Assessment of Cerebral Hemodynamic Changes in Pediatric Patients with Moyamoya Disease Using Probabilistic Maps on Analysis of Basal/Acetazolamide Stress Brain Perfusion SPECT

Ho-Young Lee, M.D.1, Jae Sung Lee, PhD1, Seung-Ki Kim, M.D.2, Kyu-Chang Wang, M.D.2, Byung-Kyu Cho, M.D.2, June-Key Chung, M.D.1, Myung Chul Lee, M.D.1 and Dong Soo Lee, M.D.1
Departments of 1Nuclear Medicine and 2Pediatric Neurosurgery, Seoul National University College of Medicine, Korea

To evaluate the hemodynamic changes and the predictive factors of the clinical outcome in pediatric patients with moyamoya disease, we analyzed pre/post basal/acetazolamide stress brain perfusion SPECT with automated volume of interest (VOIs) method. Methods: Total fifty six (M:F=33:24, age 6.7±3.2 years) pediatric patients with moyamoya disease, who underwent basal/acetazolamide stress brain perfusion SPECT within 6 before and after revascularization surgery (encephalo-duro-arterio-synangiosis (EDAS) with frontal encephalo-galeo-synangiosis (EGS) and EDAS only followed on contralateral hemisphere), and followed-up more than 6 months after post-operative SPECT, were included. A mean follow-up period after post-operative SPECT was 33±21 months. Each patient's SPECT image was spatially normalized to Korean template with the SPM2. For the regional count normalization, the count of pons was used as a reference region. The basal/acetazolamide-stressed cerebral blood flow (CBF), the cerebral vascular reserve index (CVRI), and the extent of area with significantly decreased basal/acetazolamide-stressed rCBF than age-matched normal control were evaluated on both medial frontal, frontal, parietal, occipital lobes, and whole brain in each patient's images. The post-operative clinical outcome was assigned as good, poor according to the presence of transient ischemic attacks and/or fixed neurological deficits by pediatric neurosurgeon. Results: In a paired t-test, basal/acetazolamide-stressed rCBF and the CVRI were significantly improved after revascularization (p<0.05). The significant difference in the pre-operative basal/acetazolamide-stressed CBF and the CVRI between the hemispheres where EDAS with frontal EGS was performed and their contralateral counterparts where EDAS only was done disappeared after operation (p>0.05). In an independent student t-test, the pre-operative basal rCBF in the medial frontal gyrus, the post-operative CVRI in the frontal lobe and the parietal lobe of the hemispheres with EDAS and frontal EGS, the post-operative CVRI, and ΔCVRI showed a significant difference between patients with a good and poor clinical outcome (p<0.05). In a multivariate logistic regression analysis, the ΔCVRI and the post-operative CVRI of medial frontal gyrus on the hemispheres where EDAS with frontal EGS was performed were the significant predictive factors for the clinical outcome (p = 0.002, p = 0.015). Conclusion: With probabilistic map, we could objectively evaluate pre/post-operative hemodynamic changes of pediatric patients with moyamoya disease. Specifically the post-operative CVRI and the post-operative CVRI of medial frontal gyrus with EDAS with frontal EGS was done were the significant predictive factors for further clinical outcomes. (Nucl Med Mol Imaging 2008;42(3):192-200)

Key Words: moyamoya disease, brain SPECT, acetazolamide, clinical outcome, revascularization

INTRODUCTION

Basal/acetazolamide stress SPECT is a useful tool to evaluate the cerebrovascular reserve. Recently other tools such as MRI are developed to evaluate the cerebrovascular reserve. In the cerebrovascular disease, the evaluation of
hemodynamic state and vascular reserve is necessary for selecting an appropriate treatment. Most common cerebrovascular disease in pediatric patients is moyamoya disease. Moyamoya disease is characterized by progressive stenosis or occlusion in the end portion of the internal carotid arteries (ICA) with dilated perforating arteries in the region of the basal ganglia and thalami.1-4) With the progression of stenosis or occlusion, the common symptoms such as transient ischemic attacks (TIAs) can be induced by hyperventilation. As the hemodynamic deterioration advance, there will be repeated TIAs and the risk of cerebral infarct will increase.5) For the prevention of the repeated TIAs and the deterioration of cerebral hemodynamics, there are several types of revascularization surgery.6,7) In our institute, encephalo-duro-arterio-synangiosis (EDAS) was mainly performed to correct the hemodynamic state of the internal carotid artery (ICA) territory. However, the frontal encephalo-galeo-synangiosis (EGS) was combined with EDAS if there was a symptom related to the anterior cerebral artery (ACA) territory.

