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Effects of end-tidal carbon dioxide levels in patients undergoing direct revascularization for Moyamoya disease and risk factors associated with postoperative complications

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Abstract

A history of transient ischemic attack, severity of disease, urinary output, hematocrit, hypocapnia, and hypotension during direct revascularization (superficial temporal artery to middle cerebral artery [STA-MCA]) in patients with Moyamoya disease (MMD) may lead to a poor prognosis, however, to our knowledge evidence for end-tidal carbon dioxide ($ETCO_2$) targets is lacking. Within the ranges of standardized treatment, the article was primarily designed to study the risk factors associated with the neurologic outcomes during STA-MCA for MMD especially including $ETCO_2$ ranges and the duration in different groups. The primary goals of this study were to investigate the risk factors for neurologic deterioration and explore the association between $ETCO_2$ ranges and neurologic outcome during general anesthesia for STA-MCA.

This retrospective observational study included 56 consecutively adult Moyamoya patients who underwent STA-MCA under general anesthesia between January 2015 and August 2019. $ETCO_2$ was summarized per patient every 5 minutes. Clinical outcome was assessed with clinical presentation, computed tomography findings, magnetic resonance imaging findings, cerebral angiography, and the modified Rankin Scale scores at discharge as main outcome measure. The outcomes were also compared for the duration of surgery, anesthesia, and the length of stay.

A total of 56 patients were studied, all patients had comprehensive $ETCO_2$ measurements. The incidence of postoperative complications was 44.6% (25/56). There was no association between age, sex, hypertension, diabetes, smoking history, drinking history, sevoflurane use, invasive arterial blood pressure monitoring, combined encephalomyosynangiosis and postoperative complications. Duration of surgery ($P = .04$), anesthesia ($P = .036$), hospital stay ($P = .023$) were significant correlates of postoperative complications. In the multiple logistic regression model, they were not the significant predictors. The $ETCO_2$ ranges and the length of time in different groups within the current clinical setting was not associated with postoperative complications ($P > .05$).

Within a standardized intraoperative treatment strategy, we found that postoperative complications had no significant correlation with sex, age, hypertension, diabetes, smoking history, drinking history, invasive arterial blood pressure monitoring, combined encephalomyosynangiosis, or sevoflurane use. Further, hypocapnia and hypercapnia during STA-MCA were not found to be associated with postoperative complications in patients with MMD.

Abbreviations: EMS = encephalomyosynangiosis, $ETCO_2$ = end-tidal carbon dioxide, MMD = Moyamoya disease, STA-MCA = the superficial temporal artery to the middle cerebral artery.

Keywords: complications, direct revascularization, end-tidal carbon dioxide, moyamoya

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Moyamoya disease (MMD) is characterized by chronic progressive stenosis or occlusion of the bilateral or unilateral terminal internal carotid arteries and the anterior and middle cerebral arteries. This is associated with the proliferation of dilated and fragile collateral vessels at the base of the brain that on an angiogram appear to look like "a puff of smoke." Takeuchi and Shimizu named such vessels "Moyamoya vessels" in 1957.[1–4] The clinical presentation of MMD mainly includes ischemic stroke, transient ischemic attack, headache, and seizure.[5,6] No medicines, such as antiaggregants, antiepileptics, or vasodilators, are proven to cure or reverse the progression of MMD.[6] Medicines for MMD only aim to reduce the impact of the symptoms and the risk of thrombosis and sustain normotension. Interventional procedures can manage acute endovascular ischemic events but cannot maintain the durable patency of vessels. For surgical revascularization, which is a safe intervention for patients with MMD to increase collateral blood flow by promoting neo-angiogenesis and inducing collateral vessel formation, there are numerous operative approaches, including direct revascularization, indirect revascularization, and a combination of both approaches. In adults, direct revascularization (superficial temporal artery to middle cerebral artery [STA-MCA]) decreases the recurrence of cerebral ischemic episodes by improving focal cerebral perfusion instantly, and the patency rate and clinical outcomes for this procedure are good.[3] However, the short-term outcomes of patients can be affected by various perioperative factors. Researchers have not explicitly paid attention to how end-tidal carbon dioxide ($ETCO_2$) management affects patients with MMD, despite preliminary evidence suggesting that it plays an important role. Therefore, the primary goals of this study were to investigate the risk factors for neurological deterioration and explore the association between $ETCO_2$ ranges and neurologic outcomes during general anesthesia for STA-MCA.

