Angiographically Defined Collateral Circulation and Risk of Stroke in Patients With Severe Carotid Artery Stenosis

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Background and Purpose—Blood supply through collateral pathways improves regional cerebral blood flow and may protect against ischemic events. The effect of collaterals on the risk of stroke and transient ischemic attack (TIA), in the presence of angiographic severe internal carotid artery (ICA) stenosis, was assessed.

Methods—Angiographic collateral filling through anterior communicating and posterior communicating arteries and retrograde filling through ophthalmic arteries were determined in all patients at entry into the North American Symptomatic Carotid Endarterectomy Trial. Kaplan-Meier event-free survival analyses were performed on 339 medically treated and 342 surgically treated patients.

Results—The presence of collaterals supplying the symptomatic ICA increased with severity of stenosis. Two-year risk of hemispheric stroke in medically treated patients with severe ICA stenosis was reduced in the presence of collaterals: 27.8% to 11.3% (P = 0.005). Similar reductions were observed for hemispheric TIA (36.1% versus 19.1%; P = 0.008) and disabling or fatal strokes (13.3% versus 6.3%; P = 0.11). For surgically treated patients, the perioperative risk of hemispheric stroke was 1.1% in the presence of collaterals versus 4.9% when absent. The 2-year stroke risks for surgical patients with and without collaterals were 5.9% versus 8.4%, respectively. Neither comparison in the surgical group was statistically significant. The observed reductions were independent of the degree of ICA stenosis and other vascular risk factors.

Conclusions—Collaterals are associated with a lower risk of hemispheric stroke and TIA, both long term and perioperatively. Angiographic identification of collaterals assists in identifying patients with severe ICA stenosis at lower risk of stroke and TIA. (Stroke. 2000;31:128-132.)

Key Words: carotid stenosis ■ cerebral ischemia ■ collateral circulation ■ risk

Two large clinical trials have demonstrated that the risk of stroke increases with increasing degrees of angiographically defined, symptomatic internal carotid artery (ICA) stenosis.1,2 Subsequent studies have shown that the risk is further modified by other angiographic features, such as plaque ulceration, near occlusion, and intracranial atherosclerotic disease.3–6 Although the cause of stroke is primarily thromboembolic in the presence of severe ICA stenosis, changes in large-artery hemodynamics may also have a role in determining the extent of the infarction.7,8

Cerebral collateral circulation has been reported to alter the risk of stroke.9–12 The identification of collaterals depended on angiography to identify the communications that are made by the anterior communicating (ACoA) and posterior communicating (PCoA) arteries with contributions from retrograde filling of the ophthalmic artery and from leptomeningeal arteries.13 Cerebral angiography has been used as the reference modality in correlating the identification of collateral circulation by transcranial Doppler and MR studies.14–16 Infarcts on CT have been associated with the absence of angiographic collateral pathways.12 Unexpectedly, angiographic demonstration of collaterals, or lack of collaterals, has not been shown to correlate with cerebral perfusion studies.17

Blood supply to regions of the brain through the collateral circulation occurs with increasing severity of ICA stenosis and occlusion. To what extent collaterals modify the risk of stroke, independently of increasing stenoses, is unknown. In patients undergoing carotid endarterectomy, absent or inadequate demonstration of collateral pathways by angiography and transcranial Doppler has been shown to correlate with intraoperative electroencephalographic changes.18–20 Their relationship to an ischemic event is uncertain.

The aim of the present study is to examine and quantify the effect of angiographically visualized collateral pathways that

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supply the hemisphere distal to a severe ICA stenosis on the risk of hemispheric stroke and transient ischemic attack (TIA). Data for this study are taken from the North American Symptomatic Carotid Endarterectomy Trial (NASCET).

Subjects and Methods
NASCET was a multicenter, randomized, controlled trial of carotid endarterectomy in patients with symptomatic ICA stenosis. A total of 2885 patients were enrolled who had a TIA or nondisabling ischemic stroke in the territory of a carotid bifurcation stenosis within 180 days of randomization. Patients were excluded if they had a probable cardiac source of embolism, serious disease likely to cause death within 5 years, or intracranial disease that was judged to be more significant than the surgically accessible carotid bifurcation lesion. Patient baseline characteristics and final results have been reported.\(^1,3\)

