Assessment of cerebral hemodynamics in childhood moyamoya disease using a quantitative and a semiquantitative IMP-SPECT study

Norihiro Saito,* Jyoji Nakagawara,** Hirohiko Nakamura** and Akira Teramoto*

*Department of Neurosurgery, Nippon Medical School **Department of Neurosurgery, Nakamura Memorial Hospital

Background: We evaluated the cerebral hemodynamics in childhood moyamoya disease patients before and after surgery to assess both surgical indication and the effect of revascularization using single photon emission computed tomography (SPECT) study with N-isopropyl-p-123Iiodoamphetamine (IMP). We compared results of quantitative and semi-quantitative SPECT studies to determine parameters by the semi-quantitative method to define severe hemodynamic ischemia. Methods: There were 14 pediatric patients with moyamoya disease who suffered transient ischemic attacks (TIAs) in the anterior circulation. Before and after surgical revascularization by STA-MCA bypass and encephalomyosynangiosis (EMS), quantitative IMP-SPECT studies using the autoradiographic method (IMP-ARG method) were performed. Resting regional cerebral blood flow (rCBF) and regional vascular reserve (rVR) were measured in bilateral cortical territories (ROI) and cerebellum. Semi-quantitative parameters were calculated from the ratio of ROI counts to the dominant cerebellar counts (ROI/Ce ratio) at resting and acetazolamide-activated conditions. Results: Before surgery, the mean resting rCBF and rVR in bilateral ACA and MCA territories were less than 40 ml/100 g/min and less than 10%, respectively, indicating severe hemodynamic ischemia. Except for the ACA territories, both the mean resting rCBF and mean rVR values in the entire cortex increased significantly after surgery (p < 0.05). By semi-quantitative studies, before surgery, the mean resting and acetazolamide-activated ROI/Ce ratios in bilateral ACA and MCA territories were less than 0.90 and 0.80, respectively. The mean resting and acetazolamide-activated ROI/Ce ratios increased significantly in the MCA territory after surgery. Severe hemodynamic ischemia, which categorized by the quantitative thresholds (resting rCBF < 40 ml/100 g/min and rVR < 10%) was diagnosed by the semi-quantitative thresholds (resting ROI/ Ce ratio < 0.90 and acetazolamide-activated ROI/Ce ratio < 0.85), the sensitivity and specificity of which were 87.5% and 90.9%, respectively. Conclusions: The cerebral hemodynamics in childhood moyamoya disease was improved entirely after surgery. Severe hemodynamic cerebral ischemia was diagnosed by not only quantitative but also semi-quantitative IMP-SPECT studies.

Key words: moyamoya disease, hemodynamic cerebral ischemia, single photon emission tomography, cerebral blood flow, vascular reserve

INTRODUCTION

MOYAMOYA DISEASE is characterized by progressive vascular occlusion of the circle of Willis accompanied by dilated

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For reprint contact: Norihiro Saito, M.D., Department of Neurosurgery, Nippon Medical School, 1–1–5, Sendagi, Bunkyoku, Tokyo 113–8603, JAPAN.

perforating arteries, which are so-called moyamoya vessels, in the regions of basal ganglia and thalami. In pediatric patients with moyamoya disease, common symptoms are transient ischemic attacks (TIAs) after episodes of hyperventilation. Repeated TIAs in childhood may result in progressive deterioration of cerebral hemodynamics. This hemodynamic deterioration may lead to permanent neurological deficits due to cortical infarction. Once they have developed permanent neurological deficits, there is little chance for surgical treatment to improve the neurological

Table 1 Characteristics of patients

Patient (No.)	Age (y)/sex	Cerebral Infarction or MRI	TIA Onset Age (y)	Revascularization Age (y)	Treatment
1	19F	rt. subcortex small	5	5	bilt. STA-MCA + EMS
2	27M	cortex	4		conservative
3	17 M	subcortex	7	15	bilt. STA-MCA + EMS
4	14F	cortex	4	9	bilt. STA-MCA + EMS
5	9F	intact	5	8	bilt. STA-MCA + EMS
6	20M	rt. subcortex small	14	14	bilt. STA-MCA + EMS
7	8F	lt. subcortex small	4	7	bilt. STA-MCA + EMS
8	15M	subcortex	6	12	lt. STA-MCA + EMS
9	12F	lt. subcortex small	4	7	bilt. STA-MCA + EMS
10	13F	subcortex	3	5	bilt. STA-MCA + EMS
11	24F	subcortex	15	19	bilt. STA-MCA + EMS
12	18F	subcortex small	3	3	bilt. STA-MCA + EMS
13	21M	rt. subcortex small	4	10	bilt. STA-MCA + EMS
14	18F	rt. subcortex small	6		conservative

