



Variability of Resting Carbon Dioxide Tension in Patients with Intracranial Steno-occlusive Disease

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Abstract

Introduction Controlling the partial pressure of carbon dioxide (PaCO₂) is an important consideration in patients with intracranial steno-occlusive disease to avoid reductions in critical perfusion from vasoconstriction due to hypocapnia, or reductions in blood flow due to steal physiology during hypercapnia. However, the normal range for resting PCO₂ in this patient population is not known. Therefore, we investigated the variability in resting end-tidal PCO₂ (P_{ET}CO₂) in patients with intracranial steno-occlusive disease and the impact of revascularization on resting P_{ET}CO₂ in these patients.

Setting and Design Tertiary care center, retrospective chart review

Materials and Methods We collected resting P_{ET}CO₂ values in adult patients with intracranial steno-occlusive disease who presented to our institution between January 2010 and June 2021. We also explored postrevascularization changes in resting P_{ET}CO₂ in a subset of patients.

Results Two hundred and twenty-seven patients were included [moyamoya vasculopathy ($n = 98$) and intracranial atherosclerotic disease ($n = 129$)]. In the whole cohort, mean \pm standard deviation resting P_{ET}CO₂ was 37.8 ± 3.9 mm Hg (range: 26–47). In patients with moyamoya vasculopathy and intracranial atherosclerotic disease, resting P_{ET}CO₂ was 38.4 ± 3.6 mm Hg (range: 28–47) and 37.4 ± 4.1 mm Hg (range: 26–46), respectively. A trend was identified suggesting increasing resting P_{ET}CO₂ after revascularization in patients with low preoperative resting P_{ET}CO₂ (<38 mm Hg) and decreasing resting P_{ET}CO₂ after revascularization in patients with high preoperative resting P_{ET}CO₂ (>38 mm Hg).

Conclusion This study demonstrates that resting P_{ET}CO₂ in patients with intracranial steno-occlusive disease is highly variable. In some patients, there was a change in resting P_{ET}CO₂ after a revascularization procedure.

Keywords

- ▶ resting PCO₂
- ▶ cerebrovascular reactivity
- ▶ intracranial atherosclerotic disease
- ▶ moyamoya vasculopathy
- ▶ steno-occlusive disease

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Introduction

Carbon dioxide (CO₂) is a potent modulator of cerebrovascular tone. Hence, controlling the partial pressure of carbon dioxide (PCO₂) is an important consideration in perioperative neurosurgical care. Importance of CO₂ in patients with raised intracranial pressure has been well known.^{1,2} Although preliminary evidence suggests that CO₂ management plays an important role in patients with intracranial steno-occlusive disease (SOD), researchers have not explicitly considered this in their study. In patients with intracranial SOD, hypocapnia may cause further reductions in perfusion of critical vascular beds due to vasoconstriction and hypercapnia may cause localized vasodilation resulting in steal physiology in vulnerable vascular beds leading to exacerbation of cerebral ischemia.^{3,4} Maintaining normocapnia is an important recommendation in patients with intracranial SOD undergoing cerebral revascularization procedures.⁵⁻⁷ Hence, clinicians need to know the resting CO₂ levels of a patient with SOD undergoing a surgical procedure to avoid cerebral ischemic insults and steal phenomenon.

Traditionally, the normal range of resting PaCO₂ has been considered to be within 35 to 45 mm Hg.^{8,9} The reference standard for measuring CO₂ is partial pressure of CO₂ in arterial blood (PaCO₂), which requires an arterial puncture. However, end-tidal CO₂ (P_{ET}CO₂) is a noninvasive method that is often used to predict PaCO₂ values, especially when the arterial to end-tidal gradient is known.¹⁰

We and others have observed resting P_{ET}CO₂ values outside the normal range (35–45 mm Hg) in patients with SOD presenting for surgical revascularization.^{11,12} This is important because maintaining normocapnia based on the traditional range might increase the risk of cerebral ischemia in a patient whose resting CO₂ is outside the normal range. Thus, understanding the variability of CO₂ in patients with intracranial SOD is important for individualized control of CO₂ to improve patient outcomes.

