Evaluation of the Cerebral Vasodilatory Capacity by the Acetazolamide Test Before EC-IC Bypass Surgery in Patients with Occlusion of the Internal Carotid Artery

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SUMMARY  Cerebral blood flow (CBF) was measured by xenon-133 inhalation tomography in 18 patients with cerebrovascular disease before and 4 months after extracranial-intracranial bypass surgery. Only patients who showed a reduced CBF in areas that were intact on the CT scan and relevant to the clinical and angiographical findings were operated. The majority of the patients had suffered a minor stroke with or without subsequent transient ischemic attacks. They were studied at least 6 weeks following the stroke. All patients had an occlusion of the relevant internal carotid artery.

To identify preoperatively the patients with a compromised collateral circulation and hence reduced CBF due to reduced perfusion pressure, a cerebral vasodilatory stress test was performed using acetazolamide (Diamox®). In normal subjects, Diamox has been shown to increase tomographic CBF without change of the flow distribution. In the present series 9 patients showed a significant redistribution of flow in favor of the non-occluded side ("positive" Diamox test). Two of these 9 patients showed even a paradoxical decrease in focal CBF preoperatively, i.e., a "steal" effect. These 2 patients were the only patients who improved in focal CBF after shunting. The remaining 9 patients all showed uniform flow responses ("negative" Diamox test), and none of these increased in focal CBF postoperatively. The finding of an unchanged flow map postoperatively confirmed that the low flow areas were not due to restricted flow via collateral pathways. However, an increase in the regional vasodilatory capacity was observed postoperatively in the majority of patients.

THE RECENT PUBLICATION of the large multicenter study on the clinical effects of extracranial-intracranial (EC-IC) bypass surgery has clearly demonstrated that the establishment of an additional collateral in patients with occlusive cerebrovascular disease does not improve the outcome of these patients as compared to a control group. This was true both for the incidence of transient ischemic attacks (TIA) and major strokes, as well as the mortality rate on the observation period, and furthermore, it was not possible in this study to identify any subgroups in whom the shunting procedure improved the outcome.

These results are in keeping with our previously reported finding that EC-IC bypass surgery only in a very small number of patients will increase CBF postoperatively. In that study, CBF was measured using xenon-133 inhalation and emission tomography before and 3 months after the EC-IC bypass procedure. 20 of the 22 patients had no postoperative increase in CBF indicating, that despite the occlusion of major precerebral and cerebral arteries a high proportion of the patients had adequate collateral capacity for maintenance of resting CBF at the level required by local metabolism. The remaining 2 patients showed a significant CBF increase following the shunting procedure. These patients may be presumed to have inadequate collateral capacity. They would appear to belong to a subgroup that could benefit by revascularization procedures. Baron et al. originally described one such patient who was studied by positron emission tomography and introduced the term "misery perfusion" for the finding of a decreased CBF concomittant with an augmented oxygen extraction. Similar single case observations have been reported by other authors. 4, 6

The aim of the present study was to identify preoperatively the patients having a reduced CBF due to a compromised collateral circulation, i.e. a "chronic hemodynamic insufficiency." For this purpose, the cerebral vasodilatory capacity was tested using an intravenous injection of 1 gram of acetazolamide (Diamox), a drug which increases CBF but leaves cerebral metabolic rate for oxygen unchanged. It was a priori assumed, that in the regions having an inadequate collateral supply and hence, a reduced perfusion pressure, some arteriolar vasodilation would be present already in the resting state. In such regions it could be expected that the administration of a potent cerebral vasodilator would cause a reduced CBF response. The paper discusses the use of these CBF responses for the identification of patients with a restricted collateral capacity.

Patients

A consecutive series of 18 patients aged 41 to 67 years (mean 54 years) with symptoms of occlusive cerebrovascular disease treated with an EC-IC bypass anastomosis were included in this study. Selection for surgery was based on the clinical symptoms and the findings on the angiogram, the CT scan and the tomographic CBF measurement. Twelve patients had suffered a minor stroke; eight of these 12 patients had subsequent TIAs. Four patients had suffered a moderate or severe stroke with manifest residual symptoms. All the stroke patients were studied at least 6 weeks...
after their stroke. Two patients had suffered TIAs only. Detailed questioning about symptomprovoking factors revealed that none of the patients had hemodynamic TIAs, i.e. very brief ischemic symptoms provoked by positional changes, and distal embolism was therefore considered as the most likely pathogenetic mechanism.