TIA: transient ischemic attack, bilt: bilatel, STA: superior temporal artery, MCA: middle cerebral artery,

EMS: encephalomyosynangiosis

status. Moyamoya disease can be found worldwide, especially in Asia. ^{6,7} Over 5 years only 63–77 new Japanese pediatric cases per year have been registered, and moyamoya disease does not appear to be endemic. ⁸ In Japan, there is no consensus on the proper surgical treatment for childhood moyamoya disease. Among the many different ways of treatment for moyamoya disease, our choice for pediatric cases presenting with TIAs is bilateral superficial temporal artery to middle cerebral artery (STA-MCA) bypass with encephalomyosynangiosis (EMS). ^{9–11} All patients treated in this manner in the past 13 years are currently free of TIAs and able to pursue the normal activities of daily life.

Appropriate evaluation criteria must be established to determine both surgical indication and the effect of surgical revascularization in pediatric patients with moyamoya disease. 12 Although measurement of regional cerebral blood flow (rCBF) and metabolism using positron emission tomography (PET) may be the most accurate, this method is too complicated and expensive to be used widely. 13-15 Technical advances have made it possible to accurately determine cerebral hemodynamics by quantitative single photon emission computed tomography (SPECT) study with *N*-isopropyl-*p*-¹²³I-iodoamphetamine and autoradiography (IMP-ARG method), 16,17 but this method is not yet widely adopted for pediatric cases because of its invasiveness such as blood sampling, which may make the patient cry and alter the result. Semiquantitative IMP-SPECT using the dominant cerebellar hemisphere as the reference is an easy and less invasive method. We retrospectively determined the cerebral hemodynamics of childhood moyamoya disease before and after surgical revascularization using quantitative and semi-quantitative IMP-SPECT studies. We report that semi-quantitative IMP-SPECT study is a simple alternative to quantitative IMP-SPECT study in the assessment of surgical indication, based on our results.

PATIENTS AND METHODS

The study population consisted of 14 pediatric patients who suffered TIAs in the anterior circulation. They were 5 boys and 9 girls with disease onset ages ranging from 3 to 15 years (6.0 \pm 2.6 yrs). All patients were registered for this study based on the clinical manifestations, angiographic staging according to Suzuki and Takaku, ¹ and on MRI findings. All patients had a history of hemiparesis and/or aphasia (TIA) after hyperventilation episodes; 12 suffered recent (within a few months) TIA episodes. Based on the angiographic findings, all patients were classified as stage III. Of the 14 patients, one had no ischemic lesion on MRI, 11 had a small subcortical infarction (< 10 mm) at the watershed zone and 2 had asymptomatic cortical infarctions smaller than 20 mm in diameter. The patients manifested no residual disabilities that affected their daily lives. Revascularization was performed by bilateral STA-MCA bypass with EMS in 11 cases; one patient underwent unilateral bypass because of mild hemodynamic ischemia proved in the contralateral cerebral hemisphere. The remaining 2 patients were treated conservatively with antiplatelet and anticonvulsant medications because no TIA episode had appeared for a long time prior to this study. The duration of the postoperative follow-up was between 0.6 and 11 years $(4.8 \pm 3.0 \text{ yrs})$. Our operative procedure is detailed below, and information on patients is presented in Table 1. Between 1995 and 2000, the cerebral hemodynamics was evaluated in 7 patients (number of hemispheres = 14) scheduled for surgical revascularization; 2 of these were eventually treated conservatively. In addition, 10 patients (number

of hemispheres = 20) were evaluated after surgical revascularization using the IMP-ARG method. 16,17 Two patients refused SPECT study for personal reasons. Both resting rCBF and acetazolamide-activated rCBF were measured; regional vascular reserve (rVR) was defined as (acetazolamide-activated rCBF/resting rCBF - 1) × 100%. Quantitative rCBF value using SPECT technology was generally underestimated due to inadequate scatter and attenuation corrections; we assumed the normal rCBF value in children as more than 50 ml/100 g/min using IMP-ARG method, and pediatric patients with moyamoya disease who showed both resting rCBF less than 40 ml/ 100 g/min and rVR less than 10% were categorized as having severe hemodynamic ischemia. Region of interests (ROIs) were selected in bilateral anterior cerebral artery (ACA), middle cerebral artery (MCA) and posterior cerebral artery (PCA) territories on both axial levels of the basal ganglia (ACA1, MCA1, PCA1) and the centrum semiovale (ACA2, MCA2, PCA2), and bilateral cerebellum (Fig. 1). The axial levels of the basal ganglia and the centrum semiovale were adjusted at 50 mm and 85 mm above and parallel to the orbitomeatal line, respectively. Regions with infarcted areas were excluded. We used the automatic registration tool (ART) method to improve the accuracy of our ROI analysis; this method allows identification of identical regions on different SPECT studies. Furthermore, we evaluated cerebral hemodynamics using semi-quantitative parameters calculated from mean SPECT counts as follows: resting ROI/ Ce ratio = mean resting SPECT counts in ROI/mean resting SPECT counts in the dominant cerebellum (the hemisphere which shows the higher counts): acetazolamide-activated ROI/Ce ratio = acetazolamide-activated mean SPECT counts in ROI/acetazolamide-activated mean SPECT counts in the dominant cerebellum. For statistical analysis of changes in quantitative and semi-quantitative parameters in MCA territories (number of ROIs = 27) before and after surgical revascularization, we used the non-paired t-test; significant difference was defined as p < 0.05. For statistical analysis of correlations between quantitative and semi-quantitative parameters for diagnosis of severe hemodynamic ischemia, we used the Fisher exact test, again defining significance as p < 0.05.