In this study, two research questions were investigated. First, we sought to investigate the variability of resting P_{ET}CO₂ in patients with intracranial SOD by examining the distribution of this measurement within our study population. We hypothesized that patients with intracranial SOD would have considerable variability in resting P_{ET}CO₂, extending outside the traditional range of 35 to 40 mm Hg. Second, we explored the impact of a revascularization surgery on resting P_{ET}CO₂ in patients with intracranial SOD. Given the exploratory nature of this research question, we adopted no a priori hypothesis.

Materials and Methods

Study Design

After Institutional Research Ethics Board (REB # 22-5923, December 22, 2022) approval, we conducted a retrospective chart review of all patients over 18 years old with intracranial SOD who presented to our institution between January 2010 and June 2021. We included patients with symptomatic intracranial SOD who underwent cerebrovascular reactivity

(CVR) assessment as part of their clinical care. We excluded patients with extracranial SOD and those who did not have CVR assessments.

CVR assessment is our standard clinical care for patients who present with intracranial SOD. CVR assessments are done using precisely controlled carbon dioxide [hypercapnia (resting P_{ET}CO₂ + 10 mm Hg)] as a vasodilatory stimulus and Blood Oxygen Level Dependent Magnetic Resonance Imaging (BOLD-MRI) serves as a surrogate for cerebral blood flow. CVR is calculated as a ratio of the change in the BOLD signal to the change in P_{ET}CO₂. Based on the patients' CVR assessment, a revascularization surgery (superficial temporal artery to middle cerebral artery bypass) was performed on patients that demonstrated impaired or paradoxical (steal physiology) CVR. After revascularization, patients' CVRs were reassessed at approximately 1 year to determine if the surgery improved steal physiology.

Changes in P_{ET}CO₂ were administered by an automated gas blender (RespirAct Thornhill Medical, Toronto, Canada) using sequential gas delivery.¹³⁻¹⁵ This system measures the breath-to-breath P_{ET}CO₂, which is used to calculate the gas flow for the subsequent breath to target end-tidal gases. The computer precalculates the required breath-by-breath inspired gas concentrations and adjusts the inspiratory flow accordingly, regardless of the patient's tidal volume or breathing pattern.^{15,16} The sequential gas delivery circuit contains an exhaled gas reservoir and uses rebreathed gas as reserve gas for control of end-tidal PCO₂ (more detail provided in Fisher et al 2016¹⁵ and Somogyi et al 2005¹⁴). P_{ET}CO₂ measured by this system has been shown to be equal to PaCO₂.^{10,17,18} The apparatus and technique to control P_{ET}CO₂ have been described in greater detail elsewhere.^{13,19}

Data Collection

The data sources used for the present work included the prospective CVR database described above and our institution's electronic patient record (QuadraMed Corporation, Reston, Virginia, United States). Data collected included patient demographics, clinical diagnoses, details of surgical intervention, CVR assessments, and resting P_{ET}CO₂ values. Resting P_{ET}CO₂ values were collected from preoperative and postoperative CVR assessments. They were measured prior to CVR testing (i.e., before applying hypercapnia) and the measurements were done over a 5 minutes period at rest. In addition, in a subset of patients who underwent revascularization surgery, PaCO₂ values from the preinduction arterial line were collected.

Statistical Analysis

All analyses were performed using R Statistical Software (v3.5.0; R Core Team 2018). A sample size calculation was not performed due to the exploratory nature of this study. Continuous data are presented as mean ± standard deviation. Variability in resting P_{ET}CO₂ values was presented as a range. As a part of the secondary analysis, based on preoperative resting P_{ET}CO₂ values, a median split was performed to subset patients into "high" and "low" preoperative values. Paired sample *t*-tests were used to compare preoperative

resting P_{ET}CO₂ values with postoperative resting P_{ET}CO₂ values. A statistical significance threshold of *p*-value less than 0.05 was used. Finally, a Bland–Altman plot was generated to compare P_{ET}CO₂ values from CVR testing with PaCO₂ measurements of arterial blood gas.

