



Original Article

Intraoperative monitoring of cerebrospinal fluid gas tension and pH before and after surgical revascularization for moyamoya disease

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ABSTRACT

Background: This study aimed to directly measure cerebrospinal fluid (CSF) gas tensions and pH before and after superficial temporal artery to middle cerebral artery (STA-MCA) anastomosis for moyamoya disease.

Methods: This study included 25 patients with moyamoya disease who underwent STA-MCA anastomosis combined with indirect bypass onto their 34 hemispheres. About 1 mL of CSF was collected before and after bypass procedures to measure CSF partial pressure of oxygen ($P_{\text{CSF}O_2}$), CSF partial pressure of carbon dioxide ($P_{\text{CSF}CO_2}$), and CSF pH with a blood gas analyzer. As the controls, the CSF was collected from 6 patients during surgery for an unruptured cerebral aneurysm. $P_{\text{CSF}O_2}$ and $P_{\text{CSF}CO_2}$ were expressed as the ratio to partial pressure of oxygen (PaO_2) and partial pressure of carbon dioxide ($PaCO_2$), respectively.

Results: $P_{\text{CSF}O_2}/PaO_2$ was 0.79 ± 0.14 in moyamoya disease, being lower than 1.10 ± 0.09 in the controls ($P < 0.0001$). $P_{\text{CSF}CO_2}/PaCO_2$ was 0.90 ± 0.10 in moyamoya disease, being higher than 0.84 ± 0.07 in the controls ($P = 0.0261$). $P_{\text{CSF}O_2}/PaO_2$ was significantly lower in pediatric patients than in adult patients and in the hemispheres with reduced cerebral blood flow (CBF) and cerebrovascular reactivity (CVR) to acetazolamide than in those with normal CBF but reduced CVR. STA-MCA anastomosis significantly increased $P_{\text{CSF}O_2}/PaO_2$ from 0.79 ± 0.14 to 0.86 ± 0.14 ($P < 0.01$) and reduced $P_{\text{CSF}CO_2}/PaCO_2$ from 0.90 ± 0.10 to 0.69 ± 0.16 ($P < 0.0001$). There was no difference in CSF pH between moyamoya disease and the controls.

Conclusion: $P_{\text{CSF}O_2}/PaO_2$ was significantly lower in moyamoya disease than in the controls. Its magnitude was more pronounced in pediatric patients than in adult patients and depends on the severity of cerebral ischemia. STA-MCA anastomosis carries dramatic effects on CSF gas tensions in moyamoya patients. CSF may be a valuable biomarker to monitor the pathophysiology of cerebral ischemia/hypoxia in moyamoya disease.

Keywords: Bypass surgery, Carbon dioxide, Cerebrospinal fluid, Gas analysis, Moyamoya disease, Oxygen

INTRODUCTION

Moyamoya disease is a unique cerebrovascular disease characterized by progressive stenosis of the terminal portion of the internal carotid artery and the main branches. Moyamoya disease occurs in both children and adults and induces transient ischemic attack (TIA), ischemic stroke, and/or hemorrhagic stroke.^[12,26] Previous studies have shown that surgical revascularization can improve hemodynamic compromise and reduce further cerebrovascular events. Surgical procedures

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include indirect bypass, direct bypass, and combined bypass. The clinical significance is believed to be more rapid and more apparent after direct or combined bypass procedures due to immediate restoration of cerebral blood flow (CBF).^[12] It is well known that the cerebrospinal fluid (CSF) plays an important role in oxygen (O₂) delivery to and carbon dioxide (CO₂) washout from the brain.^[7,10] However, there are no studies that denote the effect of surgical revascularization on gas tension and pH in moyamoya disease.