IMP-ARG Method

IMP (222 MBq) was infused for 1 min into the antecubital vein at a constant infusion rate. At 10 min after the start of the infusion, one arterial blood sample was taken to calibrate the previously determined standard input function. Whole-blood radioactivity concentration was counted using a well counter that was cross-calibrated to the SPECT scanner. A single SPECT scan was performed at a mid-scan time of 30 min after IMP administration. In 2-compartment analysis of IMP, the distribution volume (Vd) and the ratio of influx constant and efflux constant can be set to a constant value (41.2 ml/ml). rCBF maps

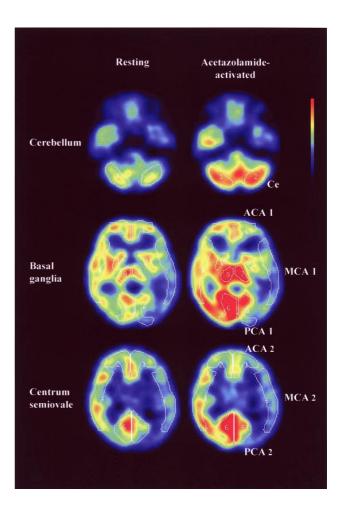


Fig. 1 Identification of regions of interest (ROIs) on different SPECT studies using the automatic registration tool (ART). *left;* resting CBF image, *right;* acetazolamide-activated CBF image. ACA; anterior cerebral artery, MCA; middle cerebral artery, PCA; posterior cerebral artery, Ce; cerebellum, ACA1, MCA1, PCA1 (level of basal ganglia), ACA2, MCA2, PCA2 (level of centrum semiovale)

were calculated pixel by pixel (128×128 matrix size) from single SPECT data and the standard input function calibrated by the one-point arterial blood sample. 16 Acetazolamide-activated rCBF maps were obtained by administering acetazolamide (15 mg/kg, intravenously) 7 min before the start of IMP infusion. 18 Appropriate scatter and attenuation correction are prerequisites for quantitative SPECT studies. In our institute triple-energy window method and Chang method with constant μ (μ = 0.146) are used for scatter and attenuation correction. The validity of which is well known. 19,20 We can achieve agreement between IMP SPECT flow and PET flow measurements by these methods. We measured resting rCBF and acetazolamide-activated rCBF separately. The interval between the studies was within a week, and so the reproduction should be valid. Concerning the safety of IMP, it is not available in some countries because the risk of very

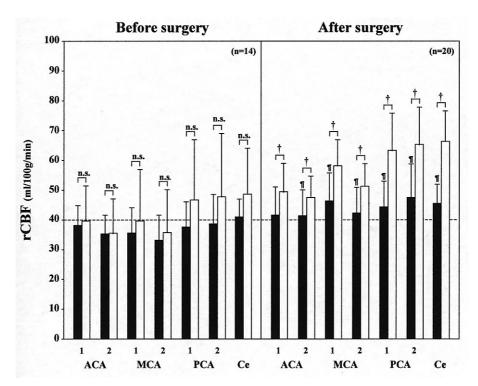


Fig. 2 Closed column demonstrating mean resting rCBF and open column demonstrating acetazolamide-activated rCBF in the respective ROIs before (14 hemispheres) and after (20 hemispheres) surgical revascularization (the bars showed S.D.). \dagger ; Significant differences between resting rCBF and acetazolamide-activated rCBF (non-paired t test p < 0.05). \P ; Significant differences between resting rCBF before and after surgical revascularization (non-paired t test p < 0.05).