All patients had occlusion of the internal carotid artery (ICA) ipsilateral to the symptomatic hemisphere. Several patients also showed arteriosclerotic lesions of other extracranial cerebral vessels as well, but only three patients showed severely stenosing lesions of the contralateral ICA, i.e. a luminal diameter less than 1.5 mm.9 10

A hypodense lesion was seen on the CT scan in all patients except one. As the CBF measurement was used to select the patient for EC-IC bypass, all patients were required to have a reduced flow in CT intact areas in accordance with the clinical and angiographical findings.

Six patients had suffered from mild or moderate hypertension for some years, but their blood pressure was kept at acceptable levels with appropriate therapy. One patient had a mild diabetes mellitus. Some patients were treated with thrombocyte aggregation inhibitors (low dose salicylate), and some received oral anticoagulants.

Study Protocol

The CBF measurements performed pre- and postoperatively included a test of the cerebral vasoreactivity. After the baseline study, 1 gram of acetazolamide (Diamox) was injected intravenously, and CBF repeated 15–20 minutes later. In our age-matched normal material, the mean CBF increase ranged from 13% to 46% following Diamox. In the present material, we therefore required a CBF increase of at least 13% in one of the hemispheres to ensure an adequate vasodilatory stimulus.

The postoperative CBF measurement was performed in average 4 months (range 2–6 months) after surgery. In 3 patients where contralateral neck vessel surgery was performed as well, the time interval between EC-IC bypass and vascular reconstruction on the neck ranged from 4 to 8 weeks. The follow up CBF measurement thus allowed evaluation of the effect of both procedures combined.

Postoperative angiography was performed in 15 patients in average 4 months after surgery. The angiograms were graded from 0 to 3 on the extent of MCA-filling: Grade 0, bypass unvisualized; grade 1, a single branch of the MCA is filled through the bypass; grade 2, two or three branches are filled; and grade 3, a major part of the MCA territory is filled through the shunt.

CBF Measurements

CBF was measured by xenon-133 inhalation and single photon emission computer tomography (Tomomatic 64). The equipment has been described in detail previously.11 12 By rapid rotation of four collimated detector banks, a sequence of 4 tomographic pictures of 3 slices of brain tissue is recorded, and displayed in a 32 × 32 pixel matrix. One study lasts 4.5 minutes, during which xenon-133 is inhaled the first 1.5 minutes. A single narrowly collimated detector monitors the lung curve, which is used as input-function to the brain. The sequence of pictures together with the input curve is used to derive a scaling constant, and CBF is then calculated for every pixel from the scaled early picture, i.e. the sum of the 2 first tomograms of each slice.13 The resolution is 1.5 to 1.7 cm in the plane and 2 cm axially (FWHM).

The patients were studied in the supine, resting state with eyes closed at a constant, but somewhat elevated noise level from the tomograph. By use of an inflatable cuff, the patient's head was centered in the aperture of the instrument and the neck positioned such that the three slices of brain tissue corresponded to the planes 1 cm, 5 cm, and 9 cm (slice 1, 2 and 3, respectively) above the orbito-meatal plane. Accurate repositioning at repeated CBF studied within the same day is possible by use of marking lines on the patient's face.

End-expiratory pCO 2 (FeCO 2) was measured before, during and just after every CBF measurement using an infrared capnograph.

The arterial blood pressure was measured by use of an arm-cuff and auscultation, and was recorded immediately after termination of every CBF measurement.

Data Analysis

Calculation of mean CBF in a given region was performed by the computer after encircling the region. This yielded the average flow value in the region of interest (ROI) as well as the average flow value in a symmetrically placed region in the contralateral hemisphere. Positioning of the ROI was performed on the flow map from the initial study, and CBF values for the similar ROIs were then calculated from all successive CBF studies. Direct comparison with the same level on the CT scan allowed delineation of hypoperfused area where no focal CT lesions were seen. The size of the ROI ranged from 15.4 cm 2 to 31.4 cm 2, in average 20.4 cm 2. The degree of side-to-side asymmetry, D, was evaluated by an asymmetry index: The difference of CBF in the symmetrical ROIs calculated in percent of the higher value. This variable was used to assess the changes in the flow distribution.

