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Hemodynamic Effect of Carotid Endarterectomy

Torben Schroeder, Henrik Sillesen, and Hans C. Engell

Cerebral blood flow was measured by the intravenous xenon-133 technique at rest and during cerebral vasodilation with acetazolamide in 32 patients before and after uncomplicated carotid endarterectomy. The results were compared with the internal carotid artery perfusion pressure measured during surgery. A significant improvement in side-to-side cerebral blood flow asymmetry occurred in 6 patients studied at baseline and in 11 patients during provoked cerebral vasodilation. These patients all belonged to a group of 14 patients who, in addition to a severe stenosis of the internal carotid artery, presented a reduction in cerebral perfusion pressure of at least 20%. No improvements occurred in 18 patients with no or only minor reduction in perfusion pressure, irrespective of the degree of stenosis. These findings indicate an improved perfusion reserve following carotid endarterectomy in most patients with marked reduction in perfusion pressure, whereas only some of these patients will experience an improvement in baseline cerebral blood flow. (*Stroke* 1987;18:204-209)

WHILE carotid endarterectomy has become one of the most common vascular operations,¹ the hemodynamic effects of the procedure are still not fully clarified, and many issues remain controversial.

Methodologic problems can to some extent explain diverging results. Cerebral blood flow (CBF) may undergo marked fluctuations from measurement to measurement.² Changes in flow resulting from carotid endarterectomy may be obscured by changes due to variations in cerebral metabolism, pharmacologically induced changes, or measurement error. As the noninvasive xenon-133 technique allows simultaneous determination of CBF in both hemispheres, such global variations may largely be eliminated by considering the changes in side-to-side asymmetry.

Conflicting results could also be due to differences between patient series. Patients with carotid artery disease constitute a hemodynamically heterogeneous group. An atheromatous process must cause a diameter reduction of at least 50% before it becomes of hemodynamic importance, i.e., produces a detectable reduction in internal carotid artery (ICA) blood flow.³ Whether perfusion pressure is reduced under these circumstances depends on the collateral circulation. A well developed collateral supply can maintain perfusion pressure within the normal range. If, however, the collateral circulation is impaired in addition to a severe ICA stenosis, a state of hypoperfusion may result, in

which the cerebral perfusion pressure is reduced to near or beyond the lower limit of autoregulation.

Current studies have focused mainly on the angiographic appearance of the ICA without regard to the collateral capacity. Also, few studies have evaluated the changes in perfusion reserve by use of a cerebral vasodilator stimulus. On these grounds, we studied CBF under baseline conditions and during cerebral vasodilation before and after carotid endarterectomy.

Subjects and Methods

The patients selected for this study presented unilateral carotid territory symptoms and underwent uncomplicated ipsilateral carotid endarterectomy. They all had pre- and postoperative CBF measurements performed at rest and after cerebral vasodilation with acetazolamide (Diamox), and the results were related to the ICA perfusion pressure determined during surgery. The procedures were in accordance with the Helsinki Declaration and approved by the regional ethical committee.

The total series comprised 32 patients, 16 women and 16 men, with a median age of 58 years (range, 41–76 years). Patients were classified into two groups according to the preoperative aortic arch arteriography. Group 1 comprised 8 patients with <50% stenosis of the operated ICA, determined as the maximal biplane diameter reduction as percent of the normal ICA diameter. Group 2 contained 24 patients with stenosis of 50% or more.

All patients were evaluated by a neurologist before and after endarterectomy. Any neurologic deficit lasting more than 24 hours was considered a stroke. Transient ischemic attacks (TIA's) referring to the relevant carotid territory were the only preoperative symptoms in 16 patients. Three had suffered a stroke with subsequent TIA, and 13 patients had suffered a stroke only. In 2 patients the TIA's were posturally provoked. All stroke patients had made good functional recovery, leaving no detectable deficits in 5 and minor to moderate nondisabling deficits in 11 patients. The median time between the latest neurologic event and surgery

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was 13 weeks (range, 7–132 weeks) for strokes and 7 weeks (range, 1 day–32 weeks) for TIA's.