For the diagnosis and evaluation of the moyamoya disease, cerebral angiography and magnetic resonance imaging (MRI) is clinically performed.5,8) These modalities can only evaluate the morphological change of the vessel such as stenosis or occlusion. However, basal/acetazolamide stress brain perfusion SPECT or PET can evaluate not only the regional cerebral blood flow (rCBF) but also the vascular reserve.9-12) The deteriorated hemodynamic state can be corrected by revascularization surgery.13,14)

There are several ways of the interpretation of basal/acetazolamide stress brain perfusion SPECT. Visual interpretation is commonly used. However, it has a limitation due to the intra-observer and the inter-observer difference. To overcome the limitation and for the objective evaluation, the quantitative analysis is necessary. In our previous study, we evaluated the basal/acetazolamide stress brain perfusion SPECT with the manually drawn region of interest (ROIs) method.15) However, the ROIs method is not enough to overcome the intra-observer and the inter-observer difference. In this study, we applied the probabilistic maps of each lobe and the ICA territories, which were made from the Korean brain template.16) Our previous study showed the usefulness of this method in the evaluation of revascularization effect in the patients with middle cerebral artery stenosis.17)

In our institute, basal/acetazolamide stress brain perfusion SPECT is performed for pre- and post-operative evaluation of pediatric patients with moyamoya disease.12,13,18) In this study, we evaluated the hemodynamic changes of the moyamoya disease by using probabilistic maps for the objective quantification of pre/post-operative basal/acetazolamide stress brain perfusion SPECT.

**MATERIALS AND METHODS**

**Patients**

The patients, who were enrolled in this study, were diagnosed as moyamoya disease in the Children’s Hospital of Seoul National University. Twenty eight patients underwent left encephalo-duro-arterio-synangiosis with left frontal encephalo-galeo-synangiosis (EDAS with frontal EGS) and encephalo-duro-arterio-synangiosis (EDAS) only followed on the contralateral hemispheres. The other twenty eight patients underwent right EDAS with frontal EGS and EDAS only followed on the contralateral hemispheres.13,14,17-21) The hemisphere, where EDAS with frontal EGS was performed, was considered as an ipsilateral hemisphere.

To all patients, basal/acetazolamide stress brain perfusion SPECT was performed within 3 months before first operation and within 6 months after the last operation. The patients were followed up more than 6 months after the post-operative SPECT.

The ratio of males to females was 32 to 24, and their mean age at the first operation was 6.8 ± 3.0 years (range 7 months to 14 years). Twenty nine patients had cerebral infarction on their pre-operative MRI. The clinical characteristics of the patients are summarized on Table 1.

**Basal/acetazolamide stress brain perfusion SPECT**

Chloral hydrate syrup was used for the sedation of patients. For basal study, 9.25 MBq/kg of $^{99m}$Tc-hexamethylpropyleneamine oxime (HMPAO) (Amersham, Buckinghamshire, England) was intravenously injected and the acquisition started 5 minutes after injection. Ten minutes before the end of basal SPECT acquisition, 20 mg/kg of
Table 1. Clinical Characteristics of Total 56 Patients