CSF partial pressure of oxygen (P_{CSF}O₂) is known to be proportional to arterial partial pressure of oxygen (PaO₂).^[6,9,23] Ventilation with 100% O₂ elevates P_{CSF}O₂ within one minute, and ventilation with 14% O₂ decreases it within 1 min in the anesthetized dogs.^[10] Hyperbaric oxygenation quickly elevates cisternal and lumbar PO₂ in non-anesthetized, spontaneously breathing humans.^[8] Furthermore, O₂ has a known paramagnetic effect and increases CSF signal intensity on fluid-attenuated inversion recovery magnetic resonance images. CSF signal intensity starts to increase just after the start of 100% O₂ inhalation.^[2] P_{CSF}O₂ rapidly decreases after cardiac arrest in pigs.^[5] CSF partial pressure of carbon dioxide (P_{CSF}CO₂) is also proportional to arterial partial pressure of carbon dioxide (PaCO₂).^[3,23] The previous studies have shown clinical significance in monitoring CSF gas tension and pH. The cross-clamping of the aorta very rapidly decreases P_{CSF}O₂ and gradually increases P_{CSF}CO₂ in the lumbar CSF.^[20,27] The amplitude of motor-evoked potential starts to drop when P_{CSF}O₂ is less than 1/4 of the control value.^[20] Histological damage in the spinal cord correlates very well with the severity of these parameters.^[4] P_{CSF}O₂ is also known as proportional to local CBF^[25], and cerebral hypoxia or ischemia rapidly reduces P_{CSF}O₂.^[21] Therefore, both P_{CSF}O₂ and P_{CSF}CO₂ may be valuable markers to monitor central nervous tissue oxygenation quickly and sensitively.^[24,28] In fact, we recently measured CSF gas tension and pH during superficial temporal artery to the middle cerebral artery (STA-MCA) anastomosis for patients with occlusive carotid artery diseases and found that their P_{CSF}O₂ was significantly lower, and P_{CSF}CO₂ was significantly higher than those in the controls. These changes were proportional to the severity of cerebral ischemia. STA-MCA anastomosis significantly improved these parameters.^[19]

In this study, therefore, we aimed to directly measure CSF gas tension and pH before and after STA-MCA anastomosis for moyamoya disease to assess the pathophysiology of cerebral ischemia and the impact of bypass procedure on brain microenvironment in moyamoya disease.

MATERIALS AND METHODS

Patients

This study was proved by the Local Institutional Review Board, and written informed consent was obtained. This study included 34 hemispheres in 23 patients who underwent

STA-MCA anastomosis and indirect bypass, encephalo-duro-myo-arterio-pericranial synangiosis (EDMAPS) for moyamoya diseases at our hospital between December 2021 and June 2023.^[13,16] The procedures were performed on 12 hemispheres of 8 children (<18 years) and 22 hemispheres of 15 adults. There were five males and 18 females. Their mean age was 9.4 ± 4.2 years (range, 4–17 years) in children and 49.4 ± 15.3 years (range, 23–65 years). All of them were symptomatic and developed TIA (*n* = 15), ischemic stroke (*n* = 4), and hemorrhagic stroke (*n* = 4) due to Moyamoya disease. All of them were Japanese and met the guidelines for the diagnosis set by the Research Committee on Moyamoya Disease of the Ministry of Health, Labor, and Welfare of Japan.^[11] Suzuki's angiographical stage included Stage 2 (*n* = 4), Stage 3 (*n* = 22), Stage 4 (*n* = 6), Stage 5 (*n* = 1), and Stage 6 (*n* = 1).^[26]

Before surgery, CBF before and after intravenous injection of 10-mg/kg acetazolamide (ACZ) was quantitatively measured with the ¹²³I-IMP injection and single-scan autoradiographic technique (GCA-9300/DI; Toshiba).^[17,18] To evaluate cerebral hemodynamics, the regions of interest were symmetrically placed in the ipsi- and contralateral MCA territories. As described previously, CVR to ACZ was quantitatively calculated as follows:

$$\text{CVR} (\%) = 100 \times (\text{CBF}_{\text{ACZ}} - \text{CBF}_{\text{rest}}) / \text{CBF}_{\text{rest}}$$

where CBF_{rest} and CBF_{ACZ} represent CBF before and after intravenous injection of ACZ, respectively. CBF was judged as reduced when the value was lower than 27 mL/min/100 g, and CVR was judged as reduced when the value was lower than <14%.^[17,18]

STA-MCA anastomosis and EDMAPS were performed on the hemispheres with the hemispheres with normal CBF but reduced CVR (Kuroda's Type 2, *n* = 7) and those with reduced CBF and CVR (Kuroda's Type 3, *n* = 27).^[13,16] Briefly, the frontal and parietal branches of the STA were harvested from the scalp. Following frontotemporal craniotomy, the dura mater was opened to expose the brain surface widely. The cortical branches of the MCA close to the Sylvian fissure were selected as the recipients. Using 10-0 nylon threads, the distal end of STA was anastomosed to the cortical branches of the MCA in an end-to-side fashion. Clamping time ranged from 15 min and to 30 min. The patency of the bypass graft was confirmed with indocyanine green video angiography during surgery. Finally, the dural window was covered with the vascularized dura mater, temporal muscle, and frontal pericranium as the indirect bypass procedure. The postoperative course was uneventful, and none of them developed stroke in perioperative periods.