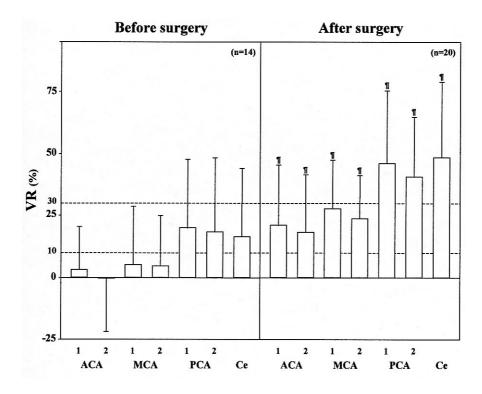


Fig. 3 Mean regional vascular reserve (rVR) before (14 hemispheres) and after (20 hemispheres) surgical revascularization (the bars showed S.D.). \P ; Significant differences between rVR before and after surgical revascularization (non-paired t test p < 0.05).

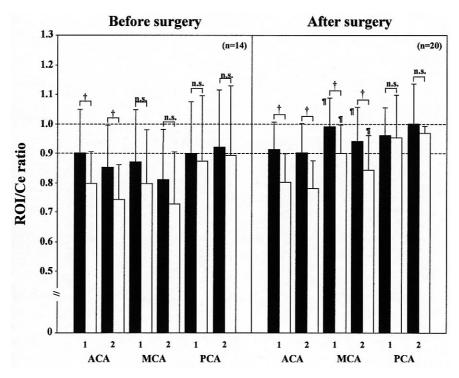


Fig. 4 Closed circle demonstrating mean resting ROI/Ce ratio and open circle demonstrating acetazolamide-activated ROI/Ce ratio in respective ROIs before and after surgical revascularization (the bars show S.D.). \dagger ; Significant differences between resting and acetazolamide-activated ROI/Ce ratios (non-paired t test p < 0.05). \P ; Significant differences between resting and acetazolamide-activated ROI/Ce ratios before and after surgical revascularization (non-paired t test p < 0.05).

high radiation exposure to the eye. However, its delivery has been commercialized in Japan. The eye and thyroid gland those are relatively small organs but contain high concentrations of radiotracer. While the thyroid can be blocked with Lugol's solution, there is no blocking method for the eye. Holman states that even with the dose levels calculated from monkey data, the radiation exposure presents no significant health problem for anticipated 111–185 MBq dosages in man,²¹ which regarded as being within a permissible range.^{22,23}

Automatic Registration Tool (ART) Method

The ART method allows the 3-dimensional superimposition of neuroimages to obtain a combined image. 24,25 After spatially recording the two-volume data from SPECT images, a common axis can be obtained by rigid-body transformation of one image onto the other. Transformation, as used here, means both rotation and translation in x, y, and z directions; this makes it possible to adjust the two-volume data from SPECT images using 6 parameters. The optimal transformations are completed by minimizing the sum of the squared differences between connected components from each image. Using this method, the same ROI can be identified on different SPECT studies involving volume data pertaining to resting rCBF and acetazolamide-activated rCBF images (Fig. 1).

Operative Procedures

We usually performed a single anastomosis between the superficial temporal artery (STA) and a cortical branch of the MCA with EMS, 9-11,26,27 bilaterally in a staged manner (3~6 month interval). After direct anastomosis, the temporal muscle with the deep temporal artery (DTA) was placed on the cerebral cortex through the dural window, preserving the middle meningeal artery (MMA). Indirect anastomosis could be obtained between the DTA, MMA and MCA via neovascularization. ^{10,26,28,29}

RESULTS

Figure 2 shows the mean values of resting and acetazolamide-activated rCBF in entire cortical territories and cerebellum before (14 hemispheres) and after (20 hemispheres) surgical revascularization, and standard deviation. In the ACA and MCA territories, the preoperative resting rCBF values were less than 40 ml/100 g/min. The differences between resting and acetazolamide-activated rCBF were not significant within entire cortical territories and cerebellum. The mean rVR was less than 20% in entire cortical territories and cerebellum; it was less than 10% in the ACA and MCA territories indicating a reduction of rVR (Fig. 3). After surgical revascularization, mean resting rCBF values were increased significantly in entire cortical territories and cerebellum (p < 0.05) except

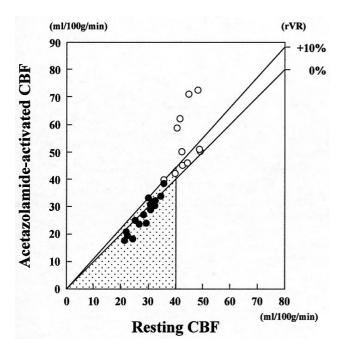


Fig. 5 Resting CBF and acetazolamide-activated CBF in the MCA territories (MCA1 and MCA2) from individual ROI data (n = 27) are plotted in *X-Y* coordinates. The slope of the oblique line shows regional vascular reserve (rVR). Sixteen closed circles () were classified as severe hemodynamic cerebral ischemia within the thresholds of both resting CBF < 40 m/100 g/min and rVR < 10%, and 11 open circles () were classified as mild hemodynamic cerebral ischemia beyond the thresholds.

for the lower ACA1 territory (p = 0.24) (Fig. 2). However, the mean resting rCBF in the ACA and MCA territories was elevated above 40 ml/100 g/min. The mean acetazolamide-activated rCBF values were also increased in entire cortical territories and cerebellum. The differences between resting rCBF and acetazolamide-activated rCBF were significant within entire cortical territories and cerebellum (p < 0.05). The mean rVR in the ACA and MCA territories increased to more than 10% (Fig. 3).

