Intracerebral steal phenomenon associated with global hyperemia in moyamoya disease during revascularization surgery

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Object. The collateral vessels in moyamoya disease appear to retain their ability to constrict during hypocapnia but not to dilate during hypercapnia. It has been claimed that hypercapnia, as well as hypocapnia, decreases the blood flow in regions perfused by collateral vessels, presumably because of intracerebral steal. If this holds true, the decrease in blood flow may be proportional to the global hyperemia in the brain. To establish appropriate hemodynamic control during revascularization surgery, the authors monitored the jugular bulb oxygen saturation (SjO₂) intraoperatively, a method that could sensitively detect global hyperemia.

Methods. A total of 17 patients, most of whom presented with transient ischemic attacks or fluctuating neurological deficits, underwent intraoperative monitoring of their SjO₂ and end-tidal carbon dioxide (ETCO₂) after a state of anesthesia had been induced with isoflurane (Group 1) or propofol (Group 2). In eight of these patients, the regional cerebral blood flow (rCBF) of the collateral vessel territory was also monitored by laser Doppler flowmetry during the period of cortical exposure, and a total of 113 data sets (averaged values during 2.5-minute intervals) was collected. There was fluctuation in the ETCO₂ levels ranging from 36 to 44 mm Hg. The mean SjO₂ level was clearly greater (p < 0.01) in Group 1 (71.8 ± 2.2%) than in Group 2 (63.3 ± 2.1%). An episodic fall in rCBF was observed in association with a transient increase in SjO₂. Such an event was not uncommon in Group 1 and there was a greater risk of rCBF decreasing when SjO₂ exceeded a cutoff level of 76% (p < 0.01). This level could sometimes be reached at a broad range of ETCO₂ readings (37–44 mm Hg). In Group 2, similar events sometimes occurred when SjO₂ increased beyond 70%. However, this level could be reached only with a higher ETCO₂ (42–44 mm Hg). The rCBF level was negatively correlated to SjO₂ (p < 0.01), but not always to ETCO₂, indicating that the episodic fall in rCBF was closely related to global hyperemia rather than the absolute level of hypocapnia.

Conclusions. The observed association between a fall in rCBF and global hyperemia supports the intracerebral steal hypothesis and indicates that it is prudent to avoid excessive global hyperemia. The optimal range of CO₂ for isoflurane is more restricted than that for propofol, presumably because isoflurane induces hyperemia by itself. Monitoring of SjO₂ appears to represent the most practical technique for detecting global hyperemia as well as global ischemia, both of which may cause ischemic complications in moyamoya disease.

KEY WORDS • cerebral blood flow • cerebrovascular reactivity • moyamoya disease • stroke

Abbreviations used in this paper: CBF = cerebral blood flow; CVP = central venous pressure; ETCO₂ = end-tidal carbon dioxide; rCBF = regional CBF; SaO₂ = arterial oxygen saturation; SjO₂ = jugular bulb O₂ saturation; SPECT = single-photon emission computerized tomography.

I SCHEMIC complications are not uncommon in revascularization surgery for moyamoya disease. Appropriate hemodynamic control during surgery plays a critical role in minimizing such complications. Moyamoya disease predominantly affects the blood supply to the frontoparietal regions of the brain. The collateral vessels perfusing these brain regions retain their ability to constrict during hypocapnia, so that hypocapnia causes a detrimental decrease in blood supply. It has been recommended therefore that normocapnia or slight hypercapnia be maintained during surgery to ensure appropriate levels of blood flow in the frontoparietal regions.

During the last decade, intraoperative monitoring of rCBF has revealed that hypercapnia also decreases blood flow in the frontoparietal regions in moyamoya disease. Preoperative rCBF measurements obtained by SPECT scanning have demonstrated that the rCBF of the frontoparietal region is reduced by acetazolamide administration, which normally causes vasodilation. The collateral vessels perfusing these brain regions do not retain an ability to dilate during hypercapnia, presumably because they are already maximally dilated. It has been hypothesized that the decreased blood flow in the frontoparietal regions may be attributable to greater vasodila-
tion of intact brain regions during hypcapnia, which diverts blood away from the frontoparietal regions. Anesthetic agents such as isoflurane, which are administered by inhalation, are also suspected to reduce the blood flow in the frontoparietal regions by a similar mechanism.

