
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<tr>
<td>Previous CABG</td>
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<tr>
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<tr>
<td>Ex-smoker</td>
<td>9</td>
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</table>

ICA indicates internal carotid artery; CABG, coronary artery bypass grafting; SD, standard deviation.
ICAs and in the ICAs of healthy control subjects, the plateau was reached after 13 minutes. Previously an effect plateau was reported in healthy control subjects at 12 minutes after acetazolamide administration. In patients with carotid artery disease, measurements performed too early (before 15 minutes) may however result in an underestimation of blood flow or vascular reactivity. In the stenosed ICAs of patients, a stepwise decrease in blood flow was observed in the 20- to 25- and the 25- to 30-minute intervals, which may be due to less measurement points or which may indicate that the vasodilatory effect of acetazolamide is wearing off. To be able to reliability assess the cerebrovascular reactivity using

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**Figure 1.** Individual blood flow measurements in the internal carotid arteries (ICAs) after the administration of acetazolamide in the ICAs of healthy control subjects (A) and in the stenosed ICA (C) and contralateral ICA (B) of patients.

**Figure 2.** Blood flow (mean±SEM) in the internal carotid arteries (ICAs) after the administration of acetazolamide in the ICAs of healthy control subjects (white) and in the stenosed ICA (dark gray) and contralateral ICA (light gray) of patients. *Statistically significant differences in blood flow (mL/min) between patients and healthy control subjects (independent t test; P<0.05) as well as between patients’ stenosed ICAs and contralateral ICAs (paired t test; P<0.05).
acetazolamide, we therefore believe that in patients with carotid artery stenosis, the optimal timing for a single measurement is between 15 to 20 minutes after administration, which is in agreement with the references timing of most reactivity studies.3–6

The absence of hemodynamic information at the brain tissue level is a limitation in this study. In absence of a significantly reduced vascular reactivity and with sufficient collateral pathways in all patients, the blood flow may be primarily restricted due to the stenosis itself. A previous study has however demonstrated impairment of the vasodilatory capacity of the cerebral vasculature distal to the ICA stenosis in symptomatic patients.14 The significantly later onset of the maximum vasodilatory effect in the stenosed ICA of patients in our study also suggests vasodilatory impairment in the more distal cerebral vasculature.

The present study shows the time course of vascular reactivity after a vasodilatory challenge in patients with carotid artery disease. The onset of maximum vascular reactivity after a vasodilatory challenge is delayed in the stenosed ICA of symptomatic patients.

Sources of Funding
N.S.H. receives support from the Netherlands Heart Foundation (Grant 2010B274). J.H. receives support from the Netherlands Heart Foundation (Grant 2010B274).

Disclosures
None.

References
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Stroke. 2012;43:553-556; originally published online November 3, 2011;
doi: 10.1161/STROKEAHA.111.637314
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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