2. Methods

After institutional ethics committee approval, data on patient characteristics, comorbidities, and long-term medication use were collected from HAITAI Electronic Medical Record System. Data on preoperative neurologic conditions, neurologic complications, and postoperative neurologic outcomes were obtained from the hospital's MMD registration database, which contains patient data from admission until discharge.

Adult patients (American Society of Anesthesiologists [ASA] II-III) who underwent selective operations for MMD were included in the study. Patients with MMD due to other clear disease entities, or who underwent a combination of STA-MCA and another surgery besides encephalomyosynangiosis (EMS), which is a temporal muscle graft, were excluded from the study. Furthermore, when no $ETCO_2$ data were recorded, patients were excluded. A CONSORT diagram describing subject recruitment is shown in Figure 1.

We retrospectively collected and analyzed the data of 56 adult patients (18–64 years of age) with MMD who received general anesthesia for STA-MCA at the First Hospital of Jilin University in China between January 2015 and August 2019. Patients were treated according to local standardized protocols, and the preferred neurosurgical treatment modality was chosen on a multidisciplinary level and irrespective of the conduct of this study.

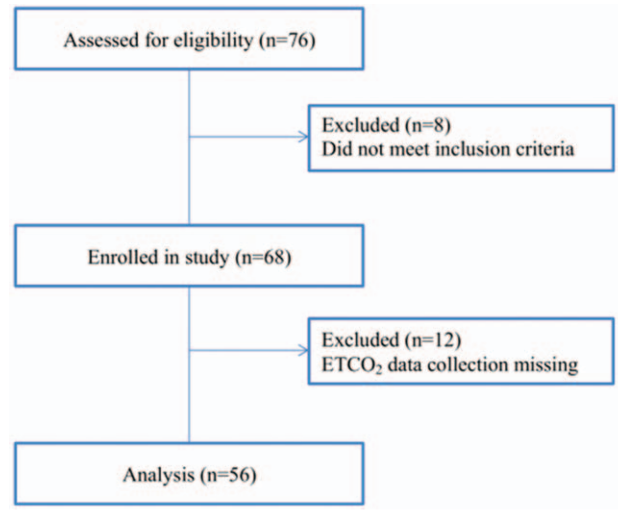

Figure 1. CONSORT flowchart showing the flow of patients through the trial.

All subjects received intravenous drugs, including propofol, opioids (fentanyl, sufentanil, remifentanil), and a muscle relaxant (cisatracurium), as required. Intraoperative data were extracted from the electronic anesthesia record-keeping system. Electrocardiography, blood pressure, heart rate, oxygen saturation, respiratory rate, tidal volume, and $ETCO_2$ data were recorded. The duration of surgery, anesthesia, and hospital stay were also recorded. $ETCO_2$ values were recorded in 5-minute intervals using side-stream CO_2 sampling from intubation to extubation. The median $ETCO_2$ value was calculated for each patient using all recorded values. Management of blood pressure and $ETCO_2$ were left to the judgment of the attending anesthesiologist. The protocol included keeping each patient's systolic blood pressure close to their baseline. All subjects were tracheally intubated and mechanically ventilated. All subjects were extubated and then transferred to the surgical intensive care unit.

Clinical outcomes (the main outcome measure) were assessed per clinical presentations, computed tomography findings, magnetic resonance imaging findings, cerebral angiography findings, and modified Rankin Scale scores at discharge. These data were collated in Microsoft Excel (Microsoft, Redmond, WA) and then transferred to IBM SPSS Statistics V22.0 (IBM, Armonk, NY) for statistical analysis.