Intraoperative measurement of CSF gas tension and pH

Before the STA-MCA bypass procedure, a small 0.5–1 cm incision was made in the arachnoid membrane overlying the recipient MCA branch close to the Sylvian fissure. Through

this arachnoid incision, a 22-gauge ethylene tetrafluoroethylene catheter attached to a 5 mL syringe was inserted deep into the Sylvian fissure and about 1 mL of CSF was collected. After the bypass procedure, the CSF was harvested in the same technique again.^[19] Arterial pH, PaO₂, and PaCO₂ were simultaneously measured with CSF pH, P_{CSF}O₂, and P_{CSF}CO₂.

All analyses of the CSF and blood samples were conducted using a blood gas analyzer (ABL800 FLEX, Radiometer, Copenhagen, Denmark) within 1 minute after sample collection. It is known that both P_{CSF}O₂ and P_{CSF}CO₂ are proportional to PaO₂ and PaCO₂, respectively, thus in this study, the values of P_{CSF}O₂ and P_{CSF}CO₂ were expressed as P_{CSF}O₂/PaO₂ and P_{CSF}CO₂/PaCO₂, respectively.^[19] As the controls, the CSF was collected from six patients with unruptured cerebral aneurysms during clipping surgery. In the controls, we made the 1-cm arachnoid incision close to the Sylvian fissure and collected the CSF from the Sylvian fissure twice with an interval of 30 min to evaluate the changes of the gas tension and pH of the CSF after the arachnoid opening.^[19]

Statistical analysis

All data were expressed as mean ± standard deviation. The data between the two groups were compared by use of

unpaired or paired *t*-tests as appropriate. The data from three groups were analyzed with one-factor analysis of variance. *P* < 0.05 was considered statistically significant.

RESULTS

In the controls, CSF gas tensions and pH did not change during the 30-min interval of CSF sampling; pH from 7.436 ± 0.047 to 7.440 ± 0.048, P_{CSF}O₂/PaO₂ from 1.10 ± 0.09 to 1.13 ± 0.10, and P_{CSF}CO₂/PaCO₂ from 0.84 ± 0.07 to 0.82 ± 0.07.

The differences in CSF gas tensions and pH were evaluated between the control (*n* = 6) and moyamoya groups (*n* = 34). P_{CSF}O₂/PaO₂ was 0.79 ± 0.14 in moyamoya disease, being significantly lower than 1.10 ± 0.09 in the controls (*P* < 0.0001). P_{CSF}CO₂/PaCO₂ was 0.90 ± 0.10 in moyamoya disease, being significantly higher than 0.84 ± 0.07 in the controls (*P* = 0.0261). Therefore, the inter-group difference in P_{CSF}O₂/PaO₂ was larger than that in P_{CSF}CO₂/PaCO₂. On the other hand, CSF pH was 7.427 ± 0.110 in the moyamoya group, which did not differ from 7.436 ± 0.047 in the controls.

Next, CSF gas tensions and pH were compared among the controls (*n* = 6), pediatric patients (*n* = 12), and adult patients (*n* = 22) [Figure 1]. P_{CSF}O₂/PaO₂ was 0.80 ± 0.17

