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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 ($PaCO_2$) 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 PCO_2 in this patient population is not known. Therefore, we investigated the variability in resting end-tidal PCO_2 ($P_{ET}CO_2$) in patients with intracranial steno-occlusive disease and the impact of revascularization on resting $P_{ET}CO_2$ in these patients.

Setting and Design Tertiary care center, retrospective chart review

Materials and Methods We collected resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ 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 ± standard deviation resting $P_{ET}CO_2$ was 37.8 ± 3.9 mm Hg (range: 26–47). In patients with moyamoya vasculopathy and intracranial atherosclerotic disease, resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ after revascularization in patients with low preoperative resting $P_{ET}CO_2$ (<38 mm Hg) and decreasing resting $P_{ET}CO_2$ after revascularization in patients with high preoperative resting $P_{ET}CO_2$ (>38 mm Hg).

Conclusion This study demonstrates that resting $P_{ET}CO_2$ in patients with intracranial steno-occlusive disease is highly variable. In some patients, there was a change in resting $P_{ET}CO_2$ after a revascularization procedure.

Keywords
- resting PCO_2
- cerebrovascular reactivity
- intracranial atherosclerotic disease
- moyamoya vasculopathy
- steno-occlusive disease

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Introduction

Carbon dioxide (CO_2) is a potent modulator of cerebrovascular tone. Hence, controlling the partial pressure of carbon dioxide (PCO_2) is an important consideration in perioperative neurosurgical care. Importance of CO_2 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 CO_2 levels of a patient with SOD undergoing a surgical procedure to avoid cerebral ischemic insults and steal phenomenon.

Traditionally, the normal range of resting $PaCO_2$ has been considered to be within 35 to 45 mm Hg.[8,9] The reference standard for measuring CO_2 is partial pressure of CO_2 in arterial blood ($PaCO_2$), which requires an arterial puncture. However, end-tidal CO_2 ($P_{ET}CO_2$) is a noninvasive method that is often used to predict $PaCO_2$ values, especially when the arterial to end-tidal gradient is known.[10]

We and others have observed resting $P_{ET}CO_2$ 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 CO_2 is outside the normal range. Thus, understanding the variability of CO_2 in patients with intracranial SOD is important for individualized control of CO_2 to improve patient outcomes.

In this study, two research questions were investigated. First, we sought to investigate the variability of resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$, extending outside the traditional range of 35 to 40 mm Hg. Second, we explored the impact of a revascularization surgery on resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ +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 $P_{ET}CO_2$. 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 $P_{ET}CO_2$ 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 $P_{ET}CO_2$, 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 PCO_2 (more detail provided in Fisher et al 2016[15] and Somogyi et al 2005[14]). $P_{ET}CO_2$ measured by this system has been shown to be equal to $PaCO_2$.[10,17,18] The apparatus and technique to control $P_{ET}CO_2$ 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, Virgina, United States). Data collected included patient demographics, clinical diagnoses, details of surgical intervention, CVR assessments, and resting $P_{ET}CO_2$ values. Resting $P_{ET}CO_2$ 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, $PaCO_2$ 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 $P_{ET}CO_2$ values was presented as a range. As a part of the secondary analysis, based on preoperative resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ values with postoperative resting $P_{ET}CO_2$ values. A statistical significance threshold of *p*-value less than 0.05 was used. Finally, a Bland–Altman plot was generated to compare $P_{ET}CO_2$ values from CVR testing with $PaCO_2$ 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 $P_{ET}CO_2$ in Patients with Steno-occlusive Disease

In the whole sample, resting $P_{ET}CO_2$ was 37.9 ± 4.0 mm Hg (range: 26–47). Resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ values across MMV and ICAD groups is shown in ►**Fig. 1**. In the entire group, the median value for preoperative resting $P_{ET}CO_2$ was 38 mm Hg.

In the whole patient sample, 41.4% (94/227) had resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ values outside the range of 35 to 40 mm Hg.

Effect of Surgical Revascularization on Resting $P_{ET}CO_2$ 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 $P_{ET}CO_2$ and found no statistically significant differences ($t = 0.10$, $p = 0.92$).

In patients with a preoperative resting $P_{ET}CO_2$ more than 38 mm Hg ($n = 22$), revascularization led to a reduction in the postoperative resting $P_{ET}CO_2$ ($t = 5.28$, $p < 0.001$). In patients with a preoperative resting $P_{ET}CO_2$ less than 38 mm Hg ($n = 21$), following revascularization there was an increase in postoperative resting $P_{ET}CO_2$ ($t = 2.74$, $p = 0.013$; ►**Fig. 2**).

