Age-dependent revascularization patterns in the treatment of moyamoya disease in a European patient population

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Object. Different revascularization procedures are used in the treatment of patients with moyamoya disease (MMD). The aim of this study was to investigate the relative contribution of direct and indirect revascularization procedures to the restoration of collateral blood supply in adult and pediatric patients with MMD.

Methods. The authors performed 39 combined cerebral revascularization procedures (standard extracranial-intracranial bypass [STA-MCA bypass] plus encephalomyosynangiosis [EMS]) in 10 pediatric and 10 adult patients. All patients underwent physical examination and digital subtraction angiography before and 6 months after surgery. The STA-MCA bypass and EMS function were graded as Grade I (poor), II (moderate), or III (good) on the basis of the angiograms.

Results. In pediatric patients, bypass function was Grade I in 12, Grade II in 8, and Grade III in 0 hemispheres; EMS function was Grade I in 0, Grade II in 12, and Grade III in 8 hemispheres. In the adult patients, bypass function was Grade I in 8, Grade II in 8, and Grade III in 3 hemispheres; EMS function was Grade I in 10 hemispheres, Grade II in 5, and Grade III in 1 hemisphere. In the pediatric patients disease was classified as improved in 14 hemispheres based on the clinical results and stable in 6. In the adults it was classified as improved in 12 hemispheres stable in 7 hemispheres.

Conclusions. Combined revascularization led to good angiographic and clinical results in both patient populations. Especially in pediatric patients, EMS represents a suitable alternative to bypass surgery. (DOI: 10.3171.2009.1.FOCUS08298)

**Key Words** • moyamoya disease • revascularization • Europe
volving children who underwent indirect or combined cerebral revascularization. They reported that direct revascularization using STA-MCA bypass led to better angiographic filling and improved clinical outcome in comparison with indirect procedures. In contrast, Houkin et al.\textsuperscript{11,12} reported that STA-MCA bypass was effective in only 68\% of their pediatric patients compared with a 100\% success rate using indirect procedures. These studies are difficult to compare, however, due to the large heterogeneity of the evaluation protocols used; also, most of the cited reports present results from an Asian patient population. Little is known about the success of surgical revascularization and the contribution of direct and indirect procedures in a European patient population. Therefore, it was our aim in the current study to investigate the success of surgical revascularization and to characterize the contribution of direct and indirect cerebral revascularization in a European population of adult and pediatric patients with MMD.

**Methods**

**Patient Population and Surgery**

Cerebral revascularization surgery (combined STA-

<table>
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<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Rt Hemisphere</th>
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<th>MMD Grade (rt/lt)</th>
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* Def = deficit; HP = hemiparesis.

MCA bypass and EMS application) was performed in 10 pediatric and 10 adult MMD patients in a consecutive manner after exclusion of an acute or subacute cerebral infarction. In 1 adult, only 1 hemisphere was revascularized because rCBF measurement in the other hemisphere showed no reduction in cerebrovascular reserve capacity. In all other patients each hemisphere was revascularized in a separate operation. (That is, the combined procedures were performed first in one hemisphere and then later in the other.) The STA-MCA bypass and EMS were performed as described previously.\textsuperscript{6,22,23} For the preparation of the EMS we dissected the temporal muscle from the skin and the underlying temporal bone and then performed an osteoplastic craniotomy underneath the previous location of the temporal muscle origin.\textsuperscript{6} We then excised and removed the dura mater and sutured the temporal muscle to the edges of the dura before reapplying the bone flap.

**Preoperative Evaluation**

Preoperatively, patients underwent conventional catheter digital subtraction angiography. Moyamoya disease was diagnosed angiographically according to the grading system proposed by Suzuki and Takaku.\textsuperscript{21} Functional rCBF studies were conducted in adult patients and consisted of the measurement of rCBF at rest and after the application of acetazolamide (15 mg/kg body weight) using stable xenon–CT technology (Diversified Diagnostic Products, Inc.). Cerebrovascular reserve capacity was calculated as described elsewhere in detail.\textsuperscript{9} Table 1 summarizes the clinical and demographic characteristics of our patient population.
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Angiographic Evaluation of Revascularization Results

All patients in our consecutive case series received early postoperative (within the first 7 days after each surgical procedure) and follow-up digital subtraction angiography (follow-up period 6–54 months after the last operation) to assess immediate revascularization success as well as revascularization status after at least 6 months. (In some patients, follow-up angiography was performed 6 months postoperatively, but in others it was performed much later. The mean follow-up time was used for purposes of analysis.)