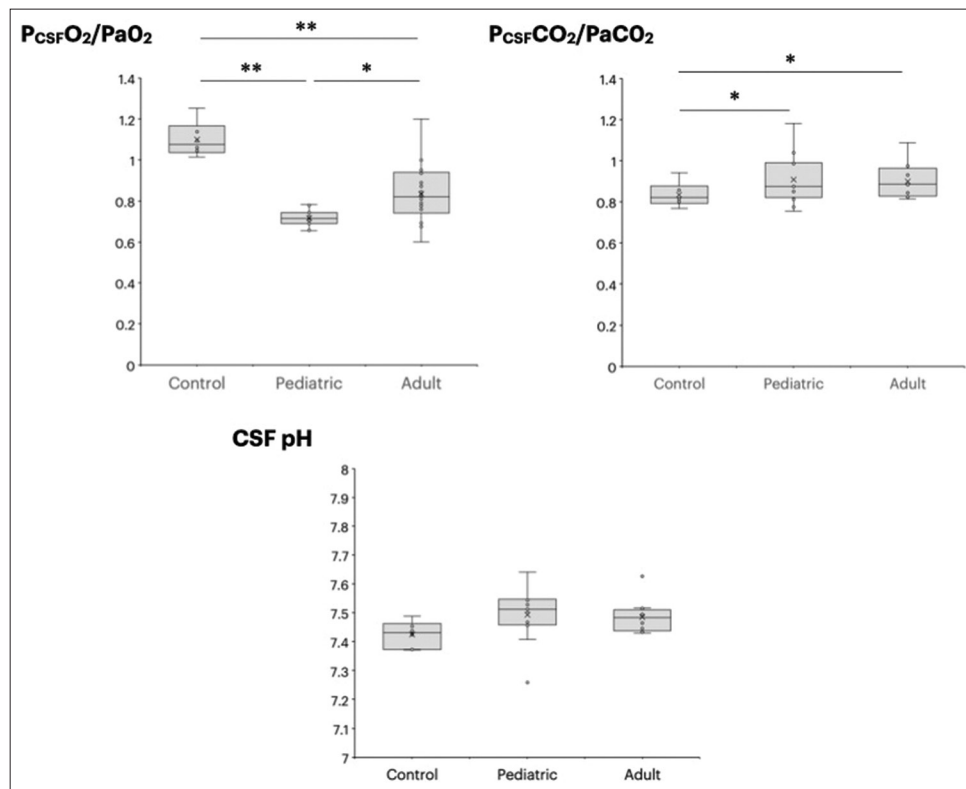


Figure 1: Box plots demonstrate the differences in P_{CSF}O₂/PaO₂, P_{CSF}CO₂/PaCO₂, and CSF pH among the controls (*n* = 6), pediatric moyamoya patients (*n* = 12), and adult moyamoya patients (*n* = 22). **P* < 0.05, ***P* < 0.01. CSF: Cerebrospinal fluid, PaO₂: Partial pressure of oxygen, PaCO₂: Partial pressure of carbon dioxide, P_{CSF}O₂: CSF partial pressure of oxygen, P_{CSF}CO₂: CSF partial pressure of carbon dioxide.

in pediatric patients and 0.86 ± 0.12 in adult patients, being significantly lower than in the controls ($P < 0.01$ and $P < 0.01$, respectively). Furthermore, $P_{\text{CSF}O_2}/\text{Pa}O_2$ was significantly lower in pediatric patients than in adult patients ($P < 0.05$). On the other hand, $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ in pediatric and adult patients was 0.89 ± 0.14 and 0.91 ± 0.08 , respectively. Both values were significantly higher than 0.84 ± 0.07 in the controls ($P < 0.05$ and $P < 0.05$, respectively). There was no significant difference in $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ between pediatric and adult patients. CSF pH was 7.474 ± 0.092 in pediatric patients and 7.426 ± 0.046 in adult patients. There was no significant difference in CSF pH among the three groups.

Furthermore, CSF gas tensions and pH were compared among the controls ($n = 6$), the hemispheres with Type-2 ischemia (normal CBF but reduced CVR; $n = 7$), and the hemispheres with Type-3 ischemia (reduced CBF and CVR; $n = 27$). As shown in Figure 2, $P_{\text{CSF}O_2}/\text{Pa}O_2$ was 0.88 ± 0.19 in Type-2 hemispheres and 0.77 ± 0.09 in Type-3 hemispheres, being significantly lower than in the controls ($P < 0.01$ and $P < 0.01$, respectively). In addition, $P_{\text{CSF}O_2}/\text{Pa}O_2$ was significantly lower in Type-3 hemispheres than in Type-2 hemispheres ($P < 0.05$). On

the other hand, $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ in the Type-2 hemispheres and Type-3 hemispheres was 0.86 ± 0.06 and 0.90 ± 0.09 , respectively. Both values were significantly higher than 0.84 ± 0.07 in the controls ($P < 0.05$ and $P < 0.05$, respectively), but there was no significant difference in $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ between Type-2 and Type-3 hemispheres. CSF pH in Type-2 hemispheres and Type-3 hemispheres was 7.547 ± 0.229 and 7.496 ± 0.057 , respectively. There was no significant difference in CSF pH among the three groups.