If the intracerebral steal hypothesis holds true, the decrease in blood flow to the frontoparietal regions may be proportional to the global hyperemia. To establish appropriate hemodynamic control during revascularization surgery, we monitored the SjO₂ intraperatively. The SjO₂ has unique characteristics that reflect a global balance of the cerebral system. An increase in the SjO₂ level, therefore, represents global hyperemia in which an increase in CBF overwhelms the metabolic demand. If a decrease in flow to the frontoparietal regions is observed in association with an increase in SjO₂, this would support the intracerebral steal hypothesis, and indicate that SjO₂ is useful for detecting hazardous hyperemia during revascularization surgery.

Clinical Material and Methods

Patients and Surgical Procedures

A total of 17 patients with moyamoya disease (nine male and eight female) who had been suffering repeated transient ischemic attacks (14 patients) or fluctuating neurological deficits (three patients) was included in this study. One patient had also suffered seizures. They ranged in age from 3 to 34 years, but most of them were less than 20 years old (14 patients). The effects of acetazolamide on rCBF were investigated preoperatively in 15 patients by using SPECT scanning. The preoperative acetazolamide blood flow study was abandoned in two patients because they suffered frequent episodes of neurological deficits. The rCBF of the frontoparietal region of the hemisphere contralateral to the transient ischemic attacks or neurological deficits was reduced in all patients examined. Acetazolamide administration clearly elicited a further decrease in the frontoparietal rCBF in three patients, indicating an intracerebral steal phenomenon. All 17 patients underwent standard procedures for either encephaloduroarteriosynangiosis or encephaloduroarteriomyosynangiosis. The patients or their families gave informed consent for all procedures described herein, except for the intraoperative CBF measurements. Informed consent for intraoperative CBF measurements to be performed during the period of cortical exposure was given by only eight patients and/or their families.

This study was approved by the Committee for Clinical Trials and Research on Humans.

Monitoring Procedures for SjO₂ and rCBF

All 17 patients underwent continuous monitoring of SjO₂. A fiberoptic No. 4 French catheter system (Opticath and Oximetrix III systems; Abbott Laboratories, Abbott Park, IL) was introduced percutaneously into the jugular bulb after induction of anesthesia. The tip of the catheter was placed in the jugular bulb at the level between the base of the skull and top of the second cervical vertebra. The side of the jugular vein was determined from the dominant side according to the findings on preoperative angiograms. The system was then calibrated in vivo by using blood that was slowly withdrawn from the catheter. At the end of the operation, the system was recalibrated and the catheter position was reconfirmed. Electrocardiographic data, arterial blood pressure, CVP, SaO₂, and ETCO₂ were monitored continuously. For the measurements of PaCO₂, arterial blood was withdrawn intermittently at 10-minute intervals and when changes in SjO₂ were observed. In eight patients (four from each group) the CBF in the frontoparietal regions was also measured by laser Doppler flowmetry (Omegaflow FLO-N1; Omega Wave, Tokyo, Japan) with a flat probe placed on the cortical surface for 25 to 35 minutes during the period of cortical exposure. We were unable to perform intraoperative CBF measurements in the remaining nine patients, because informed consent was not given for these measurements to be made during the period of cortical exposure. A laser beam with a power output of 3 mW at the probe and a wavelength of 780 nm was used. The technique of CBF measurement by a laser Doppler flowmetry has been described previously. The mean velocity and volume of moving red blood cells are detected as the mean Doppler frequency and amplitude of the Doppler spectrum, respectively. The rCBF is calculated as (blood velocity × blood volume), which is commonly expressed in millimeters per 100 g per minute. The rCBF values obtained using laser Doppler flowmetry, however, can represent only a rough estimate of the absolute values of rCBF. For this reason, caution should be exercised in drawing any conclusion from pooled data collected from different patients. To overcome this problem, we gave special attention to the temporal changes of rCBF observed on polygraphic records in each patient.
Cerebral hemodynamics in moyamoya disease

Intraoperative Management

We had used isoflurane as an anesthetic agent during the earlier part of this study (Group 1, 10 patients), because propofol was not then available in Japan. The patients were initially sedated using an infusion of thio-panitone (5 mg/kg), fentanyl, and vecuronium, and then anesthetized with a gas mixture of 60% nitrous oxide, oxygen, and isoflurane. During $\text{SjO}_2$ and rCBF monitoring, the isoflurane concentration was maintained at 0.8%. After propofol became available, we recognized a marked difference between isoflurane and propofol in their effects on $\text{SjO}_2$ and rCBF, as discussed later. To maximize the benefit to patients, we decided to use propofol as an anesthetic agent during the later part of this study (Group 2, seven patients). These patients were anesthetized with propofol (6–8 mg/kg/hr) and fentanyl (1 mg/kg/hr). During $\text{SjO}_2$ and rCBF monitoring, propofol was administered at doses of 8 mg/kg/hr. We report the data obtained with each of these different anesthetic techniques together, because the difference between them appeared to be of considerable clinical importance.