Figure 4 shows the relationship between resting and acetazolamide-activated ROI/Ce ratios in entire cortical territories before (14 hemispheres) and after (20 hemispheres) surgical revascularization, and statistical differences. Before revascularization, the mean resting ROI/Ce ratio in the ACA and MCA territories was less than 0.90. The mean acetazolamide-activated ROI/Ce ratio in the ACA and MCA territories was less than 0.80. After revascularization, the mean resting ROI/Ce ratio was increased significantly in MCA1 (p = 0.0163) and MCA2 (p = 0.0139). The mean resting ROI/Ce ratio in the ACA and MCA territories increased to more than 0.90. In addition, the mean acetazolamide-activated ROI/Ce ratio increased significantly in MCA1 (p = 0.038) and MCA2 (p = 0.034).

Figure 5 shows plots in *X-Y* coordinates of resting and

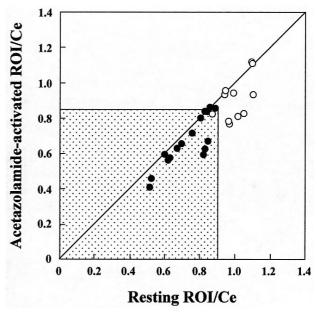


Fig. 6 Resting and acetazolamide-activated ROI/Ce ratios in the MCA territories (MCA1 and MCA2) from individual ROI data (n = 27) are plotted in X-Y coordinates. Fourteen of 16 ROIs () classified as severe hemodynamic cerebral ischemia by quantitative method were involved within the thresholds of both resting ROI/Ce ratio < 0.9 and acetazolamide-activated ROI/Ce ratio < 0.85. One of 11 plots beyond the thresholds of severe hemodynamic cerebral ischemia by quantitative method was involved within the semi-quantitative thresholds stated above. The sensitivity and specificity of the semi-quantitative method were 87.5% and 90.9%, respectively.

acetazolamide-activated rCBF values in the MCA territories (MCA1 and MCA2) from 27 of the 28 individual ROIs data sets obtained before surgery. The slope of the oblique line in Figure 5 indicates rVRs of +10% and 0%. Sixteen closed circles from patients with frequent TIAs were classified as severe hemodynamic cerebral ischemia within the thresholds of both resting CBF (less than 40 ml/100 g/min) and rVR (less than 10%), and 11 open circles including data from patients without frequent TIA were classified as mild hemodynamic cerebral ischemia out of the thresholds.

Figure 6 demonstrates plots in *X-Y* coordinates of resting and acetazolamide-activated ROI/Ce ratios in the MCA territories from 27 individual ROI data in the same manner as Figure 5. Fourteen of 16 plots classified as severe hemodynamic cerebral ischemia by the quantitative method were involved within the semi-quantitative thresholds of both resting ROI/Ce ratio less than 0.9 and acetazolamide-activated ROI/Ce ratio less than 0.85 (Sensitivity). On the other hand, one of 11 plots beyond the thresholds of severe hemodynamic cerebral ischemia by quantitative method was involved within the semi-quantitative thresholds stated above (Specificity). The sensitivity and specificity of the semi-quantitative thresholds were 87.5% and 90.9%, respectively. There was no statis-

tically significant difference with regard to the diagnosis of severe hemodynamic cerebral ischemia obtained by quantitative thresholds or semi-quantitative thresholds (by the Fisher exact test, p < 0.0001).