3. Statistical analysis

All the analyses were conducted with the IBM SPSS statistical package. Continuous variables with normal distributions were represented as the mean ± standard deviation. Continuous variables with non-normal distributions were represented by the median (Q1-Q3). Categorical variables were represented as frequency (percentage). The Kolmogorov-Smirnov test was applied to see the normality of the continuous data, and the *t*-test was used to compare 2 groups' means for various parameters. The associations of various categorically classified data for 2 groups were found using the Fisher exact test. A multivariate statistical of factors related to postoperative complications was carried out, and variables showing *P*-values <.1 in univariate analyses were selected for analysis in the final model. In all analyses, $P < .05$ was taken to indicate statistical significance.

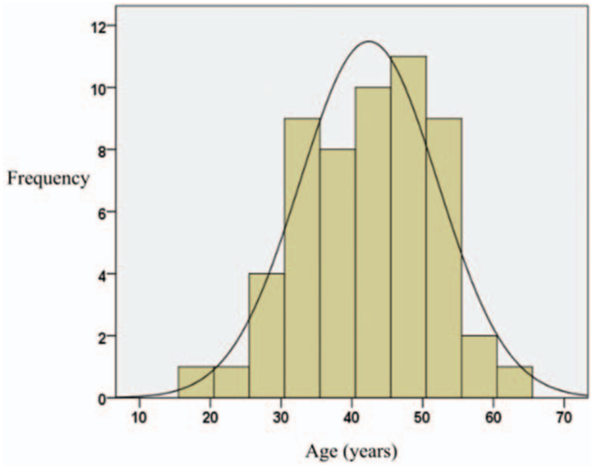

Figure 2. Histogram of patient age.

4. Results

4.1. Demographics

Of the 76 patients initially included in the study, 20 were excluded, and this subsample of 56 patients was evaluated. The patients were 42.39±9.73 years of age. A histogram of patient age is shown in Figure 2. The ratio of female (n=25) to male (n=31) patients was approximately 1:1. All patients underwent STA-MCA, and 36 (64.2%) also underwent EMS under general anesthesia. There were complications in 25 of the 56 patients (44.6%); 8 were transient neurological events, and 6 were infarctions. At the end of the procedure, all patients could be extubated. The mean duration of surgery was 275.98±78.538 minutes, the mean duration of anesthesia was 336.57±77.512 minutes, and the patients spent an average of 16.45±4.75 days in the hospital.

4.2. Complications and statistical outcomes

Patient characteristics were compared for patients with and without postoperative complications before discharge (Table 1).

Table 2

Logistic Regression Analysis examining the comparison of the patient characteristics and complications.

	Logistic Regression Analysis	
	OR (95% CI)	*P* value
Hypertension	0.541 (0.146–2.013)	.36
Sevoflurane use	0.127 (0.012–1.372)	.089
Duration of anesthesia (min)	1.008 (0.999–1.017)	.065
Length of stay (d)	1.106 (0.956–1.279)	.174

Concomitant disease states were recorded, including 20 patients with hypertension and 8 with diabetes mellitus. Interestingly, 30% of those with hypertension had complications while 70% did not. The number of diabetic patients without complications was 3 times higher than the number of diabetic patients with complications. Regrettably, although all the patients had been recorded with noninvasive blood pressure measurements, only 29 (51.8%) had been recorded with invasive blood pressure measurements. Significant differences were demonstrated in the mean durations of surgery, anesthesia, and hospital stay. The durations of surgery, anesthesia, and hospital stay were longer in the group with postoperative complications than in the group without postoperative complications (301.24±93.65 vs 255.61 ±57.72 minutes, 362.20±95.66 vs 315.9±52.01 minutes, and 18.04±4.70 vs 15.16±4.47 days, respectively). Variables were tested with logistic regression and only those with a *P*-value <.1 were considered potential risk factors. After examining the collinearity regression analysis results, the confounders of hypertension, sevoflurane used as a maintenance agent, duration of anesthesia, and duration of hospital stay were included in the logistic regression model for multivariate analysis, and no factors included in the multivariate analysis were identified as independent predictors of postoperative complications (Table 2).

