Recurrent Stroke in Patients With Symptomatic Carotid Artery Occlusion Is Associated With High-Volume Flow to the Brain and Increased Collateral Circulation

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Background and Purpose—To investigate whether the risk of recurrent ipsilateral ischemic stroke in patients with symptomatic carotid artery occlusion (CAO) is related to (1) volume flow in the contralateral internal carotid artery (ICA), basilar artery (BA), and middle cerebral arteries (MCAs), and (2) intracranial collateral flow to the symptomatic side, measured in the first 6 months after the qualifying symptoms occurred.

Methods—We prospectively studied 112 patients with symptomatic CAO. Quantitative volume flow was measured with magnetic resonance angiography (MRA) and collateral flow via the circle of Willis with MRA, via the ophthalmic artery (OA) with transcranial Doppler sonography, and via leptomeningeal anastomoses with conventional angiography.

Results—During 49±14 months of follow-up (mean±SD), 7 patients had recurrent ipsilateral ischemic stroke. Compared with patients without recurrent stroke, these patients had significantly higher total flow to the brain, ie, ICA+BA flow (mean 536 mL/min versus 410 mL/min; P<0.05), and significantly higher contralateral ICA flow (355 mL/min versus 209 mL/min; P<0.001), whereas BA and MCA flow showed no significant differences. Also, they more often had Willisian collateral flow (P<0.05), mainly caused by increased collateral flow via the posterior communicating artery (PCoA; 71% versus 28%; P<0.05), whereas collateral flow via the OA and leptomeningeal anastomoses did not differ significantly.

Conclusions—Recurrent ipsilateral ischemic stroke in patients with symptomatic CAO is associated with high volume flow to the brain and increased collateral PCoA flow. (Stroke. 2004;35:000-000.)

Key Words: cerebrovascular circulation metabolism

In patients with symptomatic carotid artery occlusion (CAO), early mechanisms that can compensate for reduced cerebral perfusion pressure include changes of blood flow through the contralateral internal carotid artery (ICA), basilar artery (BA), and middle cerebral arteries (MCAs), and development of intracranial collateral circulation.1,2 These compensatory mechanisms may lead to or protect against the development of cerebral hemodynamic compromise that is associated with the recurrence of cerebral ischemic events in patients with symptomatic CAO.3 For example, increased flow to the brain and increased collateral circulation may prevent the development of hemodynamic failure.2,4 Conversely, it may be hypothesized that compensatory increase of flow in the ICAs and BA and recruitment of collateral pathways indicate more severe cerebral hemodynamic failure.5 Therefore, the status of cerebral blood supply and collateral circulation may be an early indicator of increased risk of future ischemic events.

At present, no studies have evaluated the role of contralateral ICA and BA flow in the prognosis of patients with symptomatic CAO. MCA flow has shown no association with the recurrence of cerebral ischemic events;6 however, the mean follow-up time was relatively short (24 months). Also, intracranial collateral circulation has been studied before,4,7 but follow-up time was limited to a mean or median of 24 months, and the role of individual collaterals was not clear from these studies. In particular, individual collaterals such as the anterior communicating artery (ACoA) or posterior communicating artery (PCoA) may be important in the prognosis of patients with symptomatic CAO.8,9

The aim of the present study was to investigate whether the risk of recurrent ipsilateral ischemic stroke in patients with symptomatic CAO is related to (1) volume flow in the contralateral ICA, BA, and MCAs and (2) presence of collateral flow to the hemisphere on the side of the symptomatic CAO via the circle of Willis, the ophthalmic artery (OA), and leptomeningeal anastomoses, measured in the first 6 months after the qualifying symptoms occurred.
Materials and Methods