Results

Two hundred and twenty-seven patients who met the inclusion criteria were included in the study. Ninety-eight patients had moyamoya vasculopathy (MMV) (age: 42.2 ± 15.2 years, 63.3% female) and 129 patients had intracranial atherosclerotic disease (ICAD) (age: 57.8 ± 15.9 years, 51.9% female).

Preoperative Variability of Resting P_{ET}CO₂ in Patients with Steno-occlusive Disease

In the whole sample, resting P_{ET}CO₂ was 37.9 ± 4.0 mm Hg (range: 26–47). Resting P_{ET}CO₂ values in MMV disease and ICAD were 38.4 ± 3.7 mm Hg (range: 28–47) and 37.5 ± 4.1 mm Hg (range: 26–46), respectively. A frequency histogram of resting P_{ET}CO₂ values across MMV and ICAD groups is shown in ►Fig. 1. In the entire group, the median value for preoperative resting P_{ET}CO₂ was 38 mm Hg.

In the whole patient sample, 41.4% (94/227) had resting P_{ET}CO₂ values outside the range of 35 to 40 mm Hg; 38.8% (38/98) of patients with MMV and 43.4% (56/129) of patients

with ICAD had resting P_{ET}CO₂ values outside the range of 35 to 40 mm Hg.

Effect of Surgical Revascularization on Resting P_{ET}CO₂ in Patients with Steno-occlusive Disease

Out of 227 patients with intracranial SOD, 50 patients underwent successful surgical revascularization (i.e., CVR improved at 1 year and they were clinically asymptomatic). Within this cohort, we compared preoperative and postoperative resting P_{ET}CO₂ and found no statistically significant differences (*t* = 0.10, *p* = 0.92).

In patients with a preoperative resting P_{ET}CO₂ more than 38 mm Hg (*n* = 22), revascularization led to a reduction in the postoperative resting P_{ET}CO₂ (*t* = 5.28, *p* < 0.001). In patients with a preoperative resting P_{ET}CO₂ less than 38 mm Hg (*n* = 21), following revascularization there was an increase in postoperative resting P_{ET}CO₂ (*t* = 2.74, *p* = 0.013; ►Fig. 2).

Comparing Resting P_{ET}CO₂ and PaCO₂

In 20 patients that underwent surgical revascularization, PaCO₂ was measured from their preinduction arterial line while they were awake and without any sedation. Within this cohort, we compared resting PaCO₂ with P_{ET}CO₂ from preoperative CVR assessments. Resting PaCO₂ was 33.8 ± 4.6 mm Hg (range: 26–41) and P_{ET}CO₂ was 34.0 ± 4.7 mm Hg (range: 25–42). A Bland–Altman graph comparing resting P_{ET}CO₂ with PaCO₂ demonstrates the