Finally, post-bypass changes in CSF gas tensions and pH were evaluated using a paired *t*-test. The results are shown in Figure 3. STA-MCA anastomosis significantly increased $P_{\text{CSF}O_2}/\text{Pa}O_2$ from 0.79 ± 0.14 to 0.86 ± 0.14 ($P < 0.01$). The value was still significantly lower than the controls (1.13 ± 0.10 ; $P < 0.01$). On the other hand, STA-MCA anastomosis significantly reduced $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ from 0.90 ± 0.10 to 0.69 ± 0.16 ($P < 0.0001$). Post-bypass $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ was significantly lower than that in the controls (0.82 ± 0.07 ; $P < 0.01$). There was no significant change in CSF pH before and after STA-MCA anastomosis from 7.427 ± 0.110 to 7.451 ± 0.177 .

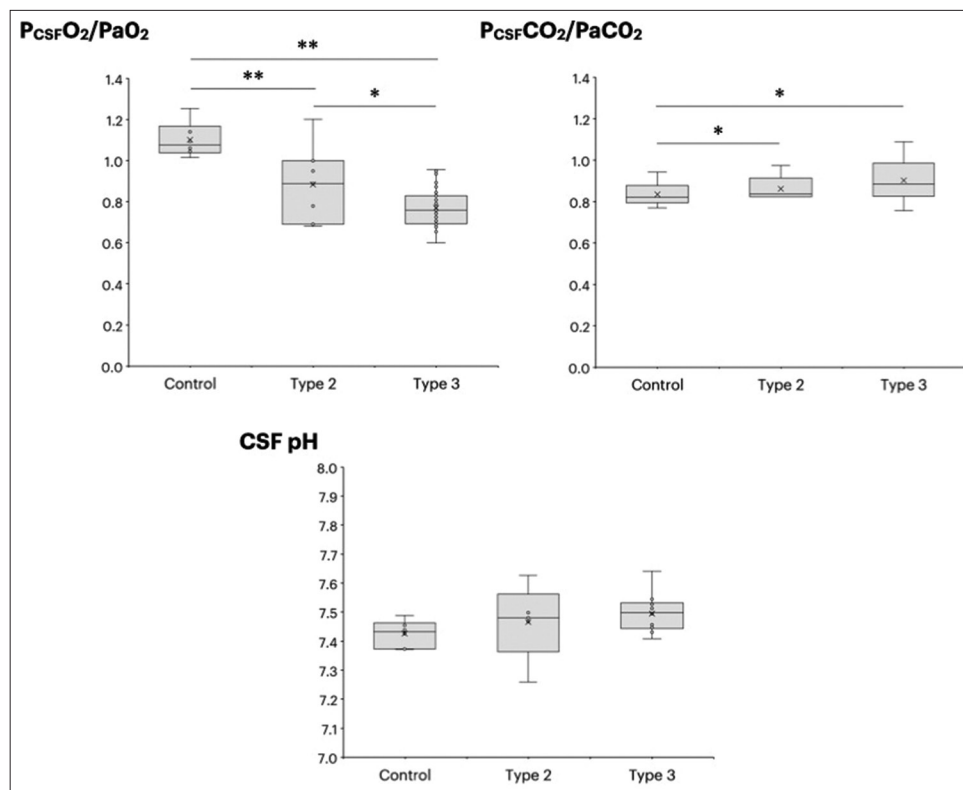


Figure 2: Box plots demonstrate the differences among the controls ($n = 6$), Type-2 hemispheres ($n = 7$), and Type-3 hemispheres ($n = 27$). * $P < 0.05$, ** $P < 0.01$. CSF: Cerebrospinal fluid, $\text{Pa}O_2$: Partial pressure of oxygen, $\text{Pa}CO_2$: Partial pressure of carbon dioxide, $P_{\text{CSF}O_2}$: CSF partial pressure of oxygen, $P_{\text{CSF}CO_2}$: CSF partial pressure of carbon dioxide.