Between September 1995 and July 1998, 115 patients with an angiographically-proven and symptomatic CAO were prospectively studied. They experienced transient (lasting <24 hours) and minor-disabling (Rankin score ≤3) neurological deficits in the supply territory of an occluded carotid artery within 6 months before referral. In 3 of the 115 patients, assessment of collateral flow failed because of technically inadequate magnetic resonance (MR) scans. Of 112 eligible patients (92 men, 20 women; mean age 61±9 years), 67 had experienced a minor cerebral ischemic stroke, 21 had experienced a transient hemispheric ischemic attack, and 24 had experienced retinal ischemia. Of these 24 patients, 3 had a retinal infarction, 19 had transient monocular blindness, and 5 had chronic ocular ischemic syndrome (3 had more than 1 type of retinal ischemia). Of the 112 eligible patients, 98 had an extracranial ICA occlusion and 14 had an occlusion of the common carotid artery (without flow in the ICA on angiography). The degree of contralateral ICA stenosis was assessed according to North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria for an average of 50 days after the qualifying symptoms occurred. In 21 patients, contralateral carotid endarterectomy was performed. In 16 patients with recurrent symptoms of presumed hemodynamic origin, high-flow extracranial/intracranial (EC/IC) bypass surgery was performed. In these 16 patients, 2 strokes occurred ipsilateral to the symptomatic CAO before surgery. These strokes were considered clinical end points. All patients received the best medical treatment, which included antithrombotic medication (predominantly low-dose aspirin) and treatment of vascular risk factors.

Patients were followed for a mean time of 49±14 (SD) months. Patients who underwent contralateral carotid endarterectomy or EC/IC bypass surgery were censored at the time of operation. An end point was defined as stroke ipsilateral to the symptomatic CAO. Stroke was diagnosed when symptoms or signs of focal cerebral deficits lasted >24 hours and caused an increase in handicap of at least 1 grade on the modified Rankin scale. A computed tomography scan or MRI scan was performed to exclude cerebral hemorrhage as cause of the stroke. End points were assessed by a panel of 2 neurologists and 1 neurosurgeon who were not participating in the MR investigations. Each patient gave informed consent to participate in the study. The Human Research Committee of our hospital approved the study protocol.

MR investigations were performed on a 1.5 T whole-body system (ACS-NT 15 model; Philips Medical Systems) for an average of 73±56 days after the qualifying symptoms occurred. Quantitative volume flow in the ICA, BA, and MCA was measured with MR angiography (MRA) according to a previously published protocol. Reference flow values were obtained in 30 age-matched control subjects (age 58±12 years; 21 men, 9 women). They were recruited from the departments of neurology and urology, where they were hospitalized for reasons other than intracranial diseases. MRI of the brain did not show cerebral abnormalities in these subjects. Collateral flow via the circle of Willis (ie, via the A1 segment and PCoA on the side of the symptomatic CAO) and via the OA were assessed with MRA and transcranial Doppler sonography (TCD), respectively, as described previously. Patients were examined with TCD for an average of 72±57 days after the qualifying symptoms occurred. Blood flow that was directed toward the symptomatic CAO was categorized as collateral flow. Collateral flow in the A1 segment was considered to indicate use of the ACoA collateral territory (after 6 months), 7 had an infarct in the territory of the recurrent artery of Heubner (after 1 month), 2 patients had infarcts in the ACA territory (after 3 months and 3.5 years, respectively), and 1 patient had an infarct in the MCA-ACA border zone (after 2.75 years). There were no significant differences in male/female ratio, age, vascular risk factors, and degree of contralateral ICA stenosis between patients with and without recurrent ipsilateral ischemic stroke (Table 1). No patients showed evidence of vasculitis, fibromuscular dysplasia, or other intracranial vessel disease on MRA or intraarterial digital subtraction angiography. None of the patients with recurrent ipsilateral stroke had contralateral stroke during follow-up. In patients without recurrent stroke on the side of the symptomatic CAO, 3 had a contralateral stroke. During follow-up, mortality did not differ between patients with and without recurrent stroke (2/7 versus 11/105; P=0.15).

The time interval between the qualifying event and the MR investigation did not differ between patients with and without

| TABLE 1. Patient Characteristics and Degree of Stenosis in the Contralateral ICA in Patients With Symptomatic CAO With or Without Recurrent Ipsilateral Ischemic Stroke During Follow-Up |
|-----------------|----------------|
| **Patient characteristic** | **Yes (n = 7)** | **No (n = 105)** |
| Males/females, n (%) | 7/0 (100/0) | 85/20 (81/19) |
| Age (mean±SD), y | 60±8 | 61±9 |
| History of hypertension, n (%) | 3 (43) | 55 (52) |
| History of diabetes mellitus, n (%) | 2 (29) | 19 (18) |
| History of ischemic heart disease, n (%) | 1 (14) | 31 (30) |
| History of vascular disease in first degree relative, n (%) | 6 (86) | 74 (70) |
| Current cigarette smoking, n (%) | 5 (71) | 77 (73) |
| Hyperlipidemia,* n (%) | 6 (86) | 89 (85) |

Degree of contralateral ICA stenosis, n (%) 0% to 29% 4 (57) 35 (33) 30% to 69% 2 (29) 21 (20) 70% to 99% 1 (14) 25 (24) 100% 0 (0) 24 (23) 0.15).