<table>
<thead>
<tr>
<th></th>
<th>Good clinical outcome (n = 28)</th>
<th>Poor clinical outcome (n = 28)</th>
<th>Total (n = 56)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Mean±SD (Range)</td>
<td>7.5±2.6 years</td>
<td>6.3±3.5 years</td>
<td>6.8±3.0 years</td>
</tr>
<tr>
<td>Sex</td>
<td>Male : Female</td>
<td>11 : 17</td>
<td>14 : 14</td>
</tr>
<tr>
<td>Highest Suzuki stages*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>II</td>
<td>6 (21%)</td>
<td>2 (7%)</td>
<td>8 (14%)</td>
</tr>
<tr>
<td>III</td>
<td>16 (57%)</td>
<td>11 (38%)</td>
<td>27 (48%)</td>
</tr>
<tr>
<td>IV</td>
<td>4 (14%)</td>
<td>12 (41%)</td>
<td>16 (29%)</td>
</tr>
<tr>
<td>V</td>
<td>1 (3%)</td>
<td>2 (7%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>VI</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cerebral infarction on preoperative MRI</td>
<td>11 (39%)</td>
<td>18 (64%)</td>
<td>29 (52%)</td>
</tr>
</tbody>
</table>

* The variable which was significantly different between good and poor clinical outcome (p<0.05).

Acetazolamide was intravenously injected. Five minutes after the end of basal study acquisition, 18.5 MBq/kg of ⁹⁹mTc-HMPAO was injected, and the acquisition of stress study began 5 minutes after. Total procedure took about 45 minutes. The acetazolamide-stressed images were obtained by decay-corrected subtraction of the basal images from the corresponding stressed images.

A triple-head gamma camera (Prism 3000, Picker International, U. S. A.) with a low-energy high-resolution fanbeam collimator was used for the acquisition. Forty step-and-shoot images per detector were acquired with intervals of 3°for 20 seconds per each step. The SPECT images were reconstructed with filtered back-projection with Metz filter on 128×128 matrix.

Two nuclear physicians, who were unaware of the patients’ medical records performed the visual interpretation of the SPECT images.

Quantitative analysis

The SPECT images of each patient were transformed to the Analyze format. After the realignment between basal and acetazolamide-stressed SPECT images, each image was spatially normalized to the Korean template with the SPM2. The regional counts were normalized using the count of the pons as a reference (50ml/100g/min).

In volume of interest (VOI) analysis, the probabilistic maps of the medial frontal gyri, the frontal, the parietal, the temporal, and the occipital lobes, the internal carotid artery territory, and whole brain were used for evaluating the basal/acetazolamide-stressed regional CBF (rCBF).

With these results we calculated the cerebral vascular reserve index (CVRI)

\[ CVRI = \frac{C_{acetazolamide} - C_{basal}}{C_{basal}} \times 100 \]

Assessment of post-operative clinical outcomes

The post-operative clinical outcome of each patient was assigned to one of the following two categories on the last follow-up by their neurosurgeons: 1) good - The pre-operative symptoms such as transient ischemic attacks (TIAs) have totally disappeared without fixed neurological deficits; 2) poor - The neurological deficits remained, the symptoms were unchanged or aggravated.

Statistical analysis

A chi-square test was performed to compare the frequency of the infarct and the highest Suzuki stage between patients with a good and poor clinical outcome. A paired t-test was performed to compare the basal/acetazolamide-stressed rCBF and CVRI between pre-operative and post-operative states, and also between the hemispheres. Multivariate logistic regression was used for the analysis of predictive factors for clinical outcomes. Age at the first operation, the highest Suzuki stage of cerebral angiography, postoperative CVRI and ΔCVRI of a whole brain,
pre-operative basal cerebral blood flow of ipsilateral medial frontal gyrus, post-operative of ipsilateral frontal, and ipsilateral parietal lobe were considered as independent variables: post-operative clinical outcome was considered as a dependent variable. An independent t-test was used for the analysis of the basal/acetazolamide-stressed rCBF and the CVRI between patients with a good and poor clinical outcome, 

We used SPSS 12.0 for Windows. For all tests, P-value of < 0.05 was considered as a statistical significance threshold.

RESULTS

1. Hemodynamic improvement after revascularization

In the paired sample t-test, the basal/acetazolamide-stressed rCBF and the CVRI of the whole brain were significantly improved after operation (p<0.05, Table 2).