Preoperative computer tomography (CT scan) showed no signs of infarction in 18 patients. A hypodense area, taken as an infarction, was seen in the ipsilateral hemisphere in 12 patients and bilaterally in 2. Ipsilateral infarction was seen in 11 of 16 (69%) stroke patients and in 3 of the 16 (19%) patients who had experienced TIA's only. Three (38%) patients of Group 1 and 11 (46%) patients of Group 2 had ipsilateral infarction.

CBF Measurements

All patients were studied 1–5 days prior to surgery and again within the first postoperative week (median, 5 days after surgery). Late postoperative studies were carried out in 11 patients (median, 77 days after endarterectomy). Each CBF study consisted of 2 measurements performed with the patient in supine position in a quiet room. After baseline measurement, 1 g of acetazolamide was given i.v., and 20 minutes later the CBF measurement was repeated.

CBF was measured with the i.v. xenon-133 technique using a mobile 10-detector unit (Novo Cerebrograph 10a).⁴ Five detectors were positioned over each region of the middle cerebral artery (MCA). After bolus injection of 10–20 mCi xenon-133 in saline into an antecubital vein, the clearance was recorded throughout 11 minutes. Air samples were drawn continuously from a tight-fitted face mask for estimation of the arterial input function and for end-tidal P_{CO_2} determination with an infrared capnograph. The arterial blood pressure was registered with each study.

Data were analyzed according to a bicompartimental model including a correction term for the air passage artifact.^{4,5} This method of reducing the influence of radiation originating from air passages made it possible to utilize the entire clearance curve. CBF was expressed by a noncompartmental flow index, calculated as the monoexponential slope between 30 and 90 seconds of the deconvoluted clearance curve times the blood-to-tissue partition coefficient, λ , set to 1.0 ml/g.

In each study the 5 regional flow values were averaged as the hemispheric CBF, and the relative side-to-side asymmetry was calculated as the difference between CBF in the asymptomatic, contralateral and the symptomatic, ipsilateral hemisphere as percent of mean CBF. Reproducibility studies with this equipment have shown that changes in hemispheric CBF from one study to another exceeding ± 9 ml/100 g/min and changes in side-to-side asymmetry exceeding $\pm 7\%$ are significant at the 5% level.⁴ Correction for CO_2 changes was not performed.

Intraoperative Measurements

Endarterectomy was performed under halothane anesthesia at hypocapnia with an arterial P_{CO_2} of 30 ± 3 mm Hg (\pm SD). Before clamping of the ICA, blood pressures across the stenosis were measured through a 21 G cannula connected via manometer line to a pressure transducer (Siemens Elema E33). We calculated a

cerebral perfusion pressure index (CPPI) as the ratio of the distal mean pressure to the proximal mean pressure (Figure 1). The ICA mean pressure was also measured after ICA clamping (stump pressure). For reference, direct radial artery blood pressure was recorded. Blood flow through the ICA was measured before and after reconstruction by an electromagnetic flowmeter (Nycotron 372).

Statistical Methods

Differences between 2 samples were compared with the Wilcoxon or Mann-Whitney rank test. When 3 samples were analyzed, the Newman-Keuls multiple range test was applied.⁶ Differences between proportions were compared with Fisher's exact test and χ^2 test. Correlation was assessed by means of the Spearman coefficient of rank correlation, ρ . All tests were performed two-tailed. Since each subset of results involved 3–6 comparisons, the Bonferroni method was applied to each subset, taking account of multiplicity.⁷ For convenience, significance was taken as $p < 0.01$ throughout the study. The calculations were performed on a Digital PC 350 computer.