Comparing Resting $P_{ET}CO_2$ and $PaCO_2$

In 20 patients that underwent surgical revascularization, $PaCO_2$ was measured from their preinduction arterial line while they were awake and without any sedation. Within this cohort, we compared resting $PaCO_2$ with $P_{ET}CO_2$ from preoperative CVR assessments. Resting $PaCO_2$ was 33.8 ± 4.6 mm Hg (range: 26–41) and $P_{ET}CO_2$ was 34.0 ± 4.7 mm Hg (range: 25–42). A Bland–Altman graph comparing resting $P_{ET}CO_2$ with $PaCO_2$ demonstrates the

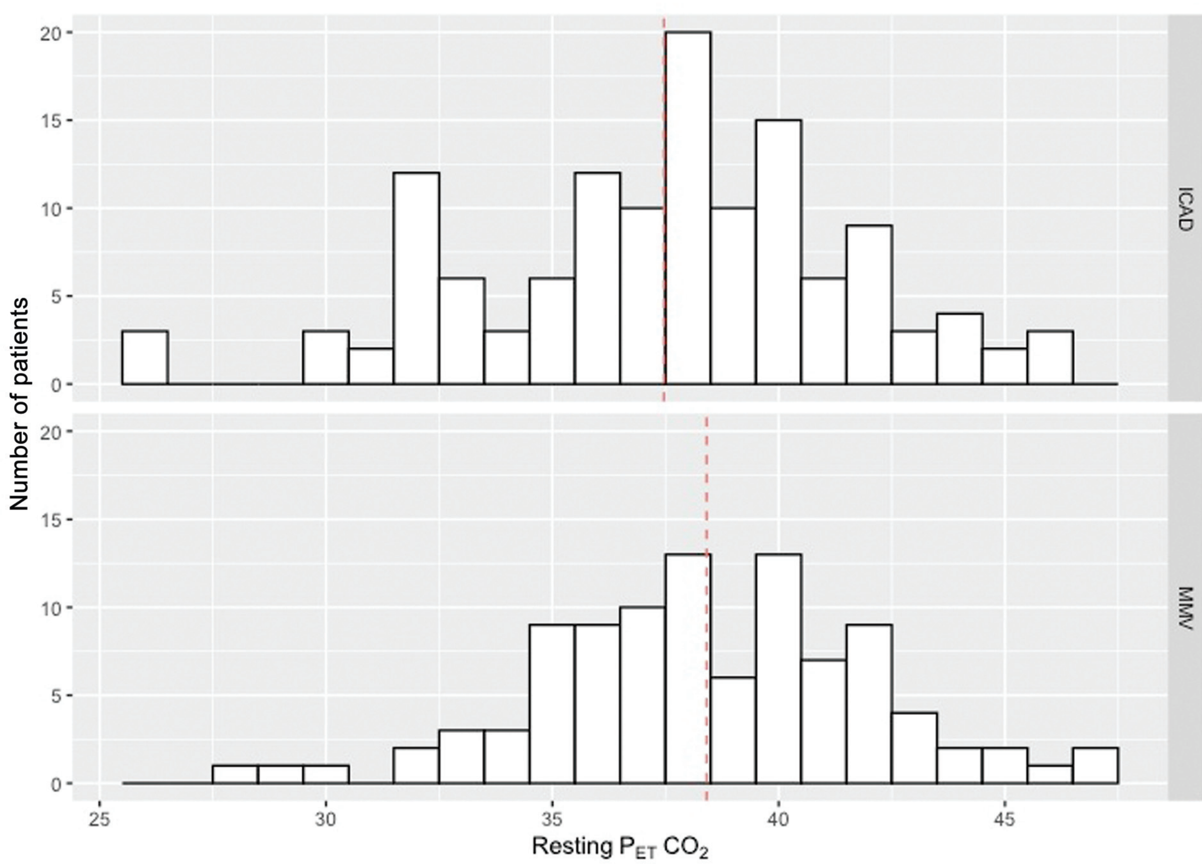

Fig. 1 Number of patients with resting $P_{ET}CO_2$ values within the total sample. ICAD, intracranial atherosclerotic disease; MMV, Moyamoya vasculopathy; $P_{ET}CO_2$, End-tidal partial pressure of carbon dioxide. The dotted vertical line illustrates the mean value.

