Long-Term Assessment of Cerebral Perfusion Following STA-MCA By-Pass In Patients

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SUMMARY A prospective study of mean hemispheric cerebral blood flow (CBF) correlated with clinical status has now been completed for the past 54 months. Thirty-eight patients underwent superficial temporal to middle cerebral artery (STA-MCA) by-pass. They were compared with 22 patients with similar arteriographic lesions and clinical symptoms, treated medically throughout the same interval of time. Assignment to either treatment group was not randomized but depended solely on choice of patient or treating physician. Both groups were matched for age, clinical symptoms, angiographic abnormalities, and CBF values. All patients had proximal occlusion of one internal carotid artery or intracranial occlusive disease of the internal carotid or middle cerebral arteries. CBF measurements and clinical evaluations were repeated at regular intervals up to 54 months following surgery or institution of medical treatment. Mean follow up interval after STA-MCA by-pass was 28.7 months and for medical treatment was 29.7 months. Mean hemispheric CBF values for STA-MCA patients became significantly increased 2 weeks after operation. After that, CBF flow values decreased. At 24 months after surgery, flow values for surgically treated patients were significantly higher than among those treated medically, although there were no differences in flow values between the two groups at 3, 6, 12, 36 and 48 months. Prospective clinical evaluations after STA-MCA by-pass were as follows: 12 (32%) improved with cessation of TIAs and/or neurological improvement, 16 (42%) remained unchanged, 7 (18%) deteriorated (due to new or recurrent strokes) and 3 (8%) expired. Clinical results were the same for medical treatment: 6 (27%) improved, 10 (46%) unchanged, 4 (18%) deteriorated due to new or recurrent stroke, and 2 (9%) expired.

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SINCE THE INTRODUCTION of extracranial-intracranial by-pass procedures by Yasargil in 1967, large numbers of patients with ischemic cerebrovascular disorders have undergone this type of treatment, the procedure being the superficial temporal-middle cerebral artery (STA-MCA) anastomosis or by-pass. Theoretically, STA-MCA Anastomosis should be most useful in patients suffering from hemodynamic types of transient ischemic attacks (TIAs). However, the procedure has not been limited to non-embolic cerebrovascular disease for a number of reasons. For example, whether a TIA is embolic or hemodynamic is not always clear from clinical evaluations alone. Furthermore, it has been argued that increased collateral flow brought to areas of marginal perfusion after embolism as a result of the by-pass should enable patients to withstand further emboli without sustaining infarction. The purpose of the procedure, it has been argued, is primarily to prevent further strokes and not to restore function to infarcted brain tissue.

Much of the available literature reports short-term benefits of the operation, without utilizing non-operated control groups for comparison. Nevertheless, most claim prevention of future strokes. Reports have shown that the procedure is technically feasible, may be carried out with low morbidity and mortality, and that high patency rates of the bypass are maintained for several years.2,3

Long term clinical follow-up after STA-MCA bypass utilizing suitable control groups remains to be reported, although such a study is nearing completion.4,5 Thus, the usefulness of the procedure for treatment of ischemic cerebral vascular disease remains to be established. The international, prospective and randomized clinical extracranial-intracranial by-pass study9,10 was designed to determine whether the incidence of stroke or death over a five year interval will be altered by the procedure. Final results will probably not be published until after 1985. The design of the international study is to evaluate clinically indications for STA-MCA by-pass in patients with TIAs or minor strokes associated with angiographic evidence of stenosis or occlusion of the middle cerebral artery or complete occlusion or intracranial stenosis of the internal carotid artery presumably of atherosclerotic origin.