Results

Clinical Results

None of the patients developed postoperative neurological complications. In patients with frequent TIA's up to the time of surgery, the attacks stopped after endarterectomy. Of the 11 patients with persistent preoperative neurological deficits only 1 improved clinically within the first postoperative week.

ICA Pressure and Flow

The 8 patients of Group 1, with $< 50\%$ ICA stenosis, all had high CPPI's, averaging 0.97 (range, 1.0–0.94), and the ICA flow did not change significantly after endarterectomy (Table 1). In Group 2 CPPI's were significantly lower ($p < 0.001$), averaging 0.72, but a great scatter was noticed (range, 1.0–0.36). After endarterectomy ICA flow doubled in this group ($p < 0.001$). Among patients of Group 2, the CPPI was not significantly correlated with the degree of ICA stenosis ($\rho = -0.3$; $p > 0.1$).

Seven of 14 (50%) patients with CPPI below 0.8 had

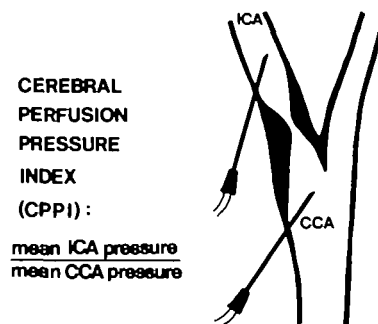


FIGURE 1. The cerebral perfusion pressure index, determined during endarterectomy before clamping of the vessels. ICA, internal carotid artery; CCA, common carotid artery.

Table 1. Internal Carotid Artery Pressure and Blood Flow

	Group 1: stenosis <50% (n = 8)	Group 2: stenosis >50% (n = 24)
Cerebral perfusion pressure index	0.97 ± 0.02	0.72 ± 0.20
Stump pressure (mm Hg)	59 ± 14	52 ± 25
ICA flow before reconstruction (ml/min)	173 ± 46	92 ± 75
ICA flow after reconstruction (ml/min)	165 ± 41	203 ± 124

Values are mean ± SD.

ipsilateral infarction on CT scan, and the CPPI was equal in patients with and without infarction (average, 0.84 vs. 0.82; $p > 0.2$).

CBF Studies

The pre- and postoperative blood pressure and end-tidal PCO_2 for all studies were unchanged (Table 2). Acetazolamide induced a significant reduction in end-tidal PCO_2 , whereas the arterial blood pressure was unchanged. Within the first postoperative week hemoglobin was reduced from 9.0 to 8.3 mmol/l ($p < 0.001$).

PREOPERATIVE CBF. The baseline hemispheric CBF and side-to-side asymmetry did not differ significantly between groups (Table 3). In the total series, cerebral vasodilation with acetazolamide increased the ipsilateral hemispheric CBF by 46% and contralateral CBF by 51%. In Group 1 vasoreactivity was of the same order of magnitude in the two hemispheres, thus any side-to-side asymmetry remained unchanged during acetazolamide. In the Group 2 patients vasodilation caused a lower CBF response in the ipsilateral hemisphere, resulting in a significant enhancement of side-to-side asymmetry, from 5 to 10% ($p < 0.01$). This asymmetry enhancement was significantly correlated with CPPI ($\rho = -0.6$; $p < 0.001$), whereas the enhancement was unrelated to the presence of ipsilateral infarction on the preoperative CT scan ($p > 0.2$).

EARLY POSTOPERATIVE CBF. For the series as a whole, baseline CBF increased by nearly 10% ($p > 0.01$), and baseline asymmetry declined from 4 to 2% ($p > 0.01$) (Table 3).

The individual changes in baseline asymmetry are related to CPPI in Figure 2. A definite improvement in baseline asymmetry, defined as a decrease of at least 7% (2 SD), occurred in 6 patients, including the 2

patients with orthostatic TIA's: 4 of 8 patients with CPPI below 0.7 improved, as did 2 of 6 patients with CPPI between 0.7 and 0.8. None of the 8 patients of Group 1 or the 10 patients of Group 2 with CPPI exceeding 0.8 showed significant changes in baseline asymmetry ($2 \times 3 \chi^2$ test; $p < 0.01$). The individual changes of hemispheric CBF were not related to the degree of hemodynamic impairment ($p > 0.2$).