Selective angiography, including intracranial views, was performed as part of the entry assessment into NASCET. The principal neuroradiologist (A.J.F.) reviewed the angiograms blinded to all clinical information. All carotid bifurcation stenoses, except those recognized as having angiographic features of near occlusion, were measured at the site of the minimal residual lumen and compared with the diameter of the distal lumen at the point at which the walls become parallel.\(^2,23\) To assess the absence or presence of collateral pathways, biplane (anterior-posterior, lateral, and/or oblique) views were examined. Collaterals were recognized on the angiogram by the contrast filling the ACoA, PCoA, or ophthalmic arteries following a carotid or vertebral injection. The appearance of the collaterals was then graded on a 3-point scale: 1, slight collateral distribution, often next to nil at moderate degrees of stenosis to nearly nil at severe stenosis; 2, some collateral supply (e.g., to anterior cerebral and some middle cerebral arteries); and 3, full collateral filling (e.g., to the middle cerebral artery). For the purpose of the present study, grades 2 and 3 were combined to indicate the presence of collateral pathways. Collaterals were considered absent if they were not visualized on the angiogram or were assigned a grade of 1.

The method of assessing the degree of ICA stenosis used in NASCET begins with the recognition of the near-occlusion state, which is characterized by the physiological reduction in pressure and overall flow through the distal ICA.\(^5,22\) Since the resulting poststenotic reduction in luminal diameter would lead to a misleading calculation of stenosis by the ratio formula for comparing the diameter at the point of greatest narrowing with that of the distal ICA well beyond the bulb where the walls are parallel, NASCET opted not to assign a calculated degree of stenosis for recognized near-occlusion cases.\(^6,22\) Instead, these cases were grouped into a separate category with an arbitrarily assigned value of 95%, representing a very severe stenosis. Clinically, patients with a reduced distal ICA lumen have been reported to have a lower risk of stroke.\(^5,6,23\)

A method to quantify distal ICA luminal diameter reduction has been proposed.\(^5\) This calculation consists of taking the ratio of the distal ICA lumen diameter at the point at which the walls become parallel, to the disease-free portion of the common carotid artery (CCA) lumen diameter. The term “collapse” has been used to designate an ICA/CCA ratio $\leq 0.42$, an indication of severe poststenotic reduction in luminal diameter beyond the normal range of observed ICA/CCA ratios in patients with minimal carotid stenosis.\(^5\)

In the present study the degree of ICA stenosis was calculated only when the ICA/CCA ratio was $\geq 0.42$ and was otherwise designated as “severe distal reduction.”

The primary outcome was the risk of hemispheric stroke at 2 years, ipsilateral to the symptomatic ICA stenosis. The risk of a hemispheric TIA and of a disabling stroke was also calculated. Disabling strokes were defined as having Rankin grades $\geq 3$.\(^3\) The risks were derived from Kaplan-Meier event-free survival curves. Cox proportional hazards regression modeling was used to assess the extent to which the presence of collaterals can predict the risk of stroke, independent of other vascular risk factors.

Results
Among the 2885 patients entered into NASCET, 280 (9.7%) were identified by angiography to have collateral pathways toward the randomized, symptomatic ICA: 195 through the ACoA only, 25 through the PCoA only, 5 retrograde through the ophthalmic arteries only, and 55 with multiple collateral pathways. Figure 1 shows that the percentage of patients with collaterals increases with the degree of ICA stenosis, from next to nil at moderate degrees of stenosis to $>50\%$ at the highest degrees of stenosis ($P<0.001$). Since collaterals were largely a feature of severe ICA stenosis and the number of patients with collaterals in the moderate stenosis categories was small, further analyses were restricted to the 681 patients (339 medically treated and 342 surgically treated) with either 70% to 99% stenosis or severe distal reduction.

Baseline characteristics of the patients are shown in the Table. In general, patients with collaterals were less likely to harbor the risk factors that are associated with stroke. Patients with collaterals were also less likely to have intracranial atherosclerotic disease in comparison to those without collaterals (24.3% versus 42.2%; $P<0.001$).

The risks of a disabling or fatal ipsilateral hemispheric stroke, any ipsilateral hemispheric stroke, and ipsilateral hemispheric TIA are shown in Figure 2 for medically treated and surgically treated patients with and without collaterals. In all analyses, the presence of collaterals was associated with a reduced risk of a hemispheric event in medically treated patients (13.3% versus 6.3%, $P=0.11$ for disabling or fatal stroke; 27.8% versus 11.3%, $P=0.005$ for any hemispheric stroke; and 36.1% versus 19.1%, $P=0.008$ for hemispheric TIA). Correction for the patient characteristics listed in the Table in a Cox proportional hazards regression did not appreciably alter this association. Reductions in risk were also observed in the surgically treated patients but were not statistically significant. The above analyses were repeated when the ACoA was considered alone, with no substantive changes in results.