4.3. Median end-tidal carbon dioxide ranges and complications

In the literature, $ETCO_2$ is considered appropriate for estimating $PaCO_2$ in some situation.[7] We hypothesized that intraoperative

Table 1

Comparison of the patient characteristics and complications.

		Postoperative complications		
	All patients	Present	Absent	*P* value
Number of patients	56	25	31	—
Sex				.53
Male	31	15	16	—
Female	25	10	15	—
Age (yrs)	42.39±9.73	41.4±9.68	43.19±9.85	.498
Hypertension	20	6	14	.1
Diabetes	8	2	6	.277
Smoking and drinking history	21	9	12	.835
Invasive arterial blood pressure monitoring	29	15	14	.269
Combined EMS	36	16	20	.968
Sevoflurane use	8	1	7	.063
Duration of surgery (minutes)	275.98±78.54	301.24±93.65	255.61±57.72	.040*
Duration of anesthesia (minutes)	336.57±77.51	362.20±95.66	315.9±52.01	.036*
Length of stay (days)	16.45±4.75	18.04±4.70	15.16±4.47	.023*

EMS = encephalomyosynangiosis.
* Statistically significant at a level of significance of $P<.05$.

Table 3

Characteristics of the patients and variables in both $ETCO_2$ groups.

	$ETCO_2$		
	<35 mm Hg	35–45 mm Hg	*P* value
Number of patients	34	22	—
Sex			0.035*
Male	15	16	—
Female	19	6	—
Age (yrs)	42.47±9.90	42.27±9.67	0.942
Hypertension	16	4	0.028*
Diabetes	5	3	1
Smoking and drinking history	10	11	0.12
Invasive arterial blood pressure monitoring	20	9	0.19
Postoperative Complications	14	11	0.517
Sevoflurane use	7	1	0.13
Combined EMS	21	15	0.625
Duration of surgery (minutes)	262.94±61.31	296.14±97.71	0.165
Duration of anesthesia (min)	326.76±62.42	351.73±96.01	0.288
Length of hospital stay (d)	16.09±4.70	17±4.90	0.488

$ETCO_2$ = end-tidal carbon dioxide

* Statistically significant at a level of significance of $P<.05$.

$ETCO_2$ values: <35 mm Hg (hypocapnia) are associated with a poor neurologic outcome in patients undergoing direct revascularization. The patients were divided into 2 groups based on median $ETCO_2$ values: <35 mm Hg or 35 to 45 mm Hg. The main results are shown in Table 3. Hypocapnia occurred in 60.7% of patients. The mean $ETCO_2$ level was 33.63±3.54 mm Hg for the entire population, 37.30±1.47 mm Hg for the normocapnia group, and 31.25±2.16 mm Hg for the hypocapnia group. There were more women and patients with hypertension in the low $ETCO_2$ group ($P<.05$). We did not observe any differences in the other factors between the 2 groups. Although the durations of surgery, anesthesia, and hospital stay were slightly shorter in the low $ETCO_2$ group compared with the high $ETCO_2$ group (262.94±61.31 vs 296.14±97.71 minutes, 326.76±62.42 vs 351.73±96.01 minutes, and 16.09±4.70 vs 17±4.90 days, respectively), they were not statistically different.

5. Discussion

In the present study, a total of 56 patients met the clinical inclusion criteria from January 2015 to August 2019. The mean age was 42.39±9.73 years. Similarly, a study noted that MMD has a bimodal age distribution with one peak in the first decade of life and the other in the fourth decade of life.[5] A previous study indicated that patient age was a significant factor to predict postoperative symptomatic hyperperfusion in patients with MMD.[8] In contrast to the previous report, this study showed that patient age was not associated with postoperative complications. This is supported by a previous study in which postoperative symptomatic hyperperfusion was not associated with patient age.[9] The main reason for this difference is likely due to differences in the study population. In our study, only adult patients were enrolled, whereas pediatric patients and adults participated in the other study.