DISCUSSION

In this study, none of the pediatric patients with moyamoya disease who underwent surgical revascularization experienced post-treatment stroke. Their TIAs subsided gradually after surgery, and their ADL improved to allow them to lead normal daily lives. In addition, no conservatively treated patients exhibited ischemic stroke. The pathological process seems to be active through about 10 years of age, and then it is considered to stabilize. Two conservatively treated patients became older than 10 years prior to this study. We evaluated all of the patients' cerebral hemodynamics before (surgical and conservative cases) and after treatment (surgical cases) to determine both surgical indication and the effect of revascularization on the cerebral cortex. We used quantitative thresholds obtained by the IMP-ARG method. 16,17 This method was developed as a simplified quantitative measurement of rCBF using IMP-SPECT and a one-point arterial blood sample. The validity of the rCBF value obtained by this method has been established.¹⁷ However, various factors such as hemoglobin, PaCO2, and blood pressure may influence quantitative values.^{30–32} Among these factors, the major factor seems to be fluctuations in PaCO₂ resulting from hyperventilation associated with procedures for one-point arterial blood sampling.³¹ However, PaCO₂ levels of sampled blood were not considered in our study. There were no patients who appeared to suffer from hyperventilation due to crying or who suffered from lung disease, blood abnormalities including anemia or polycythemia, or from hypertension. To rule out contributing factors, we examined chest X-rays and laboratory data. Mean hemoglobin (13.4 \pm 0.7 g/dl) and mean blood pressure $(120 \pm 6.4 / 71 \pm 9.6 \text{ mmHg})$ at rest were normal. Other major difficulties such as the selection of appropriate ROIs were not solved in previous SPECT studies. In an earlier SPECT study, 18 we arbitrarily selected almost the same ROIs on different SPECT images. We approached this problem by using the automatic registration tool (ART) method. Because of significant technical improvements, we can now obtain accurate ROI data for each patient.

Moyamoya disease is generally characterized as progressive cortical ischemia in the anterior circulation. Earlier it was assumed that cerebellar blood flow supplied by the vertebrobasilar system was not affected in moyamoya disease. However, the results of our study show that rCBF and rVR in the cerebellum were significantly decreased before surgical revascularization and that after surgical intervention they were increased remarkably. Furthermore surgical revascularization for MCA

territories improved both resting rCBF and rVR in the both anterior and posterior circulation territories. This suggests that improvement in the cerebral hemodynamics in the anterior circulation affected the metabolism in the entire brain. It is possible that the improvement of both rCBF and metabolic state due to normalization of neural activation in the anterior circulation territories extended to the entire brain via the extensive fiber connections between the anterior and posterior circulation territories (crossed cerebellar activation). ^{33–36} In addition, the decrease in the collateral blood supply from the posterior circulation to the ACA and/or MCA territories after surgical revascularization, the disappearance of the steal phenomenon, ³⁷ may also play a significant role in the improvement of rVR.

We could categorize the severity of hemodynamic cerebral ischemia using quantitative thresholds from our data (Figs. 2 and 3). Before surgery, the mean resting rCBF and rVR in bilateral ACA and MCA territories were less than 40 ml/100 g/min and less than 10%, respectively; however, except for the ACA territories, both the mean resting rCBF and mean rVR values in the entire cortex increased significantly after surgery (p < 0.05). The value of rVR in PCA and Ce normalized after surgery above 30%. From the above findings, we categorized the stages of hemodynamic cerebral ischemia in pediatric patients with moyamoya disease as follows: normal hemodynamics in which rVR is maintained at more than 30%; mild hemodynamic ischemia in which either the rCBF is maintained at more than 40 ml/100 g/min or the rVR is maintained at more than 10%; severe hemodynamic ischemia in which the resting rCBF is less than 40 ml/100 g/min and rVR is less than 10%. Before surgical revascularization, most of the ROIs in the ACA and MCA territories were categorized as severe hemodynamic ischemia. Severe hemodynamic ischemia could be reversed or eliminated entirely by surgical revascularization.

To establish more common parameters, we evaluated cerebral hemodynamics by semi-quantitative SPECT study using ROI/Ce ratio. We selected the cerebellum as the denominator in this equation because it is fed by the vertebrobasilar system and thus is minimally affected by moyamoya vessels. In our series there were no moyamoya vessels in the cerebellum on angiography. According to results of the quantitative SPECT method, before revascularization, the difference between resting and acetazolamide-activated rCBF was not significant in the cerebellum. However, because mean rCBF in cerebellum is higher than in cerebral cortex, we selected the cerebellum as the denominator. Results of our semi-quantitative study showed that mean resting and acetazolamide-activated ROI/Ce ratios were less than 0.90 and 0.80, respectively, indicating severe hemodynamic ischemia in the ACA and MCA territories before surgical revascularization (Fig. 4). These ratios increased significantly in the MCA territories after revascularization as a result of the surgical

treatment (Fig. 4).