In a secondary analysis, the 2-year risk of an ipsilateral hemispheric stroke in medically treated patients was ascer-
The risk of stroke approximately doubled for patients with 85% to 99% stenosis in comparison to those with 70% to 84% stenosis. Nevertheless, the presence of collaterals reduced the risk by approximately two thirds in both ICA stenosis categories. Patients in the severe distal reduction group had a lower risk of stroke in comparison to those in the 85% to 99% stenosis category, which was relatively unaffected by the presence of collaterals.

The effect of collaterals on stroke risk was also assessed in patients who underwent carotid endarterectomy (Figure 3). The 2-year risk of stroke was lowest among the surgical patients who had collateral pathways visualized on their preoperative angiogram and 70% to 99% stenosis. This reduced risk was primarily due to a low 30-day hemispheric stroke risk of 1.1%, in comparison to a 4.9% risk for patients without collaterals. In all cases, surgically treated patients with 70% to 99% stenosis had a lower risk of stroke in comparison to their medical counterparts. In contrast, surgical patients in the severe distal reduction group did not appear to have their 2-year stroke risk reduced beyond what was achieved by best medical care alone.

Discussion

The results from the present study suggest that collateral circulation is important in reducing the risk of hemispheric stroke and TIA in patients with symptomatic severe ICA stenosis. This effect is observed across all degrees of severe ICA stenosis except in the case of severe distal reduction. These results confirm the collateral circulation observations of other studies in a larger number of patients with symptomatic ICA stenosis, of whom one half underwent carotid endarterectomy. The reduction in stroke risk in the perioperative period suggests that the observations from the intraoperative electroencephalographic studies are of clinical relevance.

The beneficial effect of collateral circulation in patients with a severe ICA stenosis may be due to improved cerebral perfusion in the presence of collaterals and protection of the brain from small thromboemboli that cause stroke and TIA. Patients were also less likely to have a disabling or fatal stroke, suggesting that the underlying cerebral hemodynam-
Patients with collaterals had fewer of the risk factors associated with stroke than those without collaterals. A previous study has shown that patients with ≥2 collateral pathways were less likely to have a history of hypertension than those with 1 or no collateral pathway. The lower prevalence of hypertension among patients with collaterals in the present study supports this observation.

Several items regarding the generalizability of the present results deserve comment. First, the reduction in stroke risk for both medically and surgically treated patients was demonstrated when the presence of collaterals was defined as the angiographic visualization of ≥1 ACoA, PCoA, or ophthalmic arteries. Other collateral pathways that may be important, such as the leptomeningeal collaterals over the hemispheres, were not considered in the present study because there were too few images over the brain surfaces submitted to the NASCET data office. In addition, there were too few patients and outcome events to consider the PCoA and ophthalmic arteries alone. These limitations may not affect the generalizability of the present results to any great extent, since others have shown that the ACoA may be the functionally most important collateral pathway. The results of the present study support this since the findings were similar when the ACoA was considered alone in the analyses.

Second, it was not possible to fully assess anatomic variability in this study because only selected films from the angiographic sequence were submitted to the NASCET data office. This meant that distinction between some anatomic variation of the circle of Willis and a true collateral pathway was made by the patient’s local treating team. It is unlikely that a systematic bias in deciding which patients had vertebral studies occurred at the treating center, but rather the visualization of collateral pathways may have represented the local practice of cerebral angiography. When the analyses were repeated on the subset of patients who had full bilateral carotid and vertebral studies, the results for the primary outcome of stroke were similar to those reported in the whole group.

In conclusion, patients with collaterals that supply the hemisphere distal to a severe ICA stenosis have a lower risk of stroke and TIA, both disabling and nondisabling, than patients without collaterals. Patients with collaterals supplying the operative side were less likely to have a perioperative stroke. These results applied when the ACoA, PCoA, and ophthalmic sources were considered as a group or when the ACoA was considered alone. Assessing collateral pathways may be helpful in identifying patients with a severe ICA stenosis at a lower risk of stroke and TIA.

Acknowledgments
This study was supported by grant RO1-NS-24456 from the National Institute of Neurological Disorders and Stroke. The authors acknowledge the support of all participants in NASCET and are grateful to SmithKline Beecham for providing Ecorin for all NASCET patients.

References
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*Stroke*. 2000;31:128-132
doi: 10.1161/01.STR.31.1.128

*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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