Angiographic revascularization results were semi-quantitatively analyzed by a team of a blinded and independent neuroradiologist and neurosurgeon. The STA-MCA bypass function was graded as follows: Grade I, filling of the anastomosed MCA branch only (poor); Grade II, filling of ≥ 2 MCA branches (moderate); Grade III, ante- and retrograde filling of the entire MCA system (good). Representative examples are shown in Fig. 1A. The EMS function was graded as follows: Grade I, slight opacification (poor); Grade II, 1–4 vessels (moderate); and Grade III, > 4 vessels (good). Examples are shown in Fig. 1B. These grading systems have been described previously and been proven to represent a suitable approach for evaluation of angiographic revascularization success.

Clinical Evaluation of Revascularization Results

To analyze the clinical success of the revascularization surgery all patients underwent physical examination during early and late follow-up angiography. Clinical status was defined as “improved disease” if there was improvement in neurological symptoms such as complete disappearance of TIAs, regressing hemiparesis, or improving sensory deficits. If TIAs were the leading symptom, only complete disappearance was defined as improved disease. A reduced number of TIAs was regarded as stable disease because revascularization was clinically
not able to completely restore the hemodynamic compromise. Stable disease was in general defined as absence of new neurological deficits during the follow-up period, with persistence of manifest preoperative deficits. In our study the observed neurological symptoms were hemiparesis, sensory deficit, aphasia, and TIA; however, other similar deficits might occur. Progressive disease was defined as a worsening of neurological symptoms. All clinical symptoms were evaluated by hemisphere (that is, according to the hemispheric location of the causative lesion). Diffuse neurological symptoms, such as cognitive deficits or persisting headaches, were not included in our analysis because they may not be clearly related to a single hemisphere.

Results

Patient Population

The pediatric group consisted of 4 boys and 6 girls, with a mean age (± SD) of 8.4 ± 6.4 years. The adult group consisted of 3 men and 7 women, with a mean age of 38.4 ± 9.9 years. All hemispheres were MMD Grade III or IV according to Suzuki and Takau. In adult patients, rCBF measurement demonstrated diminished cerebrovascular reserve capacity in every hemisphere except 1 (data not shown). All patients suffered from symptoms due to cerebral ischemia, such as recurrent TAs and motor or sensory deficits. No intracranial hemorrhage was observed in any patient in either group. The clinical and demographic data are summarized in Table 1.

Angiographic Results of Revascularization

The mean clinical follow-up time was 24 ± 12 months after surgery. In our study, direct and indirect revascularization procedures represented feasible treatment options in both MMD patient populations. Both early postoperative (within 7 days of surgery) and follow-up (≥6 months) angiography demonstrated patent direct revascularization in all patients.

In the adult patients, bypass function was Grade I (poor) in 14 (73%) of the 19 hemispheres treated, Grade II (moderate) in 5 (27%) of 19, and Grade III (good) in 0 (0%) on early postoperative angiograms (Fig. 2A). On follow-up angiograms, bypass function was found to be Grade I (poor) in 8 (42%) of 19 hemispheres, Grade II (moderate) in 8 (42%), and Grade III (good) in 3 (16%) (Fig. 2B). Bypass function improved in 7 hemispheres with the grade improving from I to II in 4 hemispheres, from I to III in 2 hemispheres, and from II to III in 1 hemisphere. In comparison, no EMS function was detected in any of the surgically treated hemispheres during early postoperative angiography but at follow-up assessment EMS function was Grade I in 10 (53%) of 19 hemispheres, Grade II in 5 (26%), and Grade III in 1 (5%) (Fig. 2C). In 3 (16%) of 19 hemispheres, no EMS function was detected during follow-up angiography.

In pediatric patients bypass function was graded I (poor) in 14 (70%) of 20 hemispheres, II (moderate) in 6 (30%), and III (good) in 0 (0%) on the basis of early postoperative angiograms (Fig. 2A). On follow-up angiograms, bypass function was found to be Grade I (poor) in 12 (60%) of 20 hemispheres, Grade II (moderate) in 8 (40%), and Grade III (good) in 0 (0%) (Fig. 2B). Bypass function improved from Grade I to Grade II in 2 hemispheres and regressed from Grade II to Grade I in 1.

Clinical Results of Revascularization

In the adult patients, clinical results demonstrated improvement of disease in 12 hemispheres, and stable disease in 7 (Table 2). Patients experienced persistence of symptoms (hemiparesis, aphasia, or recurrent TAs) associated with disease in 2 of the 7 hemispheres. The other 5 hemispheres were classified as stable because patients did not experience symptoms associated with disease in...
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these hemispheres after surgery despite the progressive character of MMD.

Disease progression was not observed after surgical treatment in our study.

In the pediatric patients, clinical results demonstrated improvement of disease in 14 hemispheres during follow-up. In 6 hemispheres stable disease was achieved (Table 2), with 2 of those 6 classified as stable because of persisting TIAs and, in 1 case, hemiparesis. The other hemispheres were classified as stable because the patients remained asymptomatic with respect to disease in these hemispheres.