*Patients with a history of hyperlipidemia, patients on lipid-lowering drugs, or patients with elevated levels of cholesterol, triglycerides, or high-density lipoprotein cholesterol.

Statistical Analysis

Differences in age, male/female ratio, and degree of contralateral ICA stenosis were investigated with Student t test, \( \chi^2 \) test, or Fisher exact test. Differences in quantitative flow between patient groups and between control subjects and patients were investigated with Student t test. To analyze differences in collateral flow, \( \chi^2 \) test or Fisher exact test was used. \( P<0.05 \) was considered statistically significant.

Results

During follow-up, 7 patients had an ischemic stroke ipsilateral to the symptomatic CAO. Two patients had infarcts in the MCA territory (1 week and 3 years after the MR investigation, respectively). 1 patient had an infarct in the ACA territory (after 7 months), 1 patient had an infarct in the territory of the recurrent artery of Heubner (after 1 month), 2 patients had infarcts in the MCA-ACA border zone (after 3 months and 3.5 years, respectively), and 1 patient had an infarct in the MCA-ACA and MCA-PCA border zone (after 2.75 years). There were no significant differences in male/female ratio, age, vascular risk factors, and degree of contralateral ICA stenosis between patients with and without recurrent ipsilateral ischemic stroke (Table 1). No patients showed evidence of vasculitis, fibromuscular dysplasia, or other intracranial vessel disease on MRA or intraarterial digital subtraction angiography. None of the patients with recurrent ipsilateral stroke had contralateral stroke during follow-up. In patients without recurrent stroke on the side of the symptomatic CAO, 3 had a contralateral stroke.
Patients with recurrent stroke had higher total flow to the brain than patients without recurrent stroke (Table 2; \(P<0.05\)). In addition, they had higher flow in the contralateral ICA (\(P<0.001\)), whereas BA and MCA flow showed no significant differences. Compared with control subjects, patients with recurrent stroke had increased flow in the contralateral ICA (\(P<0.001\)). BA flow was, however, not significantly higher. The increase of contralateral ICA and BA flow resulted in normal-appearing total flow to the brain in patients with recurrent stroke compared with control subjects. In patients without recurrent stroke, no increase of contralateral ICA flow was found compared with control subjects, although BA flow was significantly higher. This resulted in relatively low total flow to the brain compared with control subjects. Both in patients with and without recurrent stroke, flow in the MCAs was significantly lower than in control subjects.

Patients with recurrent stroke more often showed collateral flow via the circle of Willis (Table 3; \(P<0.05\)), which was caused by increased collateral flow via the PCoA (71\% versus 28\%; \(P<0.05\)), rather than by increased collateral flow via the ACoA (86\% versus 50\%; \(P=0.12\)). Patients with recurrent stroke more often had collateral flow via both the ACoA and PCoA (\(P<0.05\)). There were no significant differences in presence of collateral flow via the OA or leptomeningeal collaterals between both patient groups. All 7 ischemic strokes during follow-up occurred in patients with a unilateral ICA occlusion. No recurrent stroke was found in patients with bilateral ICA occlusion (\(n=24\)). In this latter patient group, total flow to the brain, which was given by BA flow, was 285 mL/min (244 to 327 mL/min). This was lower than flow to the brain in control subjects (\(P<0.001\)). In patients with bilateral ICA occlusion, 17 (71\%) had no collateral flow via the circle of Willis; 21 patients (88\%) had collateral OA flow, and 5 of 18 (28\%) patients with suitable angiograms showed leptomeningeal collateral flow.

**Discussion**

The present study has 2 major findings. In the first 6 months after qualifying symptoms occurred, patients with symptom-
atic CAO and recurrent ipsilateral ischemic stroke during follow-up have significantly more flow in the contralateral ICA and significantly more frequently show collateral flow via the circle of Willis, mainly caused by increased collateral PCoA flow, than patients without recurrent stroke.