The arterial blood pressure was maintained within the normal range for each of the patients. The $\text{SaO}_2$ was maintained at 99 to 100%, and the CVP at 6 to 9 cm H$_2$O. In two of the earlier cases, an attempt was made to control ETCO$_2$ at a slightly hypercapnic level (range 41–47 mm Hg). The remaining 15 patients underwent surgery while in a normocapnic state, in which the ETCO$_2$ ranged mostly from 38 to 42 mm Hg. Nevertheless, there were transient fluctuations in ETCO$_2$ levels (range 36–44 mm Hg).

Data Collection and Analysis

The mean $\text{SjO}_2$ for the entire period of monitoring, and the highest and lowest $\text{SjO}_2$ levels, were averaged for all patients. In the eight patients in whom rCBF was monitored during the period of cortical exposure, we collected 10 to 20 consecutive sets of $\text{SjO}_2$, ETCO$_2$, and rCBF data in each individual. This yielded a total of 113 data sets (Group 1, 61; Group 2, 52). During the period of data collection, the arterial blood pressure, $\text{SaO}_2$, and CVP were confirmed to be maintained at stable levels within the normal ranges, and the ETCO$_2$ values were validated by intermittent measurements of PaCO$_2$. Grouped data were expressed as the means plus or minus standard deviations. Correlations between two variables were examined using linear regression analysis. Differences between the groups were analyzed using unpaired or paired t-tests. We also analyzed the temporal relationships between these variables based on polygraphic records for each patient.

Results

Relationship Between ETCO$_2$ and $\text{SjO}_2$

The mean $\text{SjO}_2$ for the entire monitoring period was greater in the 10 Group 1 patients (71.8 ± 2.2%) compared with the seven Group 2 patients (63.3 ± 2.1%; $p < 0.01$). The highest $\text{SjO}_2$ level was also greater in the Group 1 patients (80.8 ± 3%) than in the Group 2 patients (71.7 ± 3.1%; $p < 0.01$). There was no difference between these two groups in the lowest $\text{SjO}_2$ levels, which were successfully maintained at greater than 55% in all patients. Among the 113 data sets collected during the period of cortical exposure, 72 were normocapnic (ETCO$_2$, 36–41 mm Hg) and 41 were hypercapnic (ETCO$_2$, 41–44 mm Hg). The $\text{SjO}_2$ levels in the normocapnic intervals were greater ($p < 0.01$) in Group 1 (73 ± 2.8%, 42 data sets) than in Group 2 (65.6 ± 2.5%, 30 sets). The $\text{SjO}_2$ levels in the hypercapnic intervals were also greater ($p < 0.01$) in Group 1 (76.7 ± 3.3%, 19 data sets) than in Group 2 (68.6 ± 3.6%, 22 sets).

As ETCO$_2$ increased, the $\text{SjO}_2$ levels tended to increase in both groups; positive correlations between ETCO$_2$ and $\text{SjO}_2$ were demonstrated in both Group 1 ($r = 0.44$; $p < 0.01$, 61 sets; Fig. 1) and Group 2 ($r = 0.57$; $p < 0.01$, 52 sets; Fig. 1). Within a broad range of ETCO$_2$, the $\text{SjO}_2$ levels frequently increased to near 100% in Group 1, whereas the $\text{SjO}_2$ level never reached 76% in Group 2, despite similar fluctuations in ETCO$_2$. The increases in $\text{SjO}_2$ per unit of ETCO$_2$ increase estimated from the regression coefficients were not different between Group 1 (0.83%/mm Hg) and Group 2 (0.85%/mm Hg).

Relationship Between ETCO$_2$ and rCBF

The rCBF levels in the normocapnic intervals were not different between Group 1 (34.1 ± 7 ml/100 g/min, 42 data sets) and Group 2 (35 ± 3.2 ml/100 g/min, 30 sets). The rCBF levels in the hypercapnic intervals were also not different between Group 1 (37.8 ± 7.8 ml/100 g/min, 19 sets) and Group 2 (31.9 ± 5.7 ml/100 g/min, 22 sets). There was no difference in rCBF between the normocapnic and hypercapnic intervals in either group of patients.