The regional analysis was performed on the ICA territory, the medial frontal gyrus, the frontal, the parietal, the temporal, and the occipital lobes. The basal/acetazolamide-stressed rCBF of the ICA territories, the medial frontal gyrus, the frontal, the parietal and the occipital lobes was significantly improved after both types of revascularization surgery (p<0.05, Table 2). However, there was no significant difference of cerebral blood flow on the occipital lobes. The CVRI on the ipsilateral medial frontal gyrus, and bilateral ICA territories was significantly improved after operation (p<0.05, Table 2).

2. Comparison of EDAS with frontal EGS and EDAS only

In the comparison between the ipsilateral hemispheres where EDAS with frontal EGS was done and their contralateral counterparts where EDAS only was done, the pre-operative basal rCBF on the frontal, the parietal lobes, and the ICA territory of the ipsilateral hemispheres, where EDAS with frontal EGS was performed, were significantly lower than their contralateral counterparts (Fig. 1, p=0.008, p=0.033, p=0.027). Furthermore, the pre-operative acetazolamide-stressed rCBF on the medial frontal gyrus, the frontal, the parietal lobes, and the ICA territory of ipsilateral hemispheres with EDAS and frontal EGS were significantly lower than their contralateral hemispheres (Fig. 1, p=0.032, p=0.001, p=0.001). The post-operative basal/acetazolamide-stressed rCBF and the pre/post-operative CVRI had no significant differences between ipsilateral hemisphere and their contralateral counterparts.

3. Comparison of patients with a good and a poor clinical outcome

There was no difference in the frequency of infarct (p=0.108), and the age at first operation (p=0.161) between patients with a good and a poor clinical outcome. However, the highest Suzuki grade of the patients with a poor clinical outcome was more severe than the patients with a good clinical outcome (p=0.031, Table 1).

On the independent student t-test, the post-operative CVRI (good: 3.6±7.6%, poor: -2.5±10%) and ΔCVRI
**Figure 1.** The pre-operative basal rCBF on ipsilateral frontal, parietal lobes, and ICA territory, on which EDAS with EGS was performed, were significantly lower than their contralateral hemisphere. The pre-operative acetazolamide-stressed rCBF on the ipsilateral medial frontal gyrus, frontal, parietal lobes, and ICA territory were significantly lower than their contralateral hemisphere. *, statistically significant difference between pre/post-operation.

In the treatment of patients with moyamoya disease, the correction of an abnormal hemodynamic state is necessary. To correct abnormal hemodynamics, revascularization is an important method, and there are several types of revascularization. The Encephalo-duro-arterio-synangiosis (EDAS) was mainly performed to correct the hemodynamic state of the internal carotid artery (ICA) territory. The frontal encephalo-galeo-synangiosis (EGS) was for the correction of hemodynamic state of anterior cerebral artery (ACA) territory.

For the diagnosis and evaluation of the moyamoya disease, cerebral angiography and magnetic resonance imaging is usually performed. Those methods could evaluate the morphologic change of vessels, such as stenosis and occlusion. But for surgical criteria, the hemodynamic change is important. In addition, the evaluation of cerebral hemodynamic state is necessary for the assessment of the effect of bypass surgery. The hemodynamic changes as well as the morphologic change are related to the symptoms and prognosis of moyamoya disease. For the evaluation of hemodynamic changes, basal/acetazolamide stress brain perfusion SPECT is useful. With basal/
Comparing between patients with a good and a poor clinical outcome, the post-operative CVRI and ΔCVRI showed significant difference between good and poor clinical outcome. * , statistically significant difference between good and poor clinical outcome.