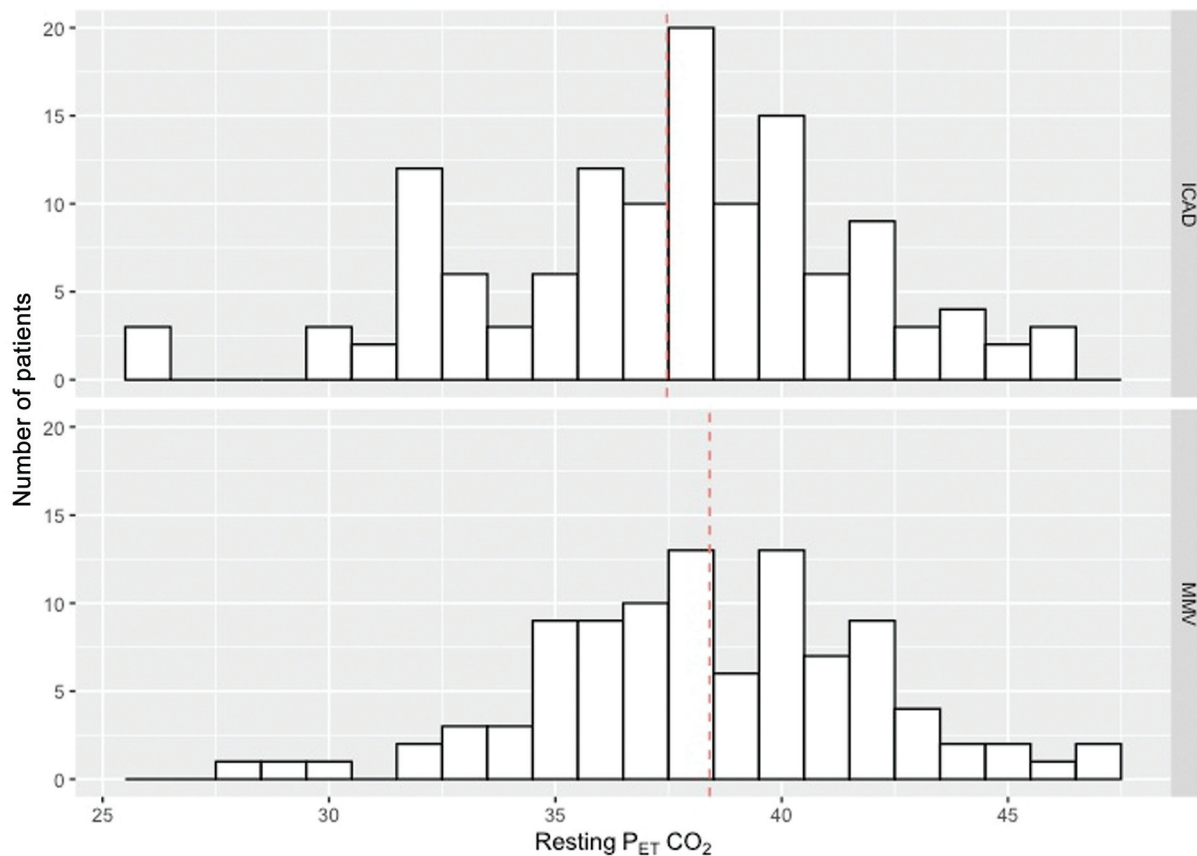


Fig. 1 Number of patients with resting P_{ET}CO₂ values within the total sample. ICAD, intracranial atherosclerotic disease; MMV, Moyamoya vasculopathy; P_{ET}CO₂, End-tidal partial pressure of carbon dioxide. The dotted vertical line illustrates the mean value.