The episodic decrease in rCBF was usually observed in association with transient increases in ETCO$_2$. Nevertheless, no negative correlation was found between ETCO$_2$ and rCBF in Group 1; a positive correlation was even demonstrated ($r = 0.36$, $p < 0.01$, 61 sets; Fig. 2). In fact, the rCBF levels varied greatly at higher levels of ETCO$_2$, indicating that the decrease in rCBF in response to increased ETCO$_2$ was not related to the absolute level of hypercapnia. A weak negative correlation was noted in Group 2 ($r = -0.35$, $p < 0.05$, 52 sets; Fig. 2).

Relationship Between $\text{SjO}_2$ and rCBF

Negative correlations were demonstrated in both Group 1 ($r = -0.37$, $p < 0.01$, 61 sets; Fig. 3) and Group 2 ($r = -0.44$, $p < 0.01$, 52 sets; Fig. 3). This indicated that the local blood flow in the region perfused by collateral vessels tended to decrease in association with global hyperemia. Episodes of rCBF decline concomitant with increases in $\text{SjO}_2$ were detected on the polygraphic records of all Group 1 patients. These events were sometimes seen repeatedly in the same patients. Among them, two were patients who had demonstrated rCBF changes indicative of intracerebral steal in the preoperative acetazolamide blood flow study. A decreased rCBF was more frequently observed when the $\text{SjO}_2$ exceeded the cutoff level of 76% in Group 1 ($p < 0.01$, 61 sets; Fig. 3). As mentioned earlier, $\text{SjO}_2$ never attained this level in Group 2. A similar episodic decrease in rCBF occurred in only one of the
patients in Group 2 when SjO$_2$ was transiently elevated; the rCBF decreased suddenly when SjO$_2$ reached 70%, and it returned to its original level as soon as SjO$_2$ fell below this point (Fig. 4). No rCBF changes indicative of intracerebral steal were noted in the preoperative acetazolamide blood flow study performed in this patient. No postoperative neurological deterioration was encountered in this series of patients.

Discussion

Carbon Dioxide Reactivity of Global Flow

In previous studies it has been demonstrated that, when

CO$_2$ vasoreactivity is evaluated from global changes in CBF in patients with moyamoya disease, no impairment is detectable for both hypocapnia and hypercapnia. The positive correlation between ETCO$_2$ and SjO$_2$ observed in this study indicates that hypercapnia causes global hyperemia in patients with moyamoya disease, similar to normal volunteers. This is consistent with an intact CO$_2$ vasoreactivity of global blood flow.

In our study, greater SjO$_2$ levels were observed in Group 1 than in Group 2 patients in normocapnic as well as hypercapnic states. This finding is consistent with the results of earlier studies, which indicated that isoflurane, but not propofol, tended to cause global hyperemia; anesthetic agents administered by inhalation, such as isoflurane, increase the CBF, leaving the cerebral metabolic rate depressed, whereas intravenously administered anesthetic agents such as propofol usually reduce both the CBF and metabolism, maintaining their coupling. From the similarity in SjO$_2$ responses per unit change in ETCO$_2$ and SjO$_2$ between patients in Groups 1 and 2 (Fig. 1), we inferred that isoflurane and propofol did not affect the CO$_2$ vasoreactivity differently. Thus, greater hyperemia is produced by hypercapnia when isoflurane is used, because this anesthetic agent causes hyperemia even in normocapnia.

Carbon Dioxide Reactivity of Local Flow

Previous studies have shown that CO$_2$ vasoreactivity is well preserved in both hypo- and hypercapnia of the occipitotemporal regions fed by intact vessels. In contrast, the collateral vessels that perfuse the frontoparietal regions through an abnormal vascular network retain CO$_2$ vasoreactivity to hypocapnia but not to hypercapnia, presumably because they are maximally dilated. The rCBF in the frontoparietal regions perfused by collateral vessels

![Fig. 2. Scatterplot showing the relationship between ETCO$_2$ and rCBF. Open circles (Group 1): data sets obtained in patients anesthetized with isoflurane (r = 0.36, p < 0.01; 61 sets); filled circles (Group 2): data sets obtained in patients anesthetized with propofol (r = -0.35, p < 0.05; 52 sets). There is some overlap of data points.](image)