The statistical analysis of these data has previously been described in detail.2 In that study, the variance of D was calculated from repeated measurements in patients with stable cerebrovascular disease. By use of the variance obtained from this material, the effect of EC-IC bypass surgery on D could be estimated by testing for the difference between 2 means.14 Thus, in patients with 2 preoperative baseline studies and 1 postoperative study, a change in D of more than 10 is required to reach statistical significance (p < 0.05).

Similar calculations performed on the absolute values show, that a change of more than 10 ml/100g/min in mean flow in the ROI was required to reach a significant level (no corrections for changes in FeCO 2 were made).
Clinical Changes Following Surgery

In none of the patients who had fixed neurological deficits before shunting was significant improvement of the clinical symptoms noted, neither immediately after surgery nor at the follow-up 4 months later.

Eleven patients had suffered TIAs preoperatively. After the early postoperative period (see below), one patient had TIAs postoperatively. These TIAs were similar to the preoperative ones and were considered of embolic type.

Complications Ascribed to the EC-IC Bypass Procedure and Postoperative Angiography

In the immediate postoperative period, two patients (no. 4 and 9) showed aggravation of their neurological symptoms, but both recovered to their habitual state within 2 days. Another 3 patients showed accumulation of small amounts of cerebrospinal fluid in the wound. One patient (case 3) had a moderate fever lasting several weeks without any clinical explanation.

Postoperative angiography was performed in 15 of the patients. Thirteen of these showed a patent shunt, yielding a patency rate of 87%. Variable filling of the territory in 3 patients. In the remaining 3 patients where postoperative angiography was not performed, a well-functioning shunt was assumed on the finding of a large pulsating vessel at the border of the craniotomy. At follow-up 3 years later, patency was confirmed by a Doppler investigation in 2 of these 3 patients.

The Diamox Test and the Mean Arterial Blood Pressure (MABP)

(MABP) was unchanged following Diamox. Preoperatively, the values were 114 ± 14 (SD) mm Hg before and 115 ± 16 mm Hg 20 minutes after Diamox. Postoperatively, the values were 120 ± 20 mm Hg and 119 ± 14 mm Hg, respectively.

CBF Results

Based on the degree of the asymmetry enhancement at the preoperative Diamox test, the material could be classified in 2 groups having either a “positive” or a “negative” Diamox test.

Patients With a “Positive” Diamox Test (n = 9)

At the preoperative Diamox test, 9 patients (case 1–9) showed a significant redistribution of flow as indicated by an enhancement in the side-to-side asymmetry which ranged from 12% to 30% (fig. 1a). In all these cases, flow was redistributed in favor of the hemisphere with the patent ICA.

The CBF response in the ROI in the affected hemisphere ranged from −11% to 20%, in average a 6% increase (calculated as percent change from the baseline value). Two patients (case 3 & 4) showed a decrease in focal CBF after Diamox, with changes of −8% and −11% below the baseline value, respectively, whereas 3 patients had essentially unchanged CBF in the ROI (fig. 2). One patient (case no. 9) underwent unsuccessful surgery, and his postoperative data have for this reason been omitted from the analysis of the effect of the shunt procedure.

At the postoperative Diamox test, an augmented CBF response in the ROI was seen in all cases except one. The CBF increase in the ROI averaged 17%, ranging from 6% to 30% (fig. 1b). This increase in regional vasoreactivity was statistically significant (p < 0.05, Wilcoxon test for pair differences). Correspondingly, enhancement of the side-to-side asymmetry at the postoperative Diamox test was lessened in all but one.

EC-IC bypass effect upon resting CBF. Only two patients in this group, case 3 and 4, showed a significant CBF increase in the ROI as evaluated by the change in side-to-side asymmetry. Case 3 showed a reduction in asymmetry from 49% to 24%, and case 4 a reduction from 20% to 6%. These two patients were the only ones who had shown a CBF decrease at the preoperative Diamox test.