Five of 14 (36%) patients with infarction on CT scan had significant improvement in baseline asymmetry, while only 1 of 18 (6%) without infarction showed such improvement ($p > 0.1$).

A postsurgical increase of acetazolamide CBF was observed in the series as a whole ($p < 0.001$). A minor, bilateral increase occurred in Group 1, whereas in Group 2 a more marked improvement appeared, most pronounced in the ipsilateral hemisphere (Table 3). Hence the CBF asymmetry during vasodilation was significantly reduced from 10 to 2% in Group 2 ($p < 0.001$), indicating an improved ipsilateral perfusion reserve.

The individual results are correlated with CPPI in Figure 3. A significant decrease of CBF asymmetry after acetazolamide occurred in 11 patients, including 5 of the 6 patients who had definite improvement of baseline asymmetry: all 8 patients with a CPPI below 0.7 and 3 of 6 patients with CPPI between 0.7 and 0.8. In none of the patients of Group 1 or Group 2 with CPPI exceeding 0.8 did definite changes occur, as was the case in the baseline studies ($2 \times 3 \chi^2$ test; $p < 0.001$). Looking instead at the individual changes in hemispheric CBF, these were largely identical to the asymmetry changes (Figure 4). However, the greater scatter made individual interpretation difficult.

The relation between improvement in asymmetry during vasodilation and the presence of infarction on the preoperative CT scan was not significant: 6 of 14 (43%) patients with infarction and 5 of 18 (28%) patients without infarction showed improvement of CBF asymmetry ($p > 0.2$).

LATE POSTOPERATIVE CBF. Eleven patients, 2 in Group 1 and 9 in Group 2, were studied two times after surgery. The significant increase in hemispheric CBF seen in the early postoperative measurements in these patients at baseline conditions as well as after acetazolamide had largely disappeared at the time of the late studies (Table 4). Looking instead at the side-to-side asymmetry, a significant reduction was seen in 2 patients at the baseline study and in 7 patients after aceta-

Table 2. Arterial Blood Pressure and End-tidal Carbon Dioxide Tension

	BP			PCO_2		
	Preoperative (n = 32)	Postoperative within 1 week (n = 32)	Postoperative 2-3 months (n = 11)	Preoperative (n = 32)	Postoperative within 1 week (n = 32)	Postoperative 2-3 months (n = 11)
Baseline	105 ± 15	102 ± 15	108 ± 8	40 ± 5	39 ± 6	39 ± 5
Acetazolamide	105 ± 11	106 ± 12	109 ± 9	35 ± 3	33 ± 5	35 ± 2

Baseline vs. acetazolamide: not significant for blood pressure; $p < 0.001$ for PCO_2 .

Pre vs. postoperatively: not significant for blood pressure or PCO_2 .

Values are mean ± SD mm Hg.

Table 3. Hemispheric CBF and Side-to-Side Asymmetry Measured Prior to and Within 1 Week After Carotid Endarterectomy in 32 Patients

	Group 1 (n = 8): stenosis <50%		Group 2 (n = 24): stenosis >50%	
	Pre	Post	Pre	Post
<i>Baseline</i>				
Operated side	39 ± 8	39 ± 4	38 ± 7	42 ± 10*
Contralateral	40 ± 8	40 ± 4	41 ± 7	42 ± 9
Asymmetry	1 ± 4	3 ± 6	5 ± 7	1 ± 5*
<i>Acetazolamide</i>				
Operated side	60 ± 5	64 ± 4	54 ± 12	63 ± 13†
Contralateral	61 ± 7	64 ± 7	60 ± 12	64 ± 13
Asymmetry	2 ± 4	1 ± 6	10 ± 12	2 ± 5†

Values are ml/100 g/min CBF and % asymmetry, mean ± SD.
* $p < 0.01$; † $p < 0.001$ compared with the preoperative results.

zolamide, and in all cases these improvements were maintained at the time of the late study. Thus, although hemispheric CBF seemed to return to preoperative levels, the relative flow gain in terms of diminished side-to-side asymmetry was maintained both at baseline conditions and following vasodilation (Table 4).