Discussion

The findings of our study demonstrate the successful use of combined revascularization procedures for the treatment of MMD in adult and pediatric patients of European origin. Direct revascularization using STA-MCA bypass revealed good immediate and long-term angiographic revascularization results in adult and pediatric patients. Bypass function may have improved in both patient populations, with better development in adult patients in our study. Encephalomyosynangiosis did not yield an immediate revascularization result, but it did result in positive angiographic revascularization results 6 months after surgery in both patient populations. Pediatric patients demonstrated better development of EMS function over the course of time than adult patients. Therefore, EMS may represent a sufficient, alternative revascularization procedure especially in pediatric patients in whom direct bypass is not suitable.

In the surgical treatment of MMD there is significant debate about the optimal indications for different revascularization techniques as well as the techniques, especially in relation to the patient’s age. Indirect revascularization procedures such as EMS are performed often and are regarded to be very effective for revascularization in pediatric patients in whom the caliber of both the STA and the distal branch of the MCA are not suitable for bypass surgery. On the other hand, especially in adult patients, indirect revascularization procedures remain a matter of controversy and have yielded only inconsistent results, whereas direct revascularization has been demonstrated to be very effective and therefore is recommended as the treatment of choice. Recent data suggest that combined revascularization procedures (STA-MCA bypass plus indirect revascularization) are more effective as a single treatment modality for revascularization in patients with MMD.

In our study, we demonstrated that a combined revascularization procedure is feasible in both pediatric and adult MMD patients. However, there seem to be distinct differences regarding the revascularization potential for direct and indirect procedures depending on the patient’s age. In adult patients, STA-MCA bypass was associated with marked improvement in the angiographic revascularization results seen at follow-up compared with the immediate revascularization effects. In 7 out of 19 STA-MCA bypass–revascularized hemispheres, bypass function progressed over the follow-up period. This contrasts with our observations in pediatric patients, in whom bypass function improved in only 2 of 20 revascularized hemispheres and even regressed in 1 hemisphere. Regarding EMS, we observed a different phenomenon. Although EMS also yielded positive revascularization results in adult patients, function was assessed primarily as Grade I and II only, with only 1 hemisphere demonstrating Grade III function. Additionally, in 3 hemispheres EMS was not detectable during follow-up angiography. In contrast, EMS produced high-grade angiographic revascularization in all pediatric patients with 12 hemispheres demonstrating Grade II and 8 hemispheres demonstrating Grade III function. Therefore, EMS revascularization seems more likely to lead to favorable angiographic revascularization in pediatric patients than in adult patients. The reason for our observation, however, remains unknown. We hypothesize that one explanation might be that the development of bypass function may be decreased over the course of time as increasing blood supply via the EMS could lead to a subsequent decrease in bypass blood flow.

Interestingly, Houkin et al. reported that indirect revascularization is the superior procedure in pediatric patients and that STA-MCA bypass is superior in adult patients. Yet, in their study of 35 cases involving adult patients, all of the patients were of Asian origin and the majority suffered from hemorrhagic type MMD. There is growing evidence that there are differences in MMD depending on the patients’ ethnic origin. With respect to the European MMD patient population, there is only scarce data. Different reports describe a predominantly ischemic type of MMD in patients of European origin. In this regard, Khan et al. demonstrated in a series of 23 patients with MMD that STA-MCA bypass produced superior revascularization results compared with indirect procedures. However, Khan et al. included 19 pediatric patients and only 4 adult patients in their case series, they did not relate their results to the patients’ ages, and they used different indirect revascularization procedures, so a definite conclusion about the superior revascularization procedure cannot be drawn from their data.

There is growing evidence that combined approaches may represent the most promising revascularization strategy, at least in pediatric MMD patients. Ishikawa et al. demonstrated that combined revascularization significantly reduces the risk of ischemic attacks, prevents intellectual deterioration, and improves overall outcome. An advantage of the combined approach seems to be the immediate supply of blood to the brain via the direct anastomosis and the subsequent vessel outgrowth from the indirect procedure eventually revascularizing a larger area of cerebral cortex as compared with a single procedure.

In our series we observed improvement or stabilization of the clinical symptoms in all revascularized hemispheres, demonstrating that combined revascularization procedures may be technically and clinically feasible in both adult and pediatric patients.

Conclusions

In this study we demonstrated successful combined revascularization surgery in adult and pediatric MMD patients and identified age-dependent characteristics of
the different revascularization procedures. In adult MMD patients, both revascularization strategies (STA-MCA bypass plus EMS) may be applied, with STA-MCA bypass showing better angiographic improvement and revascularization potential than EMS. In pediatric patients both revascularization strategies may be applied, with EMS showing better development over time.

Disclaimer

The authors do not report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper

References


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