In the interpretation of basal/acetzolamide stress SPECT, visual interpretation and region of interest (ROI) analysis could have individual difference. For the objective analysis, the quantification of SPECT is necessary. There were several methods of the quantification. Some methods need arterial sampling, and it is invasive and inconvenient. In this study, we used probabilistic map for the quantification. In the previous study, we showed the usefulness of this method to evaluate the effect of superficial temporal artery-middle cerebral artery bypass surgery. In this study, we applied probabilistic map for the quantification of rCBF and the evaluation of CVRI. This method is noninvasive. We could have more accurate anatomical information, and perform objective analysis. However, there are also limitations of our method. The EDAS is mainly for the improvement of hemodynamic state on middle cerebral artery territory, and EGS is for anterior artery territory. The probabilistic map, used in this study, does not present the vascular territory. For development of probabilistic map which present vascular territory, further research should be performed.

On whole brain analysis, basal/acetzolamide-stressed rCBF, and CVRI were significantly improved were after the revascularization. This showed the efficacy of the revascularization. On the regional analysis, the basal/acetzolamide-stressed rCBF on bilateral frontal, temporal, parietal lobes had significantly improved after revascularization, but there were no difference on both occipital lobes. The EDAS with EGS operation are mainly for the anterior and middle cerebral artery lesion. The occipital lobe is in the territory of the
Table 3. Multivariate Logistic Regression Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Age at the first operation</td>
<td>0.269</td>
</tr>
<tr>
<td>Highest Suzuki stage</td>
<td>0.438</td>
</tr>
<tr>
<td>Post-operative CVRI of whole brain</td>
<td>0.053</td>
</tr>
<tr>
<td>ΔCVRI of whole brain</td>
<td>0.002</td>
</tr>
<tr>
<td>Pre-operative CBF of the ipsilateral med. frontal gyrus</td>
<td>0.015</td>
</tr>
<tr>
<td>Post-operative CVRI of the ipsilateral frontal lobe</td>
<td>0.258</td>
</tr>
<tr>
<td>Post-operative CVRI of the ipsilateral parietal lobe</td>
<td>0.312</td>
</tr>
</tbody>
</table>

CVRI, cerebral vascular reserve index; ΔCVRI, the difference of post and pre operative CVRI of whole brain; CBF, cerebral blood flow; med.medial.

posterior circulation. So, the revascularization did not affect the hemodynamics of the occipital lobes.\(^{11}\)

In the comparison between hemispheres by the type of operation, pre-operative basal/acetazolamide-stressed rCBF of the ipsilateral frontal, parietal lobes, and ICA territory, on which EDAS with EGS was performed, were significantly lower than contralateral hemisphere. This was one of the reasons that EDAS with EGS was previously performed on ipsilateral hemisphere prior to EDAS only on the contralateral hemisphere, and mainly related with the first symptom and severity of each patient. After the revascularization, there was no significant difference in basal/acetazolamide rCBF between the ipsilateral and contralateral hemispheres. This could be another evidence of the effect of the revascularization on the cerebral hemodynamic state. However, in contrast to the significant improvement of CVRI on the whole brain, and bilateral ICA territories, there was no significant improvement of CVRI on the frontal and parietal lobes. This finding might be due to the probabilistic maps which do not represent the vascular territory.

We also compared the hemodynamic changes between patients with a good and a poor clinical outcome. The post-operative CVRI and ΔCVRI on the whole brain of patients with a good clinical outcome were significantly higher than the patients with a poor clinical outcome. In the regional analysis, the pre-operative basal rCBF on the ipsilateral medial frontal gyrus, and the post-operative CVRI on the ipsilateral frontal and parietal lobes of patients with a good clinical outcome were higher than patients with a poor clinical outcome. The patients with a good clinical outcome showed much more improvement of CVRI than patients with a poor clinical outcome. Even though the revascularization was successfully performed, the effect of revascularization was individually different. The patients, who had more improvement of vascular reserve by revascularization, had a better clinical outcome.