Although clinical data has been accumulating, long term effects of by-pass surgery on regional cerebral blood flow have not been reported and short-term effects are disputed.11-19 Lacking from available reports are data correlating long term effects of by-pass surgery on both CBF values and clinical status.26,27 Short-term results were reported from this laboratory of redistribution of regional cerebral blood flow following STA-MCA by-pass and there were early favorable clinical outcomes during the short-term follow-up of 5.8 months.28

The present report compares a larger group of STA-MCA by-pass patients, including the patients previously reported28 who have now returned for a mean follow-up interval of 28.7 months, to a control group of patients followed for a mean interval of 29.7 months. The control group had similar neurological
symptoms but received medical treatment only (i.e. aspirin and/or other antiplatelet agents plus control of risk factors). The entire group of patients has now been followed for intervals up to 54 months in order to correlate clinical status with CBF values following STA-MCA by-pass.

Methods

Clinical Case Series

STA-MCA by-pass procedures were carried out by experienced neurosurgeons who are considered in the southwest to be regional experts. All are senior members of the staff of the Department of Neurosurgery of Baylor College of Medicine and its affiliated hospitals. The cerebral angiograms were performed by members of the Department of Radiology. All cases were referred to the Cerebral Blood Flow Laboratory prior to, and at regular intervals after the procedures, for clinical evaluations and for measurement of regional cerebral blood flow (rCBF) as part of a collaborative ongoing prospective trial. The protocol for the study, for the cerebral blood flow measurements, and all consent forms used, were approved by the Institutional Review Boards of Baylor College of Medicine and the Veteran’s Administration Medical Center, Houston. Table 1 summarizes demographic, neurologic and neurovascular information relating to patients admitted to the STA-MCA by-pass treatment group.

As indicated in table 1, all patients undergoing STA-MCA by-pass had complete occlusion of one of the internal carotid arteries in the neck or severe stenosis or occlusion of the intracranial portion of the carotid or main trunk of the middle cerebral arteries. All complained of recurrent transient ischemic attacks (TIAs), reversible ischemic neurologic deficits (RINDs) or small strokes followed by minor residual neurologic deficits. Clinical symptoms consisted of hemiparesis, or monoparesis, dysphasia, hemisensory loss, dysarthria, homonymous hemianopsia and/or amaurosis fugax.

Mean age for the surgically treated group of patients was 53.7 ± 9.0 years. Clinical symptoms, risk factors for stroke, general medical and neurological examinations, CT-scans and angiographic findings for each patient were reviewed by two neurologists at the time of the initial visit. At subsequent visits each patient was re-interviewed, re-examined, completed a questionnaire, and underwent rCBF measurements.

The surgical group consisted of 38 patients. Postoperative angiograms were repeated within one month after operation. All patients showed continued patency of the by-pass and none of the surgical patients had serious post-operative complications such as death or stroke. The minimum acceptable follow-up interval for inclusion in the present report was 1 year. During follow-up visits, which were scheduled at intervals of 3-12 months, each patient was questioned about recurrent TIAs, RINDs, stroke and any change in cerebral symptomatology. A detailed questionnaire was also completed which provided information regarding general health, medical treatment and any neurological symptoms. A general medical examination as well as neurological examination were carried out prior to all rCBF measurements.

The patients’ hematocrit values were noted before and after surgery. They were found not to be altered in a manner likely to influence CBF values. As shown in table 1, patients were divided into three groups according to the type of clinical symptoms: 1) fourteen patients had TIAs without any evidence of low density lesions by CT-scans, 2) 12 patients had TIAs, combined with recent or remote small cerebral infarctions, with or without low density lesions on CT-scans and 3) 12 patients had no TIAs but had histories of RINDs or a small completed stroke with minor residual neurologic deficits with or without small low density lesions by CT-scans. Table 1 shows the number of cases in each subgroup, their gender, whether there was right or left hemisphere ischemia, whether their were intracranial or extracranial occlusions and whether or not associated risk factors were present. The by-pass procedures were all carried out on the side of the ischemic and symptomatic hemisphere which was also the side of the major occlusive arterial disease.