From evaluation of individual ROI data from the MCA territories, 16 ROIs from patients with recent TIAs were classified as severe hemodynamic cerebral ischemia within the thresholds of both resting CBF (less than 40 ml/100 g/ min) and rVR (less than 10%), and 11 ROIs including data from patients without recent TIA were classified as mild hemodynamic cerebral ischemia out of the thresholds. Fourteen of 16 ROIs classified as severe hemodynamic cerebral ischemia by quantitative method were involved within the semi-quantitative thresholds of both resting ROI/Ce ratio less than 0.9 and acetazolamide-activated ROI/Ce ratio less than 0.85 (Sensitivity; 87.5%). On the other hand, one of 11 ROIs beyond the thresholds of severe hemodynamic cerebral ischemia by quantitative method was involved within the semi-quantitative thresholds stated above (Specificity; 90.9%) (Fig. 5 and Fig. 6). Our findings suggest the semi-quantitative threshold could also easily identify that severe hemodynamic ischemia determined by use of the quantitative threshold. Therefore, we propose that the semi-quantitative parameters (ROI/Ce ratio) can be substituted for the quantitative parameters. Further studies are needed to determine appropriate ranges for the semi-quantitative thresholds that would reflect the quantitative thresholds. Once these appropriate generalized thresholds are established, they could be used to obtain accurate information concerning surgical indication and treatment strategies for pediatric patients with moyamoya disease.

CONCLUSION

The cerebral hemodynamics of pediatric patients with moyamoya disease was improved significantly in the entire brain after bilateral STA-MCA bypass with EMS. Severe hemodynamic cerebral ischemia could be diagnosed not only by quantitative IMP-SPECT study but also by semi-quantitative IMP-SPECT study. The ROI/Ce ratio represents more general and common parameters than do the quantitative parameters in the assessment of surgical indication.

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REFERENCES

- 1. Suzuki J, Takaku A. Cerebrovascular 'Moyamoya' disease. Disease showing abnormal net-like vessels in base of brain. Arch Neurol 1969; 20: 288-299.
- 2. Kurokawa T, Tomita S, Ueda K. Prognosis of occlusive disease of the circle of Willis in children. Pediatr Neurol 1985; 1: 274-277.

- 3. Fukuyama Y, Umezu R. Clinical cerebral angiographic evaluations of idiopathic progressive occlusive disease of the circle of Willis in children. Brain Dev 1985; 7: 21–37.
- 4. Imaizumi T, Hayashi K, Saito K. Long term outcomes of pediatric moyamoya disease monitored to adulthood. Pediatr Neurol 1998; 18: 321-325.
- 5. Yonas H, Smith HA, Durham SR, Pentheny SL, Johnson DW, Holly A, et al. Increased stroke risk predicted by compromised cerebral blood flow reactivity. J Neurosurg 1993; 79: 483–489.
- 6. Goto Y, Yonekawa Y. Worldwide distribution of moyamoya disease. Neurol Med Chir (Tokyo) 1992; 32: 883-886.
- 7. Yonekawa Y, Handa H, Okuno T. Moyamoya disease: diagnosis, treatment, and recent achievements. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. Stroke: Pathophysiology, Diagnosis, and Management. 2nd ed. New York, NY; Churchill Livingstone, Inc., 1992: 721–747.
- 8. Fukui M. Current state of study on moyamoya disease in Japan. Surg Neurol 1997; 47: 138-143.
- 9. Karasawa J, Kikuchi H, Furuse S, Kawamura J, Sasaki T. Treatment of Moyamoya disease with STA-MCA anastomosis. J Neurosurg 1978; 49: 679-688.
- 10. Karasawa J, Touho H, Ohonishi H, Miyamoto S, Kikuchi H. Cerebral revascularization using omental transplantation for childhood moyamoya disease. J Neurosurg 1993; 79: 192-196.
- 11. Karasawa J, Kikuchi H, Furuse S, Sasaki T, Yoshida Y, Ohnishi H, et al. A surgical treatment of 'Moyamoya disease': 'Encephalo-myo-synangiosis'. Neurol Med Chir 1997; 17 (Part 1): 29-37.
- 12. Ishikawa T, Houkin K, Kamiyama H, Abe H. Effects of surgical revascularization on outcome of patients with pediatric moyamoya disease. Stroke 1997; 28: 1170-1173.
- 13. Ikezaki K, Matsushima T, Kuwabara Y, Suzuki S, Nomura T, Fukui M. Cerebral circulation and oxygen metabolism in childhood Moyamoya disease: a perioperative positron emission tomography study. J Neurosurg 1994; 81: 843-
- 14. Kuwabara Y, Ichiya Y, Otsuka H, Takahara T, Gunasekera R, Hasuo K, et al. Cerebral hemodynamic change in the child and the adult with Moyamoya disease. Stroke 1990; 21: 272-277.
- 15. Taki W, Yonekawa Y, Kobayashi A, Ishikawa M, Kikuchi H, Nishizawa S, et al. Cerebral circulation and oxygen metabolism in moyamoya disease of ischemic type in children. Child Nerve Syst 1988; 4: 259-262.
- 16. Iida H, Itoh H, Nakazawa M, Hatazawa J, Nishimura H, Ohnishi Y, et al. Quantitative mapping of regional cerebral blood flow using iodine-123-IMP and SPECT. J Nucl Med 1994; 35: 2019-2030.
- 17. Iida H, Akutsu T, Keigo E, Fukuda H, Inoue T, Itoh H, et al. A multicenter validation of regional cerebral flow quantification using ¹²³I iodoamphetamine and single photon emission computed tomography. J Cereb Blood Flow Metab 1996; 16: 781-793.
- 18. Nakagawara J, Takeda R, Suematsu K, Nakamura J. Quantification of regional cerebral blood flow and vascular reserve in childhood Moyamoya disease using 123I IMP-ARG method. Clin Neurol Neurosurg 1997; 99: 96–99.
- 19. Ichihara T, Ogawa K, Motomura N, Kubo A, Hashimoto S. Compton scatter compensation using triple-energy window