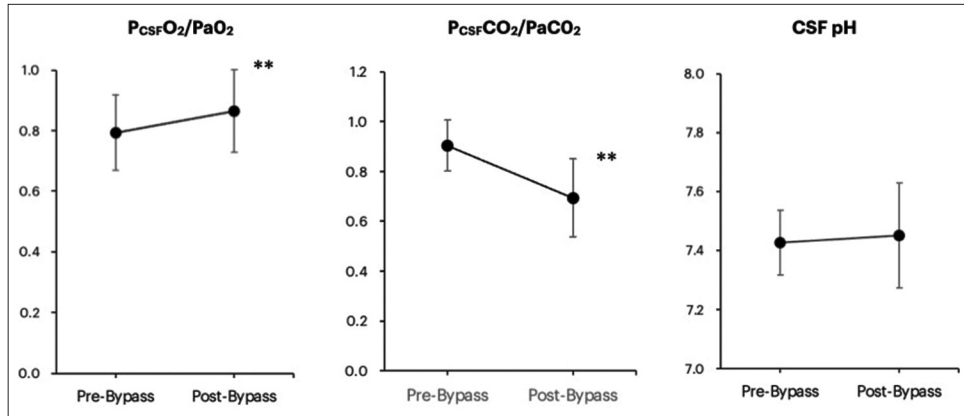


Figure 3: Line graphs demonstrate post-bypass changes in $P_{\text{CSF}O_2}/\text{Pa}O_2$, $P_{\text{CSF}CO_2}/\text{Pa}CO_2$, and CSF pH. ** $P < 0.01$. $\text{Pa}O_2$: Partial pressure of oxygen, $\text{Pa}CO_2$: Partial pressure of carbon dioxide, $P_{\text{CSF}O_2}$: CSF partial pressure of oxygen, $P_{\text{CSF}CO_2}$: CSF partial pressure of carbon dioxide.

DISCUSSION

CSF gas tension and pH

In this study, we investigated the CSF gas tension and pH during bypass surgery for 34 hemispheres in 23 patients with Moyamoya disease. To the best of our knowledge, this is the first study to measure CSF gas tension and pH in moyamoya disease directly. As a result, $P_{\text{CSF}O_2}/\text{Pa}O_2$ value in moyamoya patients was approximately 70% of the controls. The magnitude of their decrease was more pronounced than in patients with occlusive carotid artery diseases (approximately 80%).^[19] Therefore, moyamoya patients' brains may be exposed to more intense hypoxia than those of patients with occlusive carotid artery disease. More importantly, the $P_{\text{CSF}O_2}/\text{Pa}O_2$ value was significantly lower in pediatric patients than in adult patients [Figure 1]. The finding may represent the fact that normal CBF in children is much higher than that in adults.^[15] The speculation is supported by the fact that the $P_{\text{CSF}O_2}/\text{Pa}O_2$ value is significantly lower in the hemispheres with reduced CBF and CVR (Type 3 ischemia) than in those with normal CBF but reduced CVR (Type 2 ischemia; Figure 2). In Type-2 hemispheres, moderate reduction of cerebral perfusion pressure (CPP) is believed to induce compensatory cerebral vasodilation and result in reduced CVR. In Type-3 hemispheres, however, autoregulatory vasodilation can no longer compensate for CPP reduction due to inadequate collateral development, which leads to reduced CBF and CVR.^[14] Therefore, the decline of $P_{\text{CSF}O_2}/\text{Pa}O_2$ value in moyamoya disease may represent the impaired O_2 delivery from the blood to the brain due to moderate-to-severe cerebral ischemia, and its magnitude depends on the degree of ischemia.

On the other hand, the results of $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ value were different from those of $P_{\text{CSF}O_2}/\text{Pa}O_2$ value. Thus, the $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ value in moyamoya patients was approximately 107% of the controls, being similar to that in patients with

occlusive carotid artery diseases (approximately 110%).^[19] There was no difference in $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ values between pediatric and adult patients [Figure 1] and between Type-2 and Type-3 hemispheres [Figure 2]. The reason why the behavior of CSF gas tension in moyamoya disease differs between O_2 and CO_2 is unclear. Although O_2 is transported from the blood to the brain by physically operating diffusion, the washout of CO_2 from the brain may be more complicated than O_2 delivery because it is largely mediated by carbonic anhydrase in the erythrocytes.^[29] In fact, previous animal experiments showed that intravenous injection of 50 mg/kg ACZ, an inhibitor of carbonic anhydrase, induced an increase in $P_{\text{CSF}CO_2}$ of 8 mmHg.^[3] In addition, $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ value was negatively proportional to CBF in patients with occlusive carotid artery diseases,^[19] but the results were different in patients with moyamoya disease. Hence, other unknown mechanisms may be involved in the washout of CO_2 from the brain in Moyamoya disease.