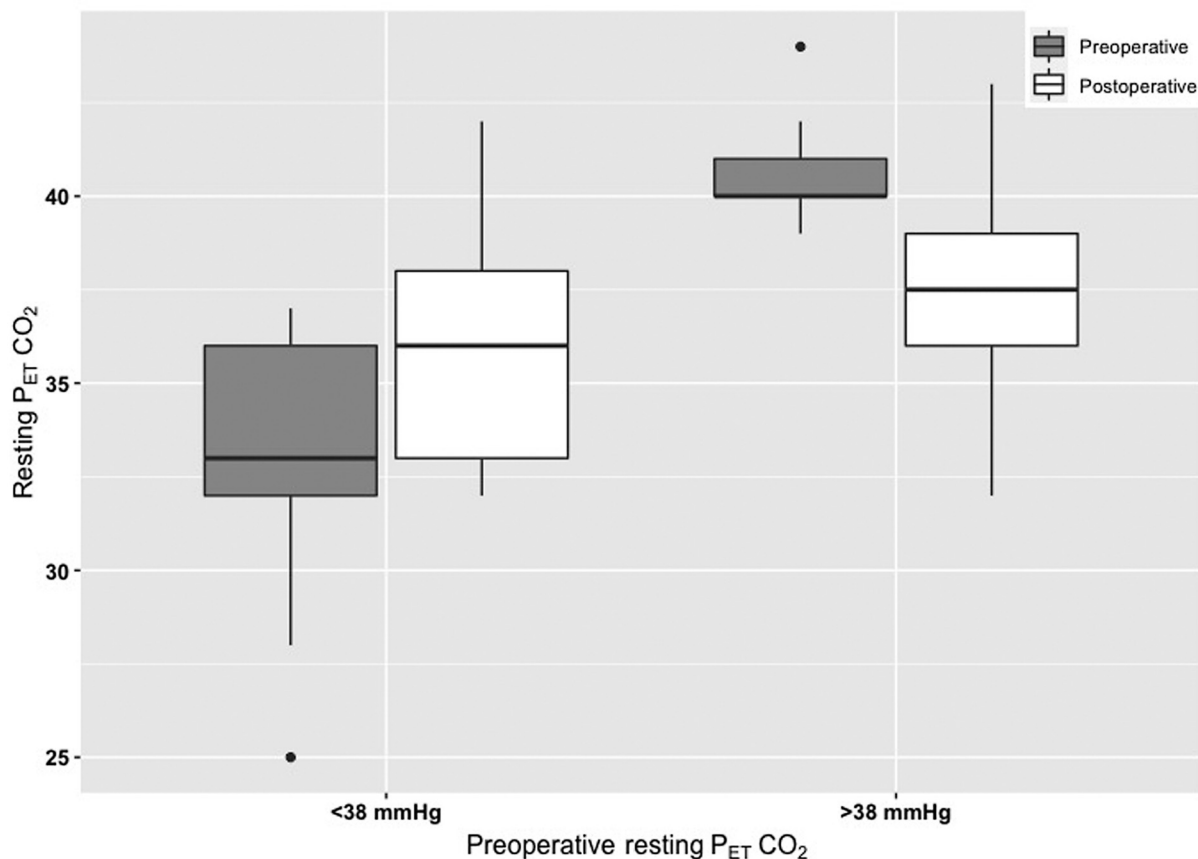


Fig. 2 Preoperative and postoperative resting P_{ET}CO₂ following revascularization in a subset of the whole sample, split by those with preoperative resting P_{ET}CO₂ values below 38 mmHg and those above 38 mmHg. P_{ET}CO₂, End-tidal partial pressure of carbon dioxide.

minimal discrepancy between these measures across the full range of average measurements (► Fig. 3); the difference between PaCO₂ and P_{ET}CO₂ values was less than or equal to 2 mm Hg in 95% (19/20) of patients.

Discussion

To the best of our knowledge, this is the first investigation to examine the variability of resting P_{ET}CO₂ in patients with intracranial SOD. Our study demonstrates that resting P_{ET}CO₂ varies considerably between individual patients. Although the mean value of P_{ET}CO₂ in our studied group was around 38 mm Hg, many individuals had P_{ET}CO₂ values lower or higher than the normal range of 35 to 40 mm Hg. Indeed, 41.4% (94/227) of patients had resting P_{ET}CO₂ values outside this range. Further, in some patients, there was a change in resting P_{ET}CO₂ subsequent to revascularization procedures. These findings suggest a role for resting PaCO₂ in the regulation of cerebral blood flow in patients with disrupted CVR and steal phenomenon.