Of the 56 patients, 25 (44.6%) experienced neurological deterioration after STA-MCA. The outcomes of patients undergoing STA-MCA for MMD depend on various perioperative factors. A recent study demonstrated that an advanced Suzuki stage and a preoperative ischemic presentation were independent risk factors for postoperative ischemia, and the modified Rankin Scale score on admission and a preoperative ischemic presentation were independently associated with postoperative cerebral hyperperfusion syndrome.[10]

5.1. Surgical procedures

Surgical procedures have been discussed in detail in previous reports of MMD. As early as 1996, Sakamoto et al observed that neurological deterioration was more often observed in patients who underwent indirect revascularization compared to those who were revascularized by direct anastomotic approaches.[11] In a meta-analysis of the surgical outcomes of symptomatic MMD in adults, Jeon et al found that bypass surgery can be effective in preventing future stroke in adult patients with MMD. Direct bypass seems to provide better stroke risk reduction than indirect bypass in these patients.[12] Direct or preferentially combined techniques are more effective in adult patients to prevent the recurrence of ischemic or hemorrhagic stroke.[10,13] However, STA-MCA and STA-MCA + EMS comparisons have not been discussed. We found no significant correlation between STA-MCA and STA-MCA + EMS in our study. Considerably more work will need to be done to compare STA-MCA with or without EMS to determine the superiority of one technique over the other in adults.

5.2. Anesthetic agents

Propofol and sevoflurane are common agents used to maintain general anesthesia in STA-MCA. Both decrease the cerebral oxygen metabolic rate. Sevoflurane decreases cerebral blood flow (CBF) at concentrations <1 minimum alveolar concentration (MAC) but increases CBF at concentrations >1 MAC, while propofol decreases CBF in a dose-dependent manner.[14] Marianna et al showed that sevoflurane anesthesia at 1 MAC can preserve cerebral autoregulation and CO_2 reactivity.[15] Intravenous anesthesia with propofol has the potential to provide brain protection and preserve regional CBF (rCBF) in the frontal lobes in revascularization surgery for MMD.[16] Our results were not significant in this regard, possibly due to the small sample size ($P=.063$). In the same vein, George et al analyzed the anesthetic management of 32 patients with MMD and showed that the use of propofol, isoflurane, and sevoflurane did not vary dramatically in a retrospective review over a 6-year period.[17] A prospective randomized controlled study by Park demonstrated that propofol-remifentanil anesthesia was comparable to sevoflurane-remifentanil anesthesia in terms of preserving regional cerebral oxygen saturation in patients undergoing carotid endarterectomy.[14] Overall, there is not enough evidence associating the use of a particular maintenance agent with better outcomes in patients with MMD. Further multicenter randomized controlled trials need to be done to establish which anesthetic agent is best for adult patients with MMD.

5.3. End-tidal carbon dioxide

CO_2 is a powerful modulator of cerebrovascular tone and a major factor in neurosurgery. CO_2 tension is a fundamental driver of CBF. Hypocapnia causes cerebral vasoconstriction and makes the areas of the brain supplied by diseased vessels more at risk of cerebral ischemia in patients with MMD. A recent study using positron emission tomography and single photon emission computed tomography demonstrated that preoperatively reduced cerebrovascular contractile reactivity to hypocapnia by hyperventilation was associated with the development of cerebral hyperperfusion syndrome after arterial bypass surgery in adult patients with cerebral misery perfusion due to ischemic MMD.[4] In a retrospective survey, Dony et al evaluated the relationships between intraoperative $ETCO_2$ values and clinical outcomes, with special attention to in- and out-of-hospital 30-day postoperative mortality as well as duration of hospital stay; they showed that low $ETCO_2$ levels during anesthesia were associated with an increased postoperative mortality rate and longer hospital stays.[7] A broadly similar point was recently made by Mutch, who argued that in older patients undergoing noncardiac surgery, the duration and severity of intraoperative hypocapnia was independently associated with the severity of postoperative delirium.[18] Similarly, David et al found a statistically and clinically significant association between higher intraoperative $ETCO_2$ levels and shorter hospital stays in patients who underwent elective colon resections and open hysterectomy.[17] Akca and colleagues found that patients who had an intraoperative PCO_2 of 5.99 kPa had significantly greater cerebral oxygen saturation and subcutaneous tissue oxygen tension than those with a PCO_2 of 3.99 kPa.[19] However, Hypercapnia dilates normal cerebral vessels, and in MMD patients, the diseased vessels show minimal response, causing less blood flow to areas supplied by the diseased vessels. Oshima et al associated the intracerebral steal phenomenon with global hyperemia in patients with MMD during revascularization surgery, and they found that the optimal range of CO_2 for isoflurane was more restricted than that for propofol by monitoring jugular bulb venous oxygen saturation, rCBF, and $ETCO_2$.[20]