Patients With a “Negative” Diamox Test (n = 9)

Nine patients (cases 10–18) showed non-significant changes in the regional flowdistribution at the preoper-
Preoperative Diamox test (fig. 1a). The CBF response after Diamox in the ROI in the affected hemisphere taken as a percent of the baseline values averaged 20%, ranging from 7% to 32%. Following surgery (which was unsuccessful in one, case 18 who was excluded from analysis), the Diamox response for the same ROI averaged 23%, ranging from 11% to 55%, an insignificant change. Six of the 9 patients showed an augmented response (fig. 2).

EC-IC bypass effect upon resting CBF. No patients in this group showed a reduction in CBF asymmetry following shunting (fig. 1b).

Patients With Successful Shunting (n = 16)
Considering all the patients together who underwent successful surgery, a significant augmentation of the Diamox induced flow response was seen in the ROI postoperatively, (i.e. p < 0.05 when using the Wilcoxon test for pair differences).

Case Story
This 67 year old man (case 3) suffered a minor stroke with a right sided hemiparesis and aphasia, which gradually subsided. Two weeks later the patient had a TIA of embolic type with aphasic symptoms lasting some hours. The CT scan showed a cortical/subcortical infarct in the left parietal lobe. Angiography showed occlusion of the left ICA with retrograde filling of the ophthalmic artery, and moderate stenosis (3 mm in diameter) of the right ICA. A left-sided EC-IC bypass anastomosis was performed.

Preoperatively, the CBF measurement showed a decreased flow in the territories of the left MCA with a side-to-side asymmetry of about 20%. After Diamox, enhancement of the side-to-side asymmetry to 38% was seen (fig. 3). After Diamox CBF decreased in the left MCA and also in the territories of both ACAs. This was taken to indicate a reduced perfusion pressure in this region. Postoperatively, the degree of side-to-side asymmetry in the ROI was reduced from 20% to 6% and the Diamox test no longer induced any marked change in the flow pattern. The postoperative angiogram showed a well functioning anastomosis, grade 3.

Discussion
It is generally accepted that most TIAs are caused by distal embolism due to fragmentation of thrombotic material. Following occlusion of the ICA, ipsilateral episodic ischemic events may still occur and even in these patients, cerebral embolism has been shown to be the more common pathogenetic mechanism. But, in a smaller group of ICA occlusion cases the collaterals are less efficient and hemodynamic TIAs may develop, in particular but not exclusively those provoked by sudden standing up. It has long been realized, that patients suffering hemodynamic TIAs should be sought among the patients having multiple severely stenosing or occluding vascular lesions. Autopsy studies of the cerebral arteries have shown that a high proportion of patients have anatomical variations.
FIGURE 3. Case 3 suffered a minor stroke and a TIA from the left hemisphere. Angiography showed an occlusion of the left internal carotid artery and the CT scan showed a small infarct in the left parietal lobe. The preoperative tomographic flow map showed a reduced flow in both slice 2 and 3 in most parts of the left hemisphere and in the frontal lobe of the right hemisphere as well. For the ROI indicated by the stippled line, the degree of side-to-side asymmetry D was 20%. Corresponding levels of the flow maps and the CT scan are shown; the left hemisphere is oriented to the left, and the nose upwards. After Diamox the side-to-side asymmetry enhanced from 20% to 38% indicating a reduced vasodilatory capacity in the left hemisphere ("positive" Diamox test). In this patient, Diamox even caused a paradoxical CBF decrease in the left fronto-parietal region. Following successful EC-IC bypass surgery, a significant CBF increase was seen in both slice 2 and 3, and D decreased to 6%. Preop = preoperatively; postop = postoperatively. The scale gives CBF in mU/100g/min.
limiting the free collateral flow in the circle of Willis.24-28 Most commonly, hypoplasia of the anterior or posterior communicating arteries are seen, and these anomalies often coexist.

The clinical relevance of these patho-anatomical findings was stressed by Fazio, who demonstrated a higher incidence of ischemic stroke in the patients having anomalies of the circle of Willis.27 Norrving et al.28 later showed, that patients with a poor clinical outcome after an ICA occlusion had an insufficient collateral circulation via the circle of Willis. Some patients who have flow limiting defects of the circle of Willis will sustain a major cerebral infarction at the time of acute ICA occlusion, but others may be expected only to develop a reduction of the perfusion pressure. These patients with a potential for future cerebral ischemic events of hemodynamic origin might constitute a subgroup of patients in whom EC-IC bypass could afford a protective role against hemodynamic TIAs or a definite stroke, provided the operative complication rate can be kept low enough. Evidently, if such a group could be identified, the protective effects of surgery would have to be evaluated by a clinical trial.