Results for the surgically treated group were compared with a medically treated control group. This consisted of 22 patients sharing similar symptoms and similar occlusive disease of the internal carotid and/or...
LONG TERM CBF IN STA-MCA BY-PASS/Tanahashi et al

Table 2 Age-Matched Medically Treated Control Group With Occlusive Disease of the Internal Carotid-Middle Cerebral Arteries

<table>
<thead>
<tr>
<th>Clinical symptoms*</th>
<th>Case numbers</th>
<th>Age mean ± SD</th>
<th>Sex</th>
<th>Angiography†</th>
<th>Affect hemisphere</th>
<th>Risk factors‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. TIA’s without cerebral infarction</td>
<td>7</td>
<td>56.4 ± 7.3</td>
<td>3 F</td>
<td>0</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>II. TIA’s with recent or remote cerebral infarction</td>
<td>7</td>
<td>55.0 ± 8.4</td>
<td>2 M</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>III. Small cerebral infarction, recent, without TIA’s</td>
<td>8</td>
<td>56.0 ± 14.2</td>
<td>3 F</td>
<td>5</td>
<td>3(2)§</td>
<td>4</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>22</strong></td>
<td><strong>55.8 ± 10.0</strong></td>
<td>14 F</td>
<td>16</td>
<td>6(5)</td>
<td>11</td>
</tr>
</tbody>
</table>

*Medically treated group had symptoms similar to the surgically treated group.
†Risk factors for stroke included one or more of the following: hypertension, hyperlipidemia, heart disease and/or diabetes mellitus.
‡Extracranial occlusion indicates complete ICA thrombosis in the neck. Intracranial occlusion indicates either severe stenosis of intracranial ICA or occlusion or stenosis of MCA.
§Indicates a single case that was included diagnosed by clinical signs, symptoms, bruits, ophthalmodynamometry but contrast angiography was refused.
(N) Parentheses indicate numbers of cases with MCA occlusion or stenosis.

Middle cerebral arteries demonstrated, with one exception, by angiograms (table 2). The single exception was a patient with a diminished carotid pulse and bruit, who had suffered a small recent stroke, but refused angiography.

Medically treated patients were chosen from patients referred at the same time as the surgical group for CBF measurements and treatment. These cases had the same selection criteria as the surgical group except that medical treatment was elected and recommended by their referring physicians. Patients with severe stroke and patients with TIA's but without angiographic abnormalities and/or without reduced CBF were excluded. The number of medically treated patients meeting these criteria were slightly less than those assigned to the surgically treated group.

The medically treated group had a mean age of 55.8 ± 10.0 years and were admitted to the study for medical treatment at the same time as the surgically treated group and were referred from comparable referral sources. Patients were not assigned to medical or surgical treatment on a randomized basis but were patients evaluated and treated at the same hospitals at the same time. The type of treatment was that elected and advised by their physicians or that requested by the patient. Although a randomized study would have been ideal and was considered in the planning stages, it was impossible to carry out in the present study, because our participating surgeons did not consider it ethically justifiable to randomize patients referred to them specifically for surgical treatment.

Table 2 summarizes demographic information about the medically treated group. Medically treated patients were comparable to surgically treated patients in all respects including general health status and risk factors. They were matched by age, degree of disease, clinical manifestations, risk factors, CBF and arteriographic finding. They were selected from a larger population of patients referred for rCBF measurements. As shown in table 2, arteriograms were not available in a single case presumed by non-invasive tests and clinical evaluation to have arteriosclerotic stenosis of the internal carotid artery with cerebral embolism from this source. Medical treatment was the same for both groups. This consisted of control of risk factors (hypertension, diabetes mellitus, hyperlipidemia, heart disease) and the use of antiplatelet aggregating agents (aspirin alone and/or with dipyridamole).