To evaluate the predictive factor of post-operative clinical outcome, multivariate logistic regression analysis was performed. In other studies, several pre-operative factors were reported as predictive factors of post-operative outcome.\(^{26,28,29}\) In our analysis, the evidence of cerebral infarction on preoperative MRI, and the age at first operation were not significantly different between good and poor clinical outcome. Considering the result of other studies and our results, Age at the first operation, the highest Suzuki stage of cerebral angiography, the post-operative CVRI on the whole brain, the ipsilateral frontal and the parietal lobes, the pre-operative basal rCBF on the ipsilateral medial frontal gyrus, and the ΔCVRI on the whole brain were considered as independent variables. Only the ΔCVRI on the whole brain and the pre-operative basal rCBF on the ipsilateral medial frontal gyrus were statistically significant prognostic factor for predicting a clinical outcome. Considering the result of multilogistic regression analysis and the comparison of the patients by the clinical outcome, the outcome of patient with moyamoya disease is correlated not only with the pre-operative state but also with the effect of revascularization surgery.

CONCLUSION

With probabilistic map, we could objectively evaluate the hemodynamic change after bypass surgery and understand the hemodynamic state of pediatric moyamoya disease. With basal/acetazolamide stress brain perfusion SPECT
이호영 외. 소아 모야모야병에서 뇌확률지도를 이용한 수술전후 혈역학적 변화 분석

요 약

목적: 본 연구의 목적은 소아 모야모야병 환자에 있어서, 수술 전후 기저/아세타졸아미드 부하 뇌혈류 단일광자방출 단층촬영(SPECT) 분석에 활률지도를 이용하여 수술로 인한 뇌혈류학적 변화 및 예후 예측인자 분석을 하여 뇌확률 지도의 유용성을 평가하는 것이다. 대상 및 방법: 연구대상으로 서울대어린이병원에서 소아 모야모야병으로 진단받고, 수술받은 56명(남:여=32:24, 나이 6.7±3.2세)이 포함되었다. 각각의 환자는 기저/아세타졸아미드 부하 뇌혈류 SPECT를 수술 전후 6-12개월 사이에 시행하였다. 각각의 환자는 한 측 반구에 encephalo-duro-arterio-synangiosis (EDAS)와 encephalo-galeo-synangiosis (EGS)를 우선적으로 시행받았고, 그 후 순차적으로 반대측 반구에 EDAS를 시행하였다. 환자들의 SPECT 영상을 SPM에서 공간정규화 하고 뇌교의 계수를 기준으로 계수정규화한 후 한국표준확률뇌지도(Korean Statistical Probabilistic Map, K-SPAM)를 이용하여 부위별 혈류를 정량화하였다. 각각 정류화된 혈류를 수술 전후, 대뇌반구간, 그리고 임상결과에 따라 비교하였다. 또한 임상결과가 좋은 군과 나쁜 군 사이에 차이가 있는 요소를 이용하여 회귀분석을 시행하였다.

결과: 수술 후 양측 내측 전두엽이랑, 전두엽, 두정엽, 측두엽, 내측경동맥 영역, 전뇌의 기저/아세타졸아미드 부하 뇌혈류가 유의하게 호전되었다(p<0.05). 대뇌반구간 비교에서는 수술전 기저/아세타졸아미드 부하 혈류예비능지표에 차이가 있었으나, 수술 후 이 차이는 사라졌다(p<0.05). 임상결과가 좋은 환자군의 수술 전 EDAS와 EGS를 시행한 내측 전두엽 뇌혈류의 기저 뇌혈류, 동측 전두엽, 측두엽, 그리고 전뇌의 수술 후 혈류예비능지표 및 수술전 혈류예비능지표차가 더 우수하였다(p<0.05). 회귀분석결과에 의하면, EDAS와 EGS를 시행한 내측 전두엽 뇌혈류의 기저 혈류예비능지표 및 수술후 혈류예비능지표차가 수술 후 임상결과를 예측할 수 있는 유의한 인자이다(p=0.002, p=0.001). Conclusion: 뇌확률지도를 이용하여 소아 모야모야병 환자의 기저/아세타졸아미드 부하 뇌혈류 SPECT를 정량화하여 분석할 수 있었다. 이 방법으로 수술에 의한 뇌혈류학적 변화를 객관적으로 평가할 수 있었으며, 모야모야병환자의 수술 결과의 예측인자를 평가할 수 있었다.

References