A Longitudinal Study of Collateral Flow Patterns in the Circle of Willis and the Ophthalmic Artery in Patients With a Symptomatic Internal Carotid Artery Occlusion

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Background and Purpose—The purpose of the present study was to assess whether the direction of flow via the circle of Willis and the ophthalmic artery (OphA) changed over time in patients with a symptomatic occlusion of the internal carotid artery (ICA) who did not experience recurrent cerebral ischemic symptoms.

Methods—Sixty-two patients with a symptomatic ICA occlusion were investigated within 6 months after symptoms occurred. The investigations were repeated after 6 and 12 months. The directions of flow in the A1 segment and the posterior communicating artery (PCoA), both on the side of the symptomatic ICA occlusion, were assessed with the use of magnetic resonance angiography. The pattern of collateral flow via the circle of Willis was categorized as via the A1 segment only, via the PCoA only, via the A1 segment plus the PCoA, or no collateral flow via the circle of Willis. The direction of flow in the OphA was investigated with transcranial Doppler sonography. CO2 reactivity was determined with transcranial Doppler sonography to investigate whether changes in flow patterns were accompanied by changes in cerebrovascular reactivity.

Results—There were no statistically significant changes over time in the direction of blood flow in the A1 segment and the PCoA or in the pattern of collateral flow via the circle of Willis. On average, 72% of patients with a unilateral ICA occlusion (n=41) had willisian collateral flow compared with 37% of patients with a bilateral ICA occlusion (n=21; P<0.05). Patients with a unilateral ICA occlusion tended to a lower prevalence of reversed flow via the OphA over time. CO2 reactivity did not change significantly in any patient group. In patients with a unilateral ICA occlusion, decreased CO2 reactivity was associated with a higher prevalence of absent willisian collateral flow and a lower prevalence of collateral flow via the A1 segment plus the PCoA.

Conclusions—The absence of recurrent cerebral ischemic symptoms in patients with a symptomatic ICA occlusion is not associated with an improvement in collateral flow via the circle of Willis or the OphA during 1.5-year follow-up.

Key Words: carotid artery occlusion ■ collateral circulation ■ follow-up studies

Patients with a symptomatic occlusion of the internal carotid artery (ICA) are at risk of future cerebral ischemic events that may at least in part be caused by hemodynamic factors.1 The reason why a large proportion of patients remain asymptomatic after the initial ischemic event is not clear. There may be a change in collateral circulation over time. This is supported by a recent PET study which reported that cerebral blood flow can improve in patients with an ICA occlusion who remain asymptomatic during follow-up, suggesting an improvement in collateral circulation.2 The anterior and posterior communicating arteries (ACoA and PCoA, respectively) are considered the primary collateral pathways in patients with an ICA occlusion.3,4 Hypothetically, preferential flow patterns may develop, such as the presence of collateral flow via the ACoA,5–7 the PCoA,4,7 or both the ACoA and PCoA.8,9 Accordingly, the time course of flow in the ophthalmic artery (OphA), which is regarded a secondary collateral pathway in patients with an ICA occlusion,3,4 is a matter of interest.

The primary aim of the present study was to investigate the pattern of flow in the circle of Willis and the OphA over time in patients with a symptomatic occlusion of the ICA who did not experience recurrent cerebral ischemic symptoms during follow-up. Magnetic resonance angiography (MRA) has proved to be a valuable technique for the study of flow in the circle of Willis in patients with an ICA occlusion,4,5,10,11
whereas flow in the OphA can be reliably assessed with transcranial Doppler sonography (TCD). In addition, we investigated whether changes in flow patterns were accompanied by changes in cerebrovascular reactivity as assessed with TCD. A decreased cerebrovascular reactivity indicates a reduced reserve capacity of cerebral autoregulation and has been shown to be related to the risk of recurrent cerebral ischemia in patients with an ICA occlusion.

Subjects and Methods

Patients

We studied 62 consecutive patients with an angiographically proven symptomatic ICA occlusion who were referred to the department of neurology or vascular surgery of our hospital between 1995 and 1998. The patients fulfilled 3 inclusion criteria: they did not experience recurrent neurological deficits during a 15-year follow-up period, they were studied repeatedly with MRA and TCD, and they were not treated by means of a contralateral carotid endarterectomy or ipsilateral extracranial-intracranial bypass procedure.