A reduced capacity for collateral flow can not be recognized by measurements of CBF at rest. The flow reserve may be estimated from the cerebral vasodilatory capacity, i.e. the flow increase upon stimulation with a cerebral vasodilator. Dyken and Norrving et al.29 both measured CBF and cerebral vasoreactivity using 5% CO2 inhalation in patients with cerebrovascular disease. Dyken showed that the group of patients with ICA occlusion had a significantly smaller increase in CBF than the group having ICA stenoses.29 Norrving et al.30 correlated the findings of cerebral vasoreactivity to the angiographical pattern, and found an impaired CO2 response in the patients with signs of poor collateral flow via the circle of Willis.

By use of positron emission tomography, sequential measurements of CBF, CMRO2, and OER are available. If performed at rest and during a moderate decrease of the systemic blood pressure regions having a reduced perfusion may be identified by an increased OER. However, such studies have yet to be published. Alternatively, measurements of regional CBF, CMRO2, and cerebral blood volume (CBV) may be performed as CBV is increased in regions with reduced perfusion pressure i.e. poor collateral flow as shown by Gibbs et al.31

In the present study, an intravenous dose of Diamox was used instead of hypercarbia. This technique was found more convenient, causing only slight discomfort to some patients such as light-headedness, paresthesia in the distal part of the limbs and around the mouth and a short lasting diuretic effect. No changes in blood pressure are induced. In normal subjects, Diamox causes a rapid inhibition of the carbonic anhydrase in the erythrocytes, an enzyme that normally catalyzes the last step in reaction

$$H^+ + HCO^- _3 \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2$$

CO2 is released in the lungs whereas the reverse reaction occurs in the tissues. Hence, after Diamox administration in doses sufficient to achieve full physiologic inhibition (doses higher than 10 mg/kg body weight)31) the unloading of CO2 in the lungs is impeded, and end-tidal pCO2 will fall. However, pCO2 in arterial blood only increases slightly (a few mm Hg),37,38 and the high CBF increase can not be explained by this. Alternatively, an increase in the pCO2 tension in the cerebral tissues could be considered responsible for the flow increase but CO2 induced changes of CBF are controlled by the arterial CO2 level and not by the tissue level of CO2.33 Finally, it has been speculated that the effect might occur via a direct inhibition of the carbonic anhydrase located in the brain tissue; large amounts of the enzyme has been demonstrated in the glial cells and in the choroid plexus,34 and recently, in the endothelium of the capillaries throughout the brain tissue.

Following administration of Diamox, a gradual decline of pH in the brain tissue has been observed despite maintenance of a constant brain tissue pCO2.35,36 The decrease in pH seems best explained by cerebral carbonic acidosis, i.e. an increase in H2CO3 and the dissociation products H+ and HCO~3, assuming that Diamox blocks the conversion of carbonic acid to CO2 and H2O inside the brain. The drop in pH corresponds to an increase of CO2 of about 15-18 mm Hg, i.e. in an order that agrees well with the observed CBF increase. Thus, the early CBF increase is probably best explained by the acute decrease in pH following carbonic anhydrase inhibition in the erythrocytes.

It follows from the discussion given above that FeCO3 values will decrease following administration of Diamox, as the inhibition of the carbonic anhydrase in the red blood cells prevents the complete exchange of CO2 in the pulmonary capillaries. On-line measurements of the arterial pCO2 may be used, and as described, will tend to increase by a few mm Hg. It is evident, however, that any corrections for changes in FeCO3 or pCO2 are futile after Diamox.