Our finding that recurrent stroke was associated with relatively high contralateral ICA flow was striking because it is commonly assumed that low flow rather than high flow in major brain feeding arteries is an unfavorable condition in patients with CAO. Possibly, high flow caused easy dislodging of emboli as opposed to low flow, as was hypothesized in the NASCET and European Carotid Surgery Trial. However, this probably did not occur in our patients because those with and without recurrent stroke did not differ significantly in contralateral ICA stenosis. Also, we found no difference in vascular risk factors. Instead, we hypothesize that high ICA flow reflects insufficient collateral blood flow to the supply territory of the carotid arteries. This is likely accompanied by compensatory cerebral vasodilatation to maintain cerebral blood flow. With the contralateral side being a primary source for collateral blood supply, high contralateral ICA flow may indicate that much effort is needed on the contralateral side to supply the occluded side with collateral blood flow. Relatively low flow in the contralateral ICA, as seen in patients without recurrent stroke, may indicate that these patients had quantitatively or qualitatively better-developed intracranial collaterals than patients with recurrent stroke, thus needing less contralateral effort to supply the occluded side with collateral flow. Although it has been suggested that the presence of collateral flow in secondary collaterals such as leptomeningeal anastomoses and the OA may protect against future ischemia, we could not confirm this. Our data suggest that the presence of collateral flow in these pathways does not differentiate between patients with and without recurrent stroke. Possibly, quantitative measurement of secondary collateral flow, instead of our qualitative measurements, can discern significant differences. Although patients with both relatively low and patients with relatively high contralateral ICA flow had approximately the same MCA flow, it may be suggested that a better-developed collateral circulation makes the brain less vulnerable to future emboli or reductions in cerebral perfusion pressure. For example, recruitment of collaterals may be related to normal cerebral blood volume, which carries a relatively favorable prognosis compared with increased cerebral blood volume. Given the absence of recurrent symptoms, patients without recurrent stroke apparently functioned well with the relatively low total cerebral blood flow in the contralateral ICA and BA. We speculate that the brain in these patients adapted well to the carotid occlusion and could stand relatively low blood flow to the brain.

In contrast to our findings, several studies suggested that reduced rather than increased collateral flow via the circle of Willis is related to the occurrence of cerebral ischemia. However, these studies were cross-sectional and investigated the association between collateral flow and qualifying symptoms rather than recurrent symptoms. Prospective studies have shown conflicting results. In patients with CAO, Vernieri et al found that the risk of recurrent stroke decreased if more collaterals were recruited. This discrepancy with our results may be explained by methodological differences because they included both symptomatic and asymptomatic patients, excluded patients with severe (>70%) contralateral carotid stenosis, and investigated symptomatic patients more than 3 months after qualifying symptoms occurred. In patients with severe carotid artery stenosis, the NASCET showed that increased collateral flow via the ACoA, PCoA, or OA was associated with a lower risk of cerebral ischemic events. In patients with more severe obstructive carotid artery disease (ie, those with severe distal ICA narrowing), no such beneficial effect was found. From our data, it may be hypothesized that once the ICA is occluded, the mere presence of collateral flow in the circle of Willis may not suffice to prevent recurrent stroke and even is associated with increased risk of stroke. In particular, the presence of collateral flow in the PCoA may reflect that the brain is hemodynamically severely compromised. This is supported by a previous study showing that patients with Willisian collateral flow had a more impaired perfusion status of the brain if there was only collateral PCoA flow than if there was collateral flow via both the ACoA and PCoA or via the ACoA only. To prevent recurrent stroke, intracranial collaterals in addition to the circle of Willis may be essential.

It should be emphasized that we measured collateral flow via the circle of Willis several months after qualifying symptoms occurred. It has been suggested that cerebral hemodynamics can change over time after qualifying symptoms occurred. Therefore, we cannot judge the relationship between the status of Willisian collateral circulation measured shortly after symptoms and the risk of recurrent stroke. A further limitation of our study is that we did not assess leptomeningeal collateral flow at the same time point as collateral flow in the circle of Willis. To fully appreciate the role of collateral pathways in CAO it would be preferable to investigate these collaterals at the same time.

In conclusion, this study shows that the amount of flow to the brain and intracranial collateral circulation is related to the prognosis of patients with symptomatic CAO. High-volume flow in the contralateral ICA and increased collateral flow via the PCoA may reflect that the hemisphere ipsilateral to the CAO is at risk of recurrent stroke.

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References


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