All patients had transient (lasting <24 hours) or minor disabling (Rankin Score of ≤3) deficits in the supply territory of an occluded ICA within 6 months before the first MRA and TCD investigation. Fifty patients had clinical features caused by hemispheric ischemia (hemispheric transient ischemic attack n=9, minor disabling ischemic stroke n=41). Twelve patients had symptoms of retinal ischemia only (transient monocular blindness n=11, chronic ocular ischemic syndrome n=1). The degree of stenosis of the contralateral ICA was assessed according to the criteria of the North American Symptomatic Carotid Endarterectomy Trial. All patients received the best medical treatment.

The direction of blood flow in the circle of Willis and the OphA was assessed on 3 occasions. The first investigation was performed within 6 months after the ischemic event. The second and third investigations were performed between 6 to 12 months and 12 to 18 months after the ischemic event.

Each patient gave informed consent to participate in the study. The Human Research Committee of our hospital approved the study protocol.

MRA Study

The MR investigations were performed with a 1.5-T whole-body system (AC/S NT 15 model; Philips Medical Systems). The circle of Willis was visualized with a 3-dimensional time-of-flight MRA sequence (TR 31 ms, TE 6.9 ms, flip angle 20°, 2 signals acquired, 50 slices, slice thickness 1.2 mm with a slice overlap of 0.6 mm, field-of-view 100×100 mm, matrix size 128×128), after which a reconstruction (256×256 matrix) was made in 3 orthogonal directions with a maximum intensity projection algorithm. The direction of blood flow in the circle of Willis was assessed with 2 consecutive 2-dimensional phase contrast (PC) measurements, of which 1 was phase encoded in the anteroposterior direction and 1 was phase encoded in the left-right direction (TR 16 ms, TE 9.1 ms, flip angle 7.5°, slice thickness 13 mm, 8 averages, field-of-view 250×250 mm, matrix size 256×256, velocity sensitivity 40 cm/s). Previous studies have indicated that a 4-MHz Doppler probe was used to assess the direction of flow in the circle of Willis. The images of the circle of Willis were evaluated independently by 2 investigators (D.R.R. and C.J.M.K.) to assess the direction of blood flow in the A1 segment of the anterior cerebral artery and in the PCoA, both ipsilateral to the symptomatic ICA occlusion. Discrepancies between the 2 investigators were reevaluated in a consensus meeting. Blood flow in the A1 segment or PCoA was categorized as retrograde flow if it was directed toward the occluded ICA (in patients with a bilateral ICA occlusion toward the occluded ICA on the symptomatic side), as no flow if no flow was observed, or as antegrade flow if blood flow was directed away from the (symptomatic) occluded ICA. Presence of retrograde flow in the A1 segment was considered to indicate use of the ACoA collateral pathway. In each patient, the pattern of collateral flow via the circle of Willis was categorized as collateral flow (1) via the A1 segment only, (2) via the PCoA only, or (3) via both the A1 segment and the PCoA or (4) no collateral flow via either the A1 segment or the PCoA (Figure 1).

TCD Study

The TCD investigations were performed with a Multi-Dop X device (DWL). A 4-MHz Doppler probe was used to assess the direction of blood flow in the OphA ipsilateral to the symptomatic ICA occlusion. Blood flow was categorized as retrograde flow if it was directed toward the symptomatic occluded ICA or as antegrade flow if it was directed away from the symptomatic occluded ICA. CO2 reactivity was measured in the middle cerebral artery (MCA) ipsilateral to the symptomatic ICA occlusion with a 2-MHz Doppler probe with the patient in the supine position. The TCD probe was fitted in a light metal frame, which was firmly fixed to the head with 2 ear pieces and an adjustable nose saddle (manufactured by DWL). After a 2-minute baseline period, patients inhaled a gas mixture of 5% CO2 and 95% O2 (Carbogene) for the next 2 minutes. The Carbogene was inhaled through a mouthpiece connected to a respiratory balloon, and the use of a nose clip ensured proper inhalation. The CO2 content of the breathing gas was monitored continuously with an infrared gas analyzer. A spectral TCD recording of 5 seconds was made after 1 minute during the baseline period and after 1.5 minutes of Carbogene inhalation. The CO2 reactivity

Figure 1. The 4 patterns of collateral flow via the circle of Willis to the hemisphere ipsilateral to the symptomatic ICA occlusion. PCoA indicates posterior communicating artery.
was expressed as the relative change in blood flow velocity (BFV) in the MCA after 1.5 minutes of Carbogene inhalation, according to the equation

\[
\frac{\text{BFV}_{\text{CO}_2} - \text{BFV}_{\text{baseline}}}{\text{BFV}_{\text{baseline}}} \times 100% 
\]