- method for single- and dual-isotope SPECT. *J Nucl Med* 1993; 34: 2216–2221.
- Iida H, Narita Y, Kado H, Kashikura A, Sugawara S, Shoji Y, et al. Effects of scatter and attenuation correction on quantitative assessment of regional cerebral blood flow with SPECT. J Nucl Med 1998; 39: 181–189.
- Holeman BL, Zimmerman RE, Schapiro JR, Kaplan ML, Jones AG, Hill TC. Biodistribution and dosimetry of *N*-isopropyl-*p*-¹²³I-iodoamphetamine in the primate. *J Nucl Med* 1983: 24: 922–931.
- Lieberman LM. The effect of radiation on the retina of the dog. PhD Dissertation, Univ. of Michigan, Ann Arbor, 1970
- 23. Merrian GR Jr, Focht EF. A clinical study of radiation cataracts and relationship to dose. *Am J Roentgen* 1957; 77: 759–785
- Babak AA, Michael B, Brian FH, Kanno I. A fully automatic multimodality image registration algorithm. *J Comput Assist Tomogr* 1995; 19: 615–623.
- Teves ST, Mitchell KD, Habboush IH. Three-dimensional image alignment, registration and fusion. *Quart J Nucl Med* 1998; 42: 83–92.
- Matsushima T, Fujiwara S, Nagata S, Fujii K, Fukui M, Kitamura K, et al. Surgical treatment for pediatric patients with Moyamoya disease by indirect revascularization procedures (EDAS, EMS, EMAS). *Acta Neurochir* 1989; 98: 135–140.
- Miyamoto S, Kikuchi H, Karasawa J, Nagata I, Yamazoe N, Akiyama Y. Pitfalls in surgical treatment of moyamoya disease: operative techniques for refractory cases. *J Neurosurg* 1998; 68: 537–543.
- 28. Houkin K, Kamiyama H, Takahashi A, Kuroda S, Abe H. Combined revascularization surgery for childhood

- moyamoya disease: STA-MCA and encephalo-duro-arterio-myo-synangiosis (EDAMS): technical note. *Child's Nerv Syst* 1997; 13: 24–29.
- Nariai T, Suzuki R, Matsushima Y, Ichimura K, Hirakawa K, Ishii K, et al. Surgically induced angiogenesis to compensate for hemodynamic cerebral ischemia. *Stroke* 1994; 25: 1014–1021.
- Mackenzie ET, Farrar JK, Fitch W, Graham DI, Gregory PC, Harper AM. Effects of hemorrhagic hypotension on the cerebral circulation. 1. Cerebral blood flow and pial arteriolar caliber. *Stroke* 1979; 10: 711–718.
- 31. Olsen J. Quantitative evaluation of normal and pathologic cerebral blood flow regulation to perfusion pressure. *Arch Neurol* 1973; 28: 143–149.
- 32. Wood JH, Polyzoidis KS, Epstein CM, Gibby GL, Tindall GT. Quantitative EEG alterations after isovolemic hemodilutional augmentation of cerebral perfusion in stroke patients. *Neurology* 1984; 34: 764–768.
- Lassen NA, Friberg L, Rizzi D, Jensen JJ. Effect of acetazolamide on cerebral blood flow and brain tissue oxygenation. *Postgrad Med J* 1987; 63: 185–187.
- Lenzi GL, Frackowiak RSJ, Jones T. Cerebral oxygen metabolism and blood flow in human cerebral ischemic infarction. J Cereb Blood Flow Metab 1982; 2: 321–335.
- Martin WRW, Raichle ME. Cerebellar blood flow and metabolism in cerebral hemispheric infarction. *Ann Neurol* 1983; 14: 168–176.
- Yamauchi H, Fukuyama H, Kimura J. Hemodynamic and metabolic changes in crossed cerebellar hypoperfusion. *Stroke* 1992; 23: 855–859.
- Bogousslavsky J, Regli F. Vertebrobasilar transient ischemic attacks in internal carotid occlusion or tight stenosis. *Arch Neurol* 1985; 42: 64–68.