Discussion

In an early study Engell et al⁸ reported an increase in ICA flow to be the main hemodynamic effect of carotid endarterectomy. The concomitant changes in CBF were less pronounced, indicating a redistribution of cerebral blood supply. Yet, patients with a minimal ICA flow due to subtotal ICA occlusion showed a marked CBF increase just after reconstruction. Similar results were reported by Sundt et al,⁹ whereas others have not been able to demonstrate any change in CBF measured immediately after surgery.^{10,11} Measurements of CBF days to weeks after surgery have also rendered conflicting results. Some found no

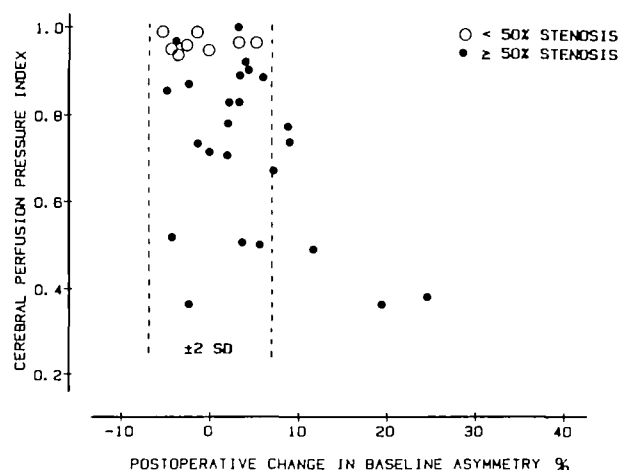


FIGURE 2. Postoperative change in baseline side-to-side asymmetry related to cerebral perfusion pressure index. Positive values denote a decrease in CBF asymmetry. The dashed lines cut off 2 standard deviations: $\pm 7\%$.

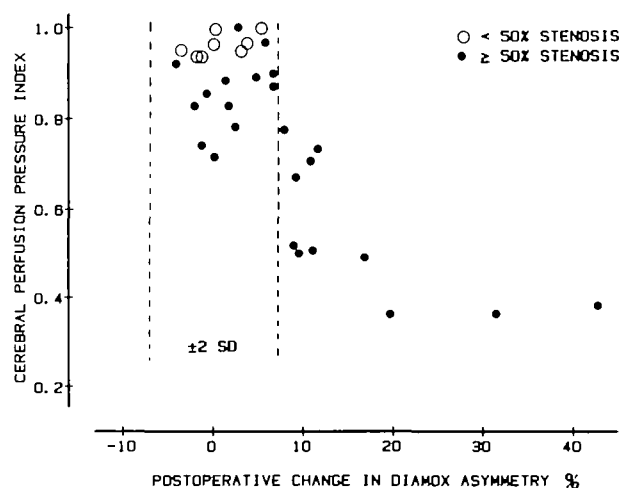


FIGURE 3. Postoperative change in side-to-side asymmetry during vasodilation with acetazolamide (Diamox) related to cerebral perfusion pressure index. Positive values denote a decrease in flow asymmetry. The dashed lines cut off 2 standard deviations: $\pm 7\%$.

change,^{12,13} while others reported a moderate to marked increase.^{14–16}

In the present study a minor though significant increase in hemispheric CBF was observed within the first postoperative week. However, this improvement was largely unrelated to the degree of preoperative hemodynamic impairment, and in the late studies the global flow increase had disappeared or diminished considerably (Table 4). A temporary increase in CBF has also been reported following extra-intracranial (EC-IC) bypass surgery^{17,18} and may be what remains of the transient cerebral hyperemia reported immediately following endarterectomy.^{19,20} Also, the hemodilution observed in the present study may in part account for a global flow increase,²¹ though no correlation was found between decrease in hemoglobin and increase in CBF.