CO₂ is a potent vasoactive stimulus and an important driver of cerebral blood flow. Hence, PaCO₂ plays an important role in patients with SOD. In patients with intracranial SOD, a global vasodilatory stimulus such as hypercapnia can lead to a paradoxical decrease in blood flow in the regions distal to stenosis as the blood flow is redistributed from more affected to lesser affected vessels. This phenomenon is known as

“vascular steal,” arising from redistribution of blood flow away from an area with exhausted vascular reserve to vascular beds with intact reserve and thus an ability to lower flow resistance. Intracerebral steal is a strong marker for the risk of cerebral ischemia.³ Kurehara et al studied the effect of hypercapnia on cortical blood flow in patients with moyamoya disease (MMD) using a laser-doppler method.²⁰ They showed a decrease in regional cortical blood flow with hypercapnia and confirmed that the normal cortical blood flow response to hypercapnia was impaired during surgery. Using positron emission tomography, another study showed that patients with MMD had severely decreased cerebrovascular responses to hypercapnia over the cerebral cortex.²¹ There have been similar findings reported in children suffering from MMD.²²

Hypocapnia, on the other hand, causes cerebral vasoconstriction and puts patients with MMD more at risk of cerebral ischemia.²³ Using positron emission tomography and single photon emission computed tomography, another study on patients with MMD has demonstrated that the reduced CVR to hypocapnia with hyperventilation preoperatively preoperatively is associated with the development of cerebral hyperperfusion syndrome after cerebral revascularization surgery.²⁴ Additionally, transient ischemic attack has been observed in children with MMD who have experienced hyperventilation due to crying or exercise.^{25–27} In a study using 133-Xe inhalation methods, Tagawa et al have shown that hyperventilation (PaCO₂ < 29 mm Hg) decreased