![Fig. 3. Scatterplots showing the relationship between SjO$_2$ and rCBF. Open circles (Group 1): data sets obtained in patients anesthetized with isoflurane (r = -0.37, regression coefficient = -0.81, p < 0.01; 61 sets); filled circles (Group 2): data obtained in patients anesthetized with propofol (r = -0.44, regression coefficient = -0.62, p < 0.01; 52 sets). There is some overlap of data points. A decreased rCBF was frequently observed when SjO$_2$ exceeded the cutoff level of 76% (vertical dotted line) in the patients in Group 1 (p < 0.01, 61 sets).](image)

![Fig. 4. Representative polygraphic record of episodic decreases in rCBF concomitant with increases in SjO$_2$ and stable arterial blood pressure (BP). A relatively rapid decrease in rCBF occurred when SjO$_2$ increased above 70% (a), and rCBF returned to the original level as soon as SjO$_2$ fell below 70% (b) in this particular patient who received propofol as an anesthetic agent.](image)
Cerebral hemodynamics in moyamoya disease does not therefore increase in response to hypercapnia. In our study, the responses of rCBF to hypercapnia varied greatly, indicating that the local vasoreactivity to CO₂ was also variable, and complex hemodynamic responses appeared to be induced by hypercapnia. There was no difference between isoflurane and propofol in their effects on rCBF in the frontoparietal regions. This is in contrast to the isoflurane-induced global hyperemia as demonstrated by SjO₂, indicating that the vasoreactivity to isoflurane within the frontoparietal regions is lost in moyamoya disease.

In agreement with previous reports, in our study it was revealed that the rCBF of the frontoparietal regions sometimes even decreased in response to hypercapnia. In a preoperative study in which SPECT scanning was performed in this series of patients, we also confirmed that acetazolamide administration sometimes decreased the rCBF in the frontoparietal regions. Our findings further demonstrated that SjO₂ and rCBF are negatively correlated (Fig. 3). An episodic decrease in rCBF in the frontoparietal regions was not uncommon in moyamoya disease, especially when isoflurane was used, and the fall in rCBF was often concomitant with global hyperemia detected as an increase in SjO₂. These observations support the intracerebral steal hypothesis. Our study failed to reveal any significant correlation between the decrease in rCBF and absolute levels of ETCO₂. This is consistent with the intracerebral steal hypothesis because, if this observation holds true, the decrease in rCBF must be directly related to global hyperemia rather than hypercapnia itself.

**Significance of Intraoperative SjO₂ Monitoring**

Various authors have recommended that normocapnia or slight hypercapnia be maintained during revascularization surgery for moyamoya disease. Our data indicate that there is a greater risk of a decrease in rCBF when isoflurane is used and SjO₂ exceeds the cutoff level of 76% (Fig. 3). This level could sometimes be attained at a broad range of ETCO₂ (37–44 mm Hg, Fig. 1). When propofol is used, a similar decrease in rCBF could occur if SjO₂ is elevated beyond 70%. However, this level could be reached only with a higher ETCO₂ (42–44 mm Hg, Fig. 1). From these findings we infer that the optimal range of CO₂ for isoflurane is more restricted than that for propofol. This may be because anesthetic agents that are administered by inhalation, such as isoflurane, induce global hyperemia by themselves.

Several techniques for revascularization surgery, such as encephaloduroarteriosynangiosis, encephaloduroarteriosynangiosis, and either of them together with superficial temporal artery–middle cerebral artery anastomosis, have been reported in moyamoya disease. It is clearly important to ensure a sufficient rCBF in the frontoparietal regions during revascularization surgery, especially when the procedures used involve temporary interruption of blood flow in the middle cerebral artery. Based on the observed association between a decrease in rCBF and global hyperemia, it would seem prudent to avoid excessive global hyperemia to prevent ischemic complications. Monitoring of SjO₂ has a unique capability for detecting global hyperemia. In addition, global ischemia, such as that caused by hypocapnia, can also be detected using this technique. We encountered no postoperative neurological deterioration in this series of patients. We assume that this was because all the episodes of rCBF decline were short-lived. It seems possible that the monitoring of SjO₂ may have helped to limit such episodes and as a consequence prevented the occurrence of postoperative neurological deterioration. Unlike rCBF measurements within the craniotomy site, SjO₂ monitoring does not interfere with the surgical procedure. Therefore, SjO₂ monitoring appears to represent the most practical technique for preventing ischemic complications of revascularization surgery in moyamoya disease.

**References**

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