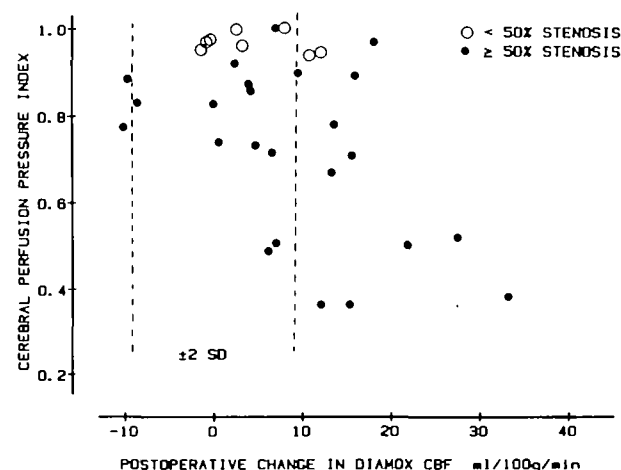


FIGURE 4. Postoperative change in ipsilateral hemispheric CBF during vasodilation with acetazolamide (Diamox) related to cerebral perfusion pressure index. The dashed lines cut off 2 standard deviations: ± 9 ml/100 g/min.

Table 4. Hemispheric CBF and Side-to-Side Asymmetry Measured Before, 1 Week, and 2 Months After Carotid Endarterectomy in 11 Patients

	Preoperative	Postoperative	
		Early	Late
<i>Baseline</i>			
Operated side	38 ± 8	45 ± 12*	41 ± 7
Contralateral	39 ± 8	45 ± 11	40 ± 7
Asymmetry	5 ± 9	1 ± 3	0 ± 3
<i>Acetazolamide</i>			
Operated side	54 ± 11	67 ± 14†	60 ± 12
Contralateral	59 ± 9	67 ± 14	60 ± 13
Asymmetry	9 ± 14	0 ± 4*	0 ± 2*

Values are ml/100 g/min CBF and % asymmetry, mean ± SD.

* $p < 0.01$, † $p < 0.001$ compared with the preoperative results.

Although no overall difference in end-tidal PCO_2 or blood pressure occurred between the pre- and postoperative studies, individual variation may contribute to the marked variation in global CBF generally observed in repeated studies, thus making the postoperative changes in absolute flow values difficult to interpret.² The side-to-side asymmetry, being considerably more reproducible, provides a more specific measure of the hemodynamic changes.⁴ In this study a significant improvement of baseline asymmetry was observed in 6 patients, all having at least a 20% reduction of perfusion pressure. Using xenon-133 inhalation and tomography, Vorstrup et al²² found a relative increase of CBF in the low-flow area in only 2 of 14 patients who underwent carotid endarterectomy. Similar results are reported in a recent study from the same group.²³ These data suggest an unchanged baseline CBF in the majority of cases, in agreement with the original perioperative findings of Boysen.²⁴ Improvements of baseline CBF indicating a reversible preoperative state of hypoperfusion, during which maximal vasodilation had occurred, may be expected in only approximately 10% of the patients. The 2 patients in the present series with orthostatic TIA's belonged to this subgroup as indicated by the disappearance of orthostatic symptoms after endarterectomy. One of these patients demonstrated within the first postoperative week a mild but definite improvement in a previous neurologic deficit. Such immediately reversible deficits are reported only occasionally. However, Spetzler et al²⁵ have recently been able to directly correlate low MCA perfusion pressure with the occurrence of neurologic improvement after EC-IC bypass surgery.