The mean of the maximal BFV values during the spectral TCD recordings was used in this calculation. To obtain reference values, we measured CO2 reactivity in 30 subjects without cerebrovascular disorders (mean±SD age 59±10 years, 25 men and 5 women) who were scheduled for the implantation of an internal cardioverter-defibrillator. In both hemispheres, the mean±SD CO2 reactivity was 51±14%. Consequently, we regarded a CO2 reactivity of <23% as abnormal (ie, mean ±2 SDs). Based on these results, CO2 reactivity was categorized as ≥23% or <23%, which was subcategorized as 0% to 23% or <0%. This latter category was considered to indicate patients with an intracerebral steal effect.19

Statistical Analysis
The χ2 test was used to compare the direction of flow in the A1 segment and the PCoA among the 3 investigations and between patient groups. Similarly, the pattern of collateral flow in the circle of Willis, the direction of flow in the OphA, and the categories of CO2 reactivity were analyzed. Statistical significance was corrected for repeated measures (Bonferroni-Holm procedure). A general linear model for repeated measures was used to investigate the time course of the mean CO2 reactivity. A P value of <0.05 was considered statistically significant.

Results
The baseline characteristics of the 62 patients and the time interval between the ischemic event and the various investigations are shown in Table 1. Typical examples of directional flow investigations for each of the 4 patterns of collateral flow via the circle of Willis are shown in Figure 2.

Figures 3 to 7 show the direction of flow in the A1 segment and the PCoA, the pattern of collateral flow via the circle of Willis, the direction of flow in the OphA, and the CO2 reactivity. We performed separate analyses for patients with a unilateral ICA occlusion and patients with a bilateral ICA occlusion. In the analysis of patients with a unilateral ICA occlusion, we pooled the data from patients with a 0% to 69% stenosis of the contralateral ICA and those with a 70% to 99% stenosis of the contralateral ICA. No statistical comparison was made between these 2 groups because of the small number of patients who had a 70% to 99% contralateral stenosis.
The A1 segment in patients with a unilateral ICA occlusion showed retrograde flow in a majority of patients in the first 6 months after the ischemic event, whereas a minority had no flow or antegrade flow (Figure 3). During follow-up, these proportions did not change significantly. Most patients with a bilateral ICA occlusion had antegrade flow in the A1 segment in the first 6 months after the ischemic event. Over time, there were no statistically significant changes in the direction of blood flow in the A1 segment in these patients. In the first investigation, the pattern of blood flow in the A1 segment differed significantly between patients with a unilateral ICA occlusion and those with a bilateral occlusion ($P<0.001$). During follow-up, the difference remained statistically significant ($P<0.05$ and $P<0.01$, respectively).

The PCoA showed retrograde flow in 39% of patients with a unilateral ICA occlusion, whereas in 61% no flow was observed (Figure 4). During follow-up, no significant changes occurred. In patients with a bilateral ICA occlusion, only a small proportion had retrograde flow in the PCoA in the first 6 months after the ischemic event, whereas in most patients no flow was observed. Although there was a trend toward a higher prevalence of retrograde flow via the PCoA over time in these patients, no statistically significant longitudinal changes occurred. Patients with a unilateral ICA occlusion tended to have a higher prevalence of retrograde flow in the PCoA compared with patients with a bilateral ICA occlusion, but there were no statistically significant differences between these groups.

The distribution of the patterns of collateral flow via the circle of Willis in patients with a unilateral ICA occlusion showed no statistically significant changes over time (Figure 5). In patients with a bilateral ICA occlusion, a majority of patients did not have collateral flow via the circle of Willis in the first 6 months after the ischemic event. Over time, there was a trend toward an increasing prevalence of collateral flow via the PCoA only and a decreasing prevalence of absent collateral flow via the circle of Willis. These changes were not statistically significant. In the first investigation, the distribution of the patterns of collateral flow via the circle of Willis differed significantly between patients with a unilateral ICA occlusion and those with a bilateral ICA occlusion ($P<0.05$). During the follow-up, this significant difference remained present. On average, 72% of patients with a unilateral ICA occlusion had collateral flow via the circle of Willis (via the A1 segment, the PCoA, or both) compared with 37% of patients with a bilateral ICA occlusion ($P<0.05$).