Our study did not demonstrate an association between any of the $ETCO_2$ ranges observed in current clinical practice and neurologic outcomes at discharge. Our results did not show that we can abandon strict $ETCO_2$ regulation; they merely indicated that in the context of current clinical practice, no further $ETCO_2$ value subgroups will increase the chance of good neurologic outcomes at discharge. A multicenter binational retrospective review showed that hypercapnic acidosis was associated with increased risk of hospital mortality in patients with cerebral injury. When compensated to normal pH during the first 24 hours of intensive care unit admission, hypercapnia may not be harmful in mechanically ventilated patients with cerebral injury.[21] Akkermans found that within a standardized intraoperative treatment strategy in accordance with the current clinical consensus, intraoperative hypocapnia, hypotension, and hypertension, as they occur in clinical practice during cerebral aneurysm clipping or coiling, were not associated with poor neurologic outcomes.[22] These findings provide strong empirical explanations and confirmation that hypocapnia and hypercapnia during STA-MCA are not associated with postoperative complications in patients with MMD.

6. Strengths and limitations

Our study has several strengths. First of all, a key strength of the present study was that it was the first to investigate the effect of $ETCO_2$ in patients undergoing direct revascularization. Secondly, in contrast to previous studies, it mainly concentrated on STA-MCA of operative approaches that may influence the result of postoperative complications. At last but not least, this research has estimated the duration of $ETCO_2$ in different groups and complications in need of further investigation (Much more details are given in supplemental content, http://links.lww.com/MD/F611).

Several potential limitations need to be noted regarding the present study. First, this was a single-center retrospective study, and MMD is not common in China, with only a few patients having undergone surgery for MMD at our institute in the past 5 years. The small sample size may affect the ability to detect significant findings in some instances. We also did not classify the clinical manifestations before and after surgery. Second, although many clinical factors were recorded, hematocrit values, urinary output values, and other intraoperative measures were not analyzed in this study. Further studies need to be carried out to assess the optimal perioperative management to reduce postoperative complications in patients with MMD.

7. Clinical implications

Our study did not demonstrate a relationship between $ETCO_2$ and postoperative complications in patients undergoing direct revascularization. As a result, we may reckon that a low $ETCO_2$ or a little high $ETCO_2$ might not be as bad as previously expected. However, it needs to be investigated further in a multicenter, prospective study. Anesthesiologists should perform thorough and detailed preoperative assessments, such as reviewing patients' long-term medications. It is also important for anesthesiologists to be familiar with the pathophysiology and surgical procedures of STA-MCA. It is clinically important to identify predictors for postoperative complications after STA-MCA anastomosis in patients with MMD. Jason concluded that most bypass procedures are similar and involve maintaining adequate cerebral perfusion to prevent cerebral ischemia.[23] Much of the current literature on anesthetic management of MMD gives particular attention to maintaining the balance between CBF and the cerebral metabolic oxygen consumption rate, as well as maintaining the balance between oxygen supply and demand.[24,25]

8. Conclusion

Within a standardized intraoperative treatment strategy, we found that postoperative complications had no significant correlation with sex, age, hypertension, diabetes, smoking history, drinking history, invasive arterial blood pressure monitoring, combined EMS, or sevoflurane use. Further, hypocapnia and hypercapnia during STA-MCA were not found to be associated with postoperative complications in patients with MMD.

Author contributions

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Writing – review & editing: Haiyang Xu, Tingting Song.

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