As the existence of a state of reversible hypoperfusion would strengthen the indication for carotid endarterectomy, it is of importance to identify such cases. Measurements of CBF during baseline conditions provide no information on flow capacity.²⁶ A unilateral reduction in CBF, manifested as a side-to-side asymmetry, may indicate a restricted blood supply. More often though, it reflects a diminished metabolic demand due to ischemic tissue damage.²² Studies of cerebral blood volume or cerebral metabolic rate by posi-

tron emission tomography have been proposed for identification of patients with hypoperfusion.^{27,28} However, these techniques are more complicated than enhancing the hemodynamic effect of localized arterial disease by the use of a potent vasodilator. For this purpose we have used the carbonic anhydrase inhibitor acetazolamide as originally proposed by Lassen.²⁹ In a previous study we have found that most patients with severely reduced perfusion pressures could be identified by considering the enhancement of side-to-side asymmetry after cerebral vasodilation with acetazolamide.³⁰ These results are given further support in the present study by the finding of a significant correlation in the preoperative measurements between asymmetry enhancement and CPPI and by the lack of correlation between asymmetry enhancement and CT infarction.

Although no untoward effects of acetazolamide were observed in this study, the potent and long-lasting action makes acetazolamide less suitable for further studies during the hyperemia of the early postoperative period. Instead, inhalation of 5% CO_2 , though more cumbersome to administer, can be recommended for future studies as it induces a vasodilation of the same order of magnitude as 1 g of acetazolamide, but can be withdrawn immediately.³¹

The change in vasoreactivity after endarterectomy has been reported in two earlier studies,^{11,16} both pointing to an increased reactivity in patients with severe stenotic lesions, but containing too few observations to allow statistical verification. Halsey et al³² studied CBF and CO_2 vasoreactivity after EC-IC bypass. They concluded that the surgery did not affect the resting CBF, but did augment the collateral reserve in those patients in which it had been most severely impaired by the arterial lesion. In the present series a significant improvement occurred in the group of patients with stenoses of 50% or more, provided they also had an impaired collateral supply as defined by a CPPI below 0.7 (Figure 3). Thus, no increase in perfusion reserve can be expected in patients with no or only minor reduction of perfusion pressure, irrespective of the degree of ICA stenosis.

It may be questioned whether the difference seen between patients could in part be due to the presence of infarcted brain tissue. Since the time between the latest stroke and surgery was 13 weeks on average and at least 7 weeks, it appears unlikely that results ascribed to surgery were simply caused by resolution of luxury perfusion or diaschisis. Moreover, in patients with infarction on CT scan the CBF asymmetry was improved only if CPPI was reduced as well. This clearly indicates that improvement of perfusion reserve was related to the degree of hemodynamic compromise rather than the presence of CT infarction.

In the present study we used the ratio of distal to proximal blood pressure measured before clamping of the vessels as an indication of cerebral perfusion pressure. Since pressures were measured during halothane anesthesia and hypocapnia, the pressure reduction across the ICA stenosis was systematically underestimated.³⁰ On the other hand, conditions were approxi-

mately equal for all patients. The influence of anesthesia and hypocapnia therefore do not invalidate the interpretation of our results.

Though an immediate beneficial effect of an increased perfusion reserve is not apparent in most cases, it should be kept in mind that the two pathophysiological mechanisms thromboembolism and hypoperfusion are not mutually exclusive. Areas of brain tissue functioning on a marginal perfusion appear to be more susceptible to the effect of microembolism.⁹ Hence, patients with a severely reduced cerebral perfusion pressure represent a group most likely to benefit from carotid endarterectomy, although they may carry a greater risk of postoperative neurologic complications.

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KEY WORDS • carotid artery surgery • cerebrovascular circulation • perfusion reserve • acetazolamide