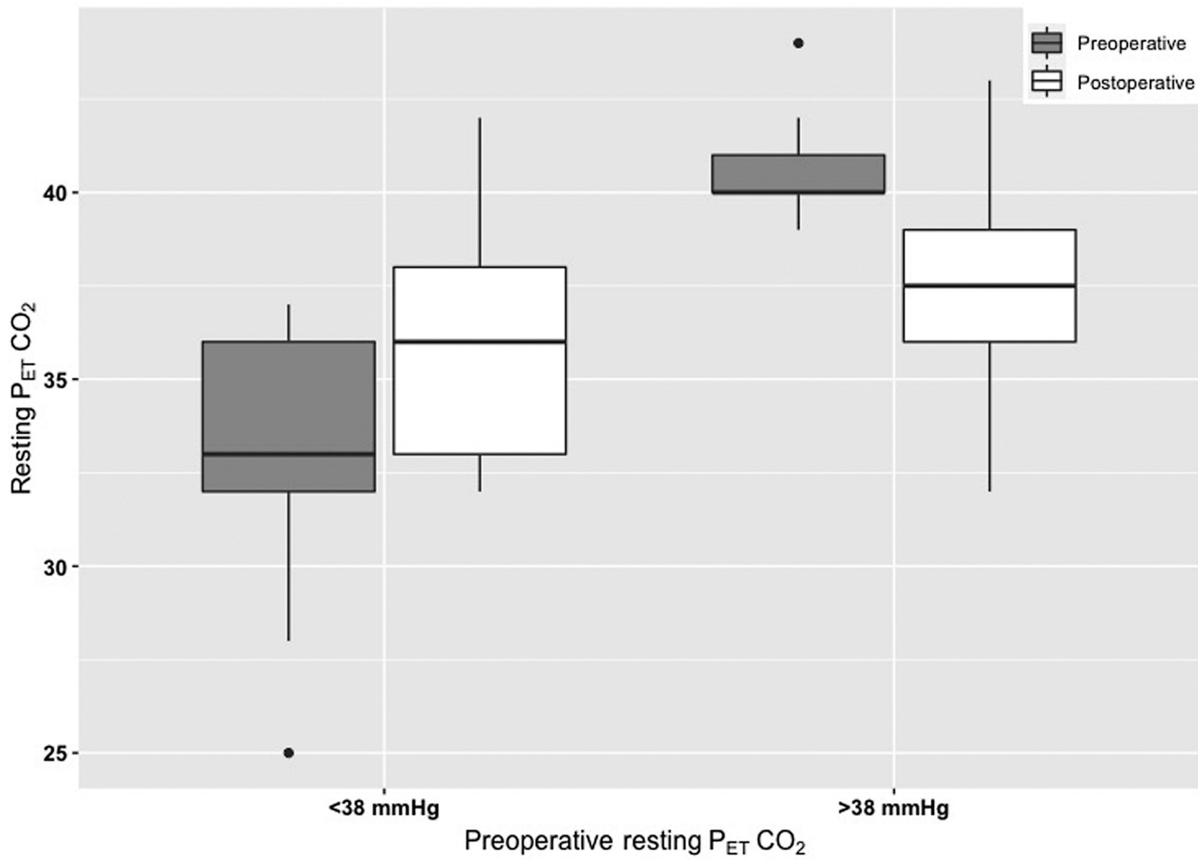

Fig. 2 Preoperative and postoperative resting $P_{ET}CO_2$ following revascularization in a subset of the whole sample, split by those with preoperative resting $P_{ET}CO_2$ values below 38 mmHg and those above 38 mmHg. $P_{ET}CO_2$, End-tidal partial pressure of carbon dioxide.

minimal discrepancy between these measures across the full range of average measurements (►**Fig. 3**); the difference between $PaCO_2$ and $P_{ET}CO_2$ 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 $P_{ET}CO_2$ in patients with intracranial SOD. Our study demonstrates that resting $P_{ET}CO_2$ varies considerably between individual patients. Although the mean value of $P_{ET}CO_2$ in our studied group was around 38 mm Hg, many individuals had $P_{ET}CO_2$ values lower or higher than the normal range of 35 to 40 mm Hg. Indeed, 41.4% (94/227) of patients had resting $P_{ET}CO_2$ values outside this range. Further, in some patients, there was a change in resting $P_{ET}CO_2$ subsequent to revascularization procedures. These findings suggest a role for resting $PaCO_2$ in the regulation of cerebral blood flow in patients with disrupted CVR and steal phenomenon.

CO_2 is a potent vasoactive stimulus and an important driver of