**Ophthalmic Artery**

Most patients with a unilateral ICA occlusion had retrograde flow via the OphA in the first 6 months after the ischemic event (Figure 6). In the following investigation, this percentage decreased significantly ($P<0.05$). In patients with a bilateral ICA occlusion, nearly all patients had retrograde flow via the OphA in the first 6 months after the ischemic event; this did not change significantly during follow-up. In the first investigation, the prevalence of retrograde flow via
the OphA did not differ significantly between patients with a unilateral ICA occlusion and those with a bilateral ICA occlusion. During the second and third investigations, significantly less patients with a unilateral ICA occlusion had retrograde flow via the OphA compared with patients who had a bilateral ICA occlusion ($P<0.05$).

**CO₂ Reactivity**

In patients with a unilateral ICA occlusion, the mean CO₂ reactivity in the first 6 months after the ischemic event was 22% (95% CI 14% to 31%). In the following investigations, the mean CO₂ reactivities were 23% (95% CI 16% to 29%) and 24% (95% CI 18% to 30%). The proportion of patients with a unilateral ICA occlusion who had a normal CO₂ reactivity (ie, $\geq 23\%$) changed over time from 46% to 59% (Figure 7). Neither the mean CO₂ reactivity nor the distribution of the categories of CO₂ reactivity changed significantly in patients with a unilateral ICA occlusion. In patients with a bilateral ICA occlusion, the mean CO₂ reactivity changed over time from 14% (95% CI 5% to 23%) to 15% (95% CI 6% to 24%) and 18% (95% CI 13% to 24%). The proportion of patients with a bilateral ICA occlusion who had a normal CO₂ reactivity varied over time between 32% and 40% (Figure 7). Neither the mean CO₂ reactivity nor the distribution of categories of CO₂ reactivity changed significantly in these patients.

Figure 8 shows the comparison of collateral flow patterns via the circle of Willis between patients with a decreased CO₂ reactivity ($<23\%$) and those with a normal CO₂ reactivity ($\geq 23\%$). The data for all 3 measurements (0 to 6, 6 to 12, and 12 to 18 months after the ischemic event) were pooled in this analysis. In patients with a unilateral ICA occlusion, the distribution differed significantly between groups ($P<0.05$). In patients with a decreased CO₂ reactivity, a higher proportion had no willisian collateral flow, and a lower proportion had collateral flow via both the A1 segment and the PCoA, compared with patients who had a normal CO₂ reactivity. In patients with a bilateral ICA occlusion who had a decreased CO₂ reactivity, a lower proportion tended to have collateral flow via the PCoA only and a higher proportion had collateral flow via the A1 segment only, compared with patients who had a normal CO₂ reactivity. No significant differences were found between groups. In the pooled data of patients with a unilateral ICA occlusion, there was no significant difference in the prevalence of retrograde flow via the OphA between patients with a decreased CO₂ reactivity (64% retrograde OphA flow) and those with a normal CO₂ reactivity (68% retrograde OphA flow). In the pooled data of patients with a bilateral ICA occlusion, the prevalence of retrograde flow via the OphA also did not differ significantly between patients with a decreased CO₂ reactivity (92%) and those with a normal CO₂ reactivity (100%).

In patients with a unilateral ICA occlusion, 22 had a decreased CO₂ reactivity ($<23\%$) in the first investigation. Of these patients, 41% showed a normal CO₂ reactivity in the third investigation, whereas 59% still had a decreased CO₂ reactivity. The patients who improved and who did not improve in CO₂ reactivity did not differ significantly in
collateral flow patterns via the circle of Willis or the OphA in either the first or the third investigation. In patients with a bilateral occlusion, 13 had a decreased CO2 reactivity. Of these patients, 15% had a normal CO2 reactivity in the third investigation, whereas 85% had a decreased CO2 reactivity. No statistical comparison was made between these groups because of the small number of patients who changed to normal CO2 reactivity.

Discussion
The present study shows that there was no change over time in the pattern of collateral flow via the circle of Willis in patients with a symptomatic ICA occlusion who did not experience recurrent neurological deficits during a period of 1.5 years after the symptoms occurred. The prevalence of retrograde flow via the OphA tended to decrease in patients with a unilateral ICA occlusion, whereas it did not change in patients with a bilateral ICA occlusion. In both patients with a unilateral ICA occlusion and those with a bilateral ICA occlusion, there were no statistically significant changes over time in CO2 reactivity.

Few studies have assessed the development of collateral flow specifically in patients with obstructive carotid artery disease who did not have recurrent neurological deficits. Both a PET study2 and a TCD study19 have suggested that an improvement in collateral blood flow can take place in patients with an ICA occlusion, but changes in collateral pathways itself have not been studied. Our study suggests that the absence of recurrent neurological features in patients with a symptomatic ICA occlusion is not accompanied by an improvement in collateral flow patterns via the circle of Willis or the OphA. We speculate from these results that it is unlikely that patients with a symptomatic ICA occlusion in general will manifest improvement in the circle of Willis or the OphA within a period of at least 1.5 years.