The Diamox Test

Due to the rather wide range of CBF responses seen in the controls, the hemispheric CBF response to Diamox could not be used to assess the vasodilatory response in the individual case, although a significant correlation has been found between the CBF response after Diamox and the perfusion pressure in the ICA as measured during carotid endarterectomy.38 In the pres-
ent study we therefore chose to evaluate the change in the flow pattern by calculating the enhancement in side-to-side asymmetry. To ascertain a sufficient vasodilatory stimulus, a CBF increase of at least 13% was required in one hemisphere, a value derived from the elderly control group. In some patients with bilateral ICA occlusion or severe stenoses, the perfusion pressure may be severely reduced in both hemispheres. These patients will show an inadequate flow increase at the Diamox test. Repeated Diamox studies may then be needed to certify the vasodilatory potential.

According to this, 9 patients showed a significant redistribution of flow at the preoperative Diamox test in favor of the hemisphere contralateral to the occluded ICA. The side-to-side asymmetry was enhanced by 10% to 30% in the ROI. Two of these patients showed a CBF decrease in the hemisphere ipsilateral to the ICA occlusion ("steal effect"). Although none of these 9 patients suffered TIAs in relation to positional changes suggesting a hemodynamic origin, the finding of a limited vasodilatational capacity in some regions indicated a rather marked reduction in the regional perfusion pressure due to restricted compensatory flow via collaterals.

The 2 patients with a regional flow decrease at the preoperative Diamox test both showed a significant improvement in CBF postoperatively in these regions as judged from the lesser side-to-side asymmetry. In three patients, Diamox caused essentially no increase in CBF in the ipsilateral ROI preoperatively. Shunting was successful in two of these patients, and neither of these showed a significant improvement in CBF postoperatively. Although the material is too small to derive firm conclusions, the findings suggest that only when Diamox causes a paradoxical decrease in CBF a postoperative CBF increase may be anticipated after successful surgery.

Fourteen patients showed an essentially unchanged CBF distribution with preserved asymmetry at the 3 months follow-up whereas 2 patients even showed aggravation in the side-to-side asymmetry. The finding of a persistent low flow area despite successful shunting indicates that the focal low flow area was not caused by a regional reduction of the perfusion pressure below the lower limit of CBF autoregulation. Although all the patients had an occlusion of the ipsilateral ICA and several had other arteriosclerotic lesions as well, the flow through the compensatory collateral pathways sufficed to maintain resting CBF at a level which met the metabolic demands. It may therefore be concluded — in agreement with our previous findings and the study of Halsey et al.39 that in most patients selected by clinical and angiographical criteria, resting CBF will not increase following EC-IC bypass surgery. Thus, the common preoperative finding of a reduced flow in the peri-infarct areas — and the occasional finding of a focal low flow area in patients without any CT lesions whatsoever — therefore suggests, in most but not all instances, that permanent ischemic lesion has occurred. This interpretation is supported by the findings by Gibbs et al.,35 who showed that the oxygen utilization was reduced in the presence of more than adequate oxygen delivery. We have previously discussed the possible pathogenetic mechanisms to this finding, and have considered disconnection or diffuse but selective neuronal cell loss or microscopic infarcts as likely explanations. Although the effect upon the vasodilatory potential has been considered to be one of the major indications for this surgical procedure, the results of the large cooperative study unequivocally showed that this does not afford a prophylactic effect against future ischemic events.

Concluding Remarks

EC-IC bypass surgery improved the regional vasodilatational capacity as judged from the flow responses to Diamox at the 4 months follow-up in the majority of patients with successful surgery (13 of 16 patients). Although the effect upon the vasodilatory potential has been considered to be one of the major indications for this surgical procedure, the results of the large cooperative study unequivocally showed that this does not afford a prophylactic effect against future ischemic events.

The clinical benefit of EC-IC bypass surgery in the patients with a severely impaired collateral capacity could not be assessed from the large cooperative study, although attempts were made to classify the patients according to the severity of the vascular lesion. In the present study, a simple stress test using Diamox was applied and a subgroup of hemodynamically threatened patients were identified. A limited vasodilatory response ipsilateral to the ICA occlusion was observed in half of the patients. Two patients (about 10% of the material) even showed a paradoxical decrease in CBF — "steal effect" — which indicated a regional reduction of the perfusion pressure below the lower limit of CBF autoregulation. Although surgical treatment would appear to be a rational procedure in these patients, any protective effect should be measured against the peri-operative morbidity and mortality, which may be higher in these particular patients. To document a clinical effect, new randomized studies with carefully selected patients will be needed.

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