STA-MCA by-pass surgery has gone through a considerable vogue of popularity in this vicinity during the past decade, so that the number of cases assigned to the medically treated group is slightly smaller than those undergoing surgical treatment. A preliminary report of cerebral hemodynamic changes and short-term clinical outcome of 17 cases in the surgically treated group and of 13 cases in the medically treated group has been reported previously in this publication in 1982.

Cerebral Blood Flow Procedures

Regional cerebral blood flow values were measured utilizing the 133Xe inhalation method. This was modified after the technique described by Obrist et al. Briefly, 14 collimated sodium iodide crystal scintillation detectors were distributed in a radial array over both hemispheres including frontal, precentral, sylvian-opercular, parietal, posterior temporal, occipital and inferior temporal regions by means of a lead shielded helmet. 133Xe gas mixed with room air (5–8 mCi/L) was inhaled for 1 minute by means of a face mask. Clearance curves from both head and end-tidal air were recorded throughout the ensuing 10 minutes of desaturation by means of a PDP 11-05 minicomputer. Arterial concentrations for 133Xe, were estimated from the end-tidal air curves and were used to deconvolute the head curves in order to correct for arterial recirculation and estimate fast and slow flow compartments by a two-compartmental model of analysis. The fast clearing compartment (F1) is considered to represent gray matter flow and was used for all analyses. End-tidal partial pressures for carbon dioxide (PECO2) and oxygen (PEO2) were monitored from the face mask and were recorded on a polygraph along with blood.
pressure, pulse rate, EEG and ECG. CBF measurements were made shortly before surgery and at the initial visit for the medically treated patients and subsequently CBF measurements were repeated at regular intervals.

Methods Used For Statistical Analysis

Results of mean CBF measurements were analyzed by Wilcoxon’s signed-rank test or Wilcoxon’s rank-sum test. Results of clinical outcomes were analyzed by Chi square tests. Results were not considered significant unless a confidence level exceeding 95 percent was achieved.

Results

Longitudinal Effects of STA-MCA By-Pass Compared to Medical Treatment on Bihemispheric Gray Matter Flow

There were no significant changes in PECO₂ or blood pressure before or after surgical or medical treatment. Likewise hematocrit and hemoglobin values were within normal limits before and after treatment. Initial mean hemispheric F₁ values were 63.4 ± 9 ml/100 g brain/min for the surgically treated group and 64.5 ± 11.4 ml/100 g brain/min for the medically treated group. Differences for initial CBF values between groups were not significant. However, when compared to age-matched normal control F₁ values of 76 ± 10 ml/100 g brain/min, both medically and surgically treated groups showed significantly reduced initial mean values prior to treatment (p < 0.001).

Figure 1 illustrates results of longitudinal analysis of rCBF measurements in patients treated by STA-MCA by-pass compared to those treated medically. Serial gray matter flow or F₁ measurements are expressed as percentage change of mean hemispheric F₁ values compared to initial or preoperative values repeated at intervals up to 54 months. In the group treated medically, serial flow values showed no increases, but instead there was gradual and significant reductions throughout the second, third, and fourth years (~14% reduction at 24 months, ~13% at 36 months and ~15% at 48 months). Among the surgically treated patients, increases in F₁ values occurred about 2 weeks after STA-MCA by-pass. After that F₁ values gradually became reduced after 3 months. At 2 years following surgery, flow values for the surgically treated group were significantly higher than among the medically treated group. However, F₁ values measured among the surgical group showed sharp declines between the second and third years following operation and from that point on the two groups converged. No statistically significant differences could be found for mean bihemispheric CBF values between surgically and medically treated groups at 3, 6, 12, 36 and 48 months.