In previous angiographic9,20 MRA,5,8,11,21,22 and TCD23 studies of patients with a unilateral ICA occlusion, the proportion of patients with collateral flow via the A1 segment (A1 segment only or A1 segment plus PCoA) varied between 46% and 80%, whereas the prevalence of collateral flow via the PCoA (PCoA only or PCoA plus A1 segment) varied between 32% and 76%. The proportions we found in the present study in patients with a unilateral ICA occlusion are in line with these percentages. In studies of patients with a bilateral ICA occlusion, collateral flow via the A1 segment was demonstrated in 0% to 11% of patients, and collateral flow via the PCoA was demonstrated in 67% to 78% of patients.8,22 These percentages differ from the proportions in our study. Possibly, this is due to a different composition of our study group in that patients were not included if they were asymptomatic or if they experienced recurrent cerebral ischemia during follow-up.

We found that a relatively large proportion of our patients had collateral OphA flow, compared with previous studies in
patients with an ICA occlusion that reported proportions varying from 35% to 56%.

In our study, the prevalence of collateral OphA flow tended to decrease over time in patients with a unilateral ICA occlusion. Collateral flow via the OphA is often regarded as a marker of insufficient cerebral perfusion. Consequently, our results may imply that in patients with a unilateral ICA occlusion cerebral perfusion improved over time. However, some have suggested that the OphA does have a functional contribution to cerebral circulation. A decrease in collateral flow via the OphA would then indicate a worsening of blood supply to the brain. Based on our study, we cannot discriminate between the 2 interpretations.

The pattern of collateral flow differed significantly between patients with a unilateral ICA occlusion and those with a bilateral ICA occlusion. With respect to the circle of Willis, patients with a unilateral ICA occlusion had collateral flow via the A1 segment more often than did patients who had a bilateral ICA occlusion. Collateral flow via the A1 segment arises when there is a reversed blood pressure gradient across the vessel. When the ICA is occluded on both sides, the pressure difference is likely to be canceled out. This explains why many patients with a bilateral ICA occlusion did not have collateral flow via the A1 segment. In our series, most patients with a bilateral ICA occlusion did not need collateral flow via the circle of Willis to remain asymptomatic during follow-up. Probably, other collateral pathways were important, such as leptomeningeal anastomoses or connections between the internal and external carotid arteries. This hypothesis may be supported by the observation that nearly all patients with a bilateral ICA occlusion had retrograde flow via the OphA.

Previously, it has been shown that CO2 reactivity can improve over time in patients with a carotid artery occlusion. The finding that there were no significant changes in CO2 reactivity in our patient group suggests that the absence of recurrent symptoms is not necessarily accompanied by an improvement in CO2 reactivity. In patients with a unilateral ICA occlusion, we found that those who had a decreased CO2 reactivity more often showed absent willisian collateral flow and less often showed collateral flow via both the A1 segment and the PCoA compared with patients who had a normal CO2 reactivity. This suggests that the pattern of collateral flow via the circle of Willis is related to vasomotor reactivity. Similar observations have been made previously.

The present study may have several limitations. Small vessels in the circle of Willis may have remained invisible on the directional flow images as a consequence of the applied techniques, but we speculate that collateral flow that was not detected on these images probably did not contribute substantially to cerebral perfusion. No information was obtained about the amount of collateral flow. Unfortunately, reliable quantitative flow measurements could not be performed because of the small diameter of the involved arteries. Finally, it cannot be excluded that changes in collateral flow patterns have taken place in the first weeks after the symptoms occurred. However, results from previous longitudinal studies suggest that collateralization may develop slowly over months in patients with an ICA occlusion. We believe that the time interval between the ischemic event and the various investigations in our study allowed us to monitor whether changes in flow patterns via the circle of Willis and the OphA occur in the long term.

In conclusion, the flow pattern via the circle of Willis does not change over time in patients with a symptomatic ICA occlusion who do not experience recurrent cerebral ischemia during follow-up. In a majority of patients, retrograde flow via the OphA remains present over time. In only a minority of patients with a bilateral ICA occlusion is willisian collateral flow important during follow-up.

Acknowledgment

Dr Rutgers is supported by the Netherlands Organization for Scientific Research (NWO) grant 920-03-091.

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Stroke. 2000;31:1913-1920
doi: 10.1161/01.STR.31.8.1913

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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