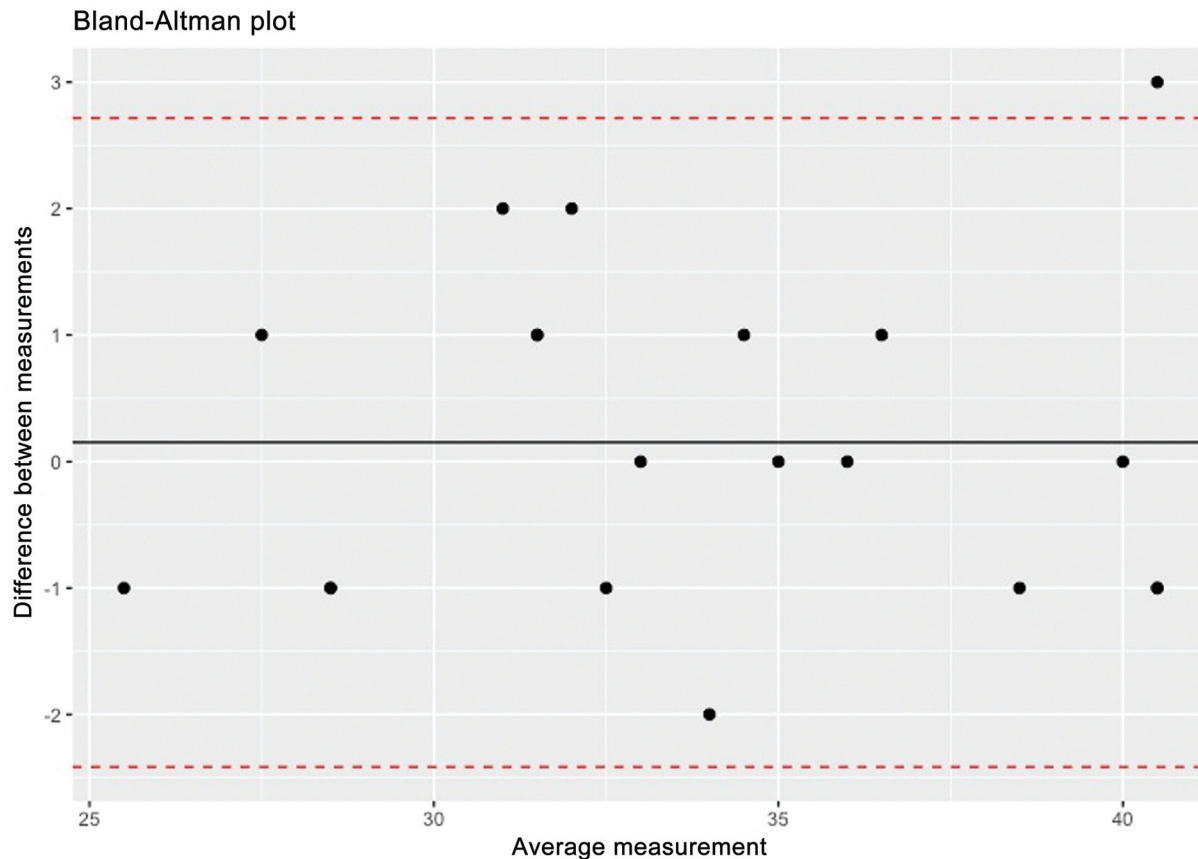


Fig. 3 Bland-Altman plot comparing resting $P_{ET}CO_2$ with $PaCO_2$ in patients with the intracranial steno-occlusive disease. $P_{ET}CO_2$ was measured using the RespirAct machine, whereas $PaCO_2$ values were obtained from pre-induction arterial lines. The observed discrepancy between $P_{ET}CO_2$ with $PaCO_2$ is minimal across the full range of average measurements.

regional cerebral blood flow in children with MMD.²⁸ Hence, one of the important goals in patients with intracranial SOD undergoing cerebral revascularization is to maintain normocapnia and avoidance of hypotension.^{11,29,30}

The published literature describes a normal resting $PaCO_2$ range of 35 to 45 mm Hg.^{8,9,31} However, variability in the resting $PaCO_2$ has been observed both in healthy subjects and in patients with intracranial SOD.^{1,12,31} Crosby and Robbins observed within-subject, between-day variability, and between-subject variations in the level of $PaCO_2$.³¹ They observed within-subject, between-day $PaCO_2$ differences of 4 mm Hg. Recently, Song et al explored the association between $P_{ET}CO_2$ levels and neurological outcomes in patients undergoing revascularization for MMD.¹¹ In their study, 60.7% of patients were hypocapnic (< 35 mm Hg) and the mean $P_{ET}CO_2$ level was 33.63 ± 3.54 . In our study, 41.4% (94/227) of patients had resting $P_{ET}CO_2$ values outside the traditional normal range (35–40 mm Hg), emphasizing the importance of identifying the baseline $PaCO_2$ immediately prior to induction using the arterial blood gas sample to then titrate the intraoperative PCO_2 near baseline.

Maintaining normocapnia based on the traditional range might increase the risk of cerebral ischemia in a patient whose resting CO_2 is outside the normal range. For example, a patient with a resting $PaCO_2$ of 26 mm Hg will be at a high risk of cerebral ischemia due to intracerebral steal phenom-

enon if intraoperative $PaCO_2$ is kept within the traditional range of 35 to 40 mm Hg. Conversely, hypocapnia can lead to severe vasoconstriction in a patient with a resting $PaCO_2$ of 46 mm Hg. Thus, understanding the variability of CO_2 in patients with intracranial SOD is important for individualized control of CO_2 to improve patient outcomes.

The reason for the variability in resting $P_{ET}CO_2$ in patients with intracranial SOD is not known. We postulate that the low resting $P_{ET}CO_2$ in this patient population may be to minimize the steal phenomenon associated with hypercapnia. Conversely, a high resting $P_{ET}CO_2$ may be a compensatory mechanism in some patients to facilitate collateral flow. For example, MMV is often a bilateral disease; hence, these patients may have higher than normal PCO_2 at rest to maintain cerebral blood flow. Hence, resting $PaCO_2$ might play a role in the regulation of cerebral blood flow in patients with disrupted CVR and steal phenomenon. While an increase in blood pressure is a well-established compensatory mechanism for cerebral ischemia, it is possible that changes in resting $PaCO_2$ can similarly be a compensatory mechanism in patients with intracranial SOD to prevent cerebral ischemia.^{32–34} We speculate that blood flow changes to the central chemoreceptors may be causing the resting $PaCO_2$ changes.