Longitudinal Effects of STA-MCA By-Pass on CBF Comparing Ischemic To Contralateral Hemispheres

Initial mean hemispheric F₁ values were 61.9 ± 9.2 ml/100 g brain/min for ischemic hemispheres and 64.9

± 11.9 ml/100 g brain/min for contralateral hemispheres. All STA-MCA by-pass procedures were made on the side of the ischemic hemisphere. Serial F₁ measurements were calculated as percentage change compared to initial or preoperative hemispheric F₁ values. Figure 2 illustrates comparisons between percentage changes from ischemic and contralateral hemispheres at various time intervals following surgery. Hemispheric F₁ values increased significantly for both ischemic and contralateral hemispheres around 2 weeks after operation. Thereafter both hemispheric F₁ values gradually decreased and remained at preoperative levels for up to 2 years after operation. Three years after operation, both ischemic and contralateral hemispheric F₁ values had decreased significantly compared to preoperative values. There were no significant differences between ischemic and contralateral hemisphere F₁ values for any intervals after STA-MCA by-pass.
Clinical Outcome Comparisons of Medical and Surgical Treatment

Clinical evaluations after an average follow-up interval of 28.7 months (range; 12 to 54 months) for surgically treated patients and after an average follow-up interval of 29.7 months (range; 12 to 54 months) for medically treated patients were classified into 4 categories (improved, no change, deteriorated, expired). Clinical outcomes were graded according to results of neurological examinations and histories taken at each visit. Details of deaths were obtained from family members who were asked to describe pre-terminal events and to obtain copies of all available medical records. Reductions in frequency of TIAS and/or improvement of neurological deficits were classified as "improved." Increased frequency of TIAS or worsening of neurological deficits due to strokes were classified as "deteriorated." For example, patients with TIAS who suffered one or more strokes or patients with RINDs or completed strokes who had recurrent strokes, were classified as "deteriorated."

In the surgically treated group, 12 cases (32%) improved, 16 cases (42%) remained unchanged, 7 cases (18%) deteriorated due to stroke and 3 cases (8%) expired. In the medically treated group, 6 cases (27%) improved, 10 cases (46%) were unchanged, 4 cases (18%) deteriorated and 2 cases (9%) expired. In the surgically treated group, two patients died of myocardial infarction and in the remaining case, cause of sudden death was undetermined but apparently was due to severe stroke or fatal heart attack. In the medically treated group, one patient died of myocardial infarction and the other died of severe, recurrent strokes. Clinical analyses did not indicate statistically significant differences in outcome between the two treatment groups or among clinical subdivisions (I, II, III) of the treatment groups.

Discussion

It remains to be established whether or not rCBF measurements are useful for evaluating patients that may benefit from STA-MCA by-pass. It has been reported from measurements made with the $^{133}$Xe carotid injection method that best probabilities for good post-operative results are patients showing focal cerebral
ischemia or moderately diffuse reductions of CBF with an ischemic focus. The operation has been considered to be contraindicated in patients with either normal or severely reduced CBF values. Severely reduced CBF values were described as less than 60% of normal. Patients with diffuse reductions of CBF were said to show no clinical improvement and to exhibit high rates for postoperative graft occlusion.

Another study utilizing the $^{133}$Xe intravenous injection method reported that decreases in CBF in frontal gray matter of 25% or greater was an hemodynamic indicator favoring STA-MCA by-pass. Studies using positron emission tomography report that relative preservation of regional cerebral oxidative metabolism despite decreased rCBF with increased oxygen extraction termed focal “misery perfusion syndrome,” is a good indicator for carrying out STA-MCA by-pass procedures. In a report from this laboratory statistically significant decreases of mean hemispheric $F_r$ values were noted in patients with occlusive disease of the carotid-middle cerebral arteries prior to surgery compared to age-matched normal controls. CBF reductions were predominantly in the middle cerebral artery distribution and were consonant with reports from other laboratories.

So far serial examinations of rCBF in patients with STA-MCA by-pass have only been carried out for short follow-up intervals, and no consensus has been reported concerning expected CBF changes after STA-MCA by-pass. Differences in results can be attributed to small sample sizes as well as technical differences in methods used for measuring CBF. For example, the intracarotid $^{133}$Xe injection method is obviously less suitable for use in patients with complete occlusion of the internal carotid artery than the $^{133}$Xe inhalation method.