In this study, no significant alterations in CSF pH values were observed in moyamoya disease. Even though $P_{\text{CSF}CO_2}/\text{Pa}CO_2$ values are elevated due to severe cerebral ischemia, CSF pH may be maintained by the mechanism of acid-base equilibrium.^[1]

Post-bypass changes

This is the first study to directly evaluate the post-bypass changes in CSF gas tensions and pH in moyamoya disease. Following the completion of STA-MCA anastomosis, $P_{\text{CSF}O_2}/\text{Pa}O_2$ value significantly increased from 0.79 ± 0.14 to 0.86 ± 0.14 . The fact may represent the improvement of O_2 delivery to the brain through the bypass flow, which correlates very well with previous findings that STA-MCA anastomosis improved cerebral oxygenation state during surgery on a two-dimensional optical intrinsic signal map.^[22] However, the post-bypass value was still lower than the control value (1.13 ± 0.10). This result is very different from that of occlusive carotid artery

disease, which recovered from 0.88 ± 0.16 to 1.05 ± 0.26 , almost equal to the control, after bypass surgery.^[19] There are several explanations for this discrepancy. First, moyamoya disease may have been exposed to a higher degree of hypoxia before bypass surgery than occlusive carotid artery diseases and, thus, may not have fully recovered to normal levels immediately after bypass surgery. One limitation of this study is that CSF samples could only be collected intraoperatively, not postoperatively. Although the postoperative collection of CSF through lumbar puncture could be considered to evaluate the longer-time effects of bypass surgery, we did not perform lumbar puncture in this study due to the high possibility of dilution of postoperative changes while the CSF reached the spinal canal. Second, the smaller diameter of the recipient artery in Moyamoya disease makes it difficult for the effect of bypass surgery on the brain oxygenation state to be immediately reflected.

Following the bypass procedure, the $P_{\text{CSF}}\text{CO}_2/\text{PaCO}_2$ value significantly decreased from 0.90 ± 0.10 to 0.69 ± 0.16 , suggesting the improvement of the washout of CO_2 from the brain. Post-bypass value was significantly lower than the control value (0.82 ± 0.07). It is unclear whether this overshoot after the bypass procedure was temporary or persisted over a while due to the nature of this study, but the changes may have persisted to some extent since previous animal experiments showed the aorta clamping of the pigs induced a gradual increase of spinal $P_{\text{CSF}}\text{CO}_2$ followed by post-reperfusion recovery to the lower level of the control values for some time.^[4]

Limitation of study

Finally, the limitations of this study should be noted. In this study, CSF was collected during craniotomy under general anesthesia. The results may not directly represent the situation in the awake state since intraoperative PaO_2 is higher than in the awake state, and cerebral O_2 metabolism is considered to be suppressed.

CONCLUSION

This is the first study in which we collected CSF before and after STA-MCA anastomosis and directly measured changes in CSF gas tensions and pH in moyamoya disease. As the results, $P_{\text{CSF}}\text{O}_2/\text{PaO}_2$ was significantly lower in moyamoya disease than in the controls, and the magnitude was more pronounced in pediatric patients than in adult patients and Type-3 hemispheres than in Type-2 hemispheres. $P_{\text{CSF}}\text{CO}_2/\text{PaCO}_2$ was significantly higher than in the controls. STA-MCA anastomosis significantly improved these findings. Moyamoya disease exhibited different behavior of CSF gas tensions and pH from occlusive carotid artery diseases. Based on these observations, the CSF should be recognized as a valuable biomarker to monitor the pathophysiology of cerebral ischemia/hypoxia.

Acknowledgments

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Ethical approval

The research/study was approved by the Institutional Review Board at Toyama University Hospital, number R2019057, dated August 30, 2019.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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