As a part of an exploratory secondary analysis, we also compared preoperative and postoperative resting $P_{ET}CO_2$ in a subset of patients who underwent successful revascularization

to test the hypothesis if the change in ischemic burden can lead to a change in resting P_{ET}CO₂. Though there were no significant differences between preoperative and postoperative resting P_{ET}CO₂ values overall, a trend was identified suggesting increasing resting P_{ET}CO₂ after revascularization in patients with low preoperative resting P_{ET}CO₂ and decreasing resting P_{ET}CO₂ after revascularization in patients with high preoperative resting P_{ET}CO₂.

The reference standard for measuring PCO₂ is PaCO₂, which requires an arterial puncture. However, P_{ET}CO₂ is a noninvasive method that is often used to predict PaCO₂ values, especially when the arterial to end-tidal gradient is known.¹⁰ The normal PaCO₂-P_{ET}CO₂ gradient is considered to be 2 to 5 mm Hg.³⁵ This difference in healthy individuals is related to the alveolar dead space, where alveoli that are ventilated but not perfused lead to the dilution of P_{ET}CO₂ and the creation of the gradient. In our study, resting P_{ET}CO₂ was measured using the sequential gas delivery method and P_{ET}CO₂ measured by this system has been shown to be equal to PaCO₂.^{17,18} We also confirmed this finding in our study.

This study has a number of major limitations, including its retrospective design. First, preoperative resting P_{ET}CO₂ was measured with the RespirAct during CVR testing and PaCO₂ was measured from the awake pre-induction arterial blood gas on the day of surgery, resulting in a time gap of approximately 3 months. Second, we did not investigate changes in resting P_{ET}CO₂ in patients who underwent intracranial stenting procedures, which may have produced different results. Finally, despite a sample size calculation not being performed a priori, the effect sizes observed in the current work within the median split analyses investigating the impact of revascularization procedures on patients with “high” and “low” preoperative values (“high” 1.13 and “low” 0.59) would require 9 and 25 participants, respectively, at an alpha probability of 0.05 and power of 0.8 in a two-tailed investigation.

Conclusion

In conclusion, patients with intracranial SOD displayed considerable variability in resting P_{ET}CO₂. Further, in some patients, there was a change in resting P_{ET}CO₂ subsequent to a revascularization procedure. Future work is necessitated to replicate these findings using matched controls and controlling for possible confounding factors.

Note

Controlling the partial pressure of carbon dioxide is an important consideration in perioperative neurosurgical care, as both hypocapnia and hypercapnia may lead to complications. This study shows that the resting (i.e., baseline) partial pressure of carbon dioxide in patients with intracranial steno-occlusive disease is highly variable and may be impacted by revascularization procedures. Further research is necessitated to improve our understanding of this phenomenon.

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Authors' Contributions

E.P. contributed to conceptualization, experimental studies, data acquisition, and provided guarantee. L.V. helped in experimental studies. S.A. was involved in conceptualization, designing, literature search, clinical studies, experimental studies, data acquisition, statistical analysis, and provided guarantee. V.R., T.C., O.S., and E.S.S. contributed to conceptualization, designing, literature search, clinical studies, experimental studies, data analysis, statistical analysis, and provided guarantee. J.P., J.D., D.M., and J.F. helped in literature search and experimental studies and provided guarantee.

Ethical Approval

UHN REB # 22-5923, December 22, 2022

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Conflict of Interest

RespirAct is currently a noncommercial research tool assembled and made available by Thornhill Research Inc. (TRI), a spin-off company from the University Health Network to research institutions to enable CVR studies. J.F. is the Chief Scientist and J.D. is the Senior Scientist at TRI, and J.P., O.S., and D.M. have contributed to the development of RespirAct and have received payments from, or shares in, TRI.

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