One of the earlier studies did make comparison with a control group and was similar in design to the present report. Ten patients undergoing STA-MCA by-pass were compared to 10 patients treated medically. No differences were found in outcomes between surgically and medically treated groups as judged by CBF values, EEG findings and/or clinical evaluations during only 3 months of follow-up. Considering variabilities in CBF measurements, the short-term follow-up and small samples of patients reported, the possibility of a type II error with false-negative results, should be considered.

Another study reported a 25 month follow-up of serial CBF measurements in patients who had undergone STA-MCA by-pass surgery. These authors reported 15% reductions in CBF 2 years after operation, similar to those reported here. However, statistical analyses of data were not carried out and there was no medically treated control group available for comparison. Control groups are essential because normal elderly subjects have been reported to show similar age-related CBF declines over similar intervals of time.

Results of the current study demonstrate that following STA-MCA by-pass in patients with occlusive disease of the internal carotid and middle cerebral arteries there are statistically significant increases in mean hemispheric flow values which are measurable around 2 weeks after the operation. Thereafter, flow values decline although they do not fall below preoperative CBF levels until around 2 years following surgery. Age-matched patients treated medically show similar progressive CBF decreases throughout the same 4 year interval.

Present results suggest that in patients with occlusive disease of the internal carotid and middle cerebral arteries, STA-MCA by-pass enhances cerebral collateral circulation only in the early stage after surgery or at most for up to two years following surgery. However, if operative risks are considered, the benefit to risk ratio becomes small particularly since medically treated patients from the point of view of clinical outcome appear to do as well as those treated surgically. However, to avoid a Type II error clinical outcome of the procedure can only be determined by comparison of much larger treatment groups.

Four year longitudinal (prospective) analyses of age related changes in cerebral blood flow have been measured in normal, middle-aged and healthy elderly volunteers and compared to a similar asymptomatic group with risk factors. There were significant declines for CBF in both groups but the rate of decline was much steeper among risk factored healthy volunteers.

Results of the current study for both medically and surgically treated groups indicate declines of 13% for gray matter CBF occurring over a 3 year interval of follow-up. These CBF declines are almost identical to those measured among risk factored groups in our normal aging studies. The cause for these declines in CBF in both surgically and medically treated groups in the current study presumably are due to the natural consequences of normal aging which include progressive cerebral atrophy, neuronal loss, decreased metabolic demand and progressive rigidity of cerebral vessels; as well as progressive atherogenesis that is known to occur in subjects at risk for atherothrombotic stroke.

Neurosurgeons have measured contralateral internal carotid artery (ICA) stump pressure in 11 patients before and after STA-MCA anastomosis. Compression of the bypass graft produced a 60% drop in the ICA stump pressure. This clearly indicates that contralateral hemispheric intraluminal blood pressure is enhanced after STA-MCA by-pass and the collateral circulatory reserve is increased.

Results reported here have compared both ischemic and contralateral hemispheres before and after STA-MCA by-pass. There were increases in CBF for both hemispheres and confirm that cerebral interhemispheric collateral reserve is improved.

Early reports from this laboratory showed that patients undergoing STA-MCA by-pass after a short follow-up interval of 5.8 months, showed more encouraging clinical results (85% improved, 9% unchanged, 6% deteriorated). The present results, which include the same patients with longer follow-up, indicate that this clinical improvement is temporary (32% improved, 42% unchanged, 18% deteriorated, 8% ex-
piried) and probably results from temporary enhancement of the collateral circulation. Present results appear pessimistic in terms of possible long-term benefits for patients undergoing STA-MCA by-pass. However, it should be borne in mind that the final word regarding clinical indications must await reports of larger clinical trials involving randomized samples of patients undergoing either STA-MCA by-pass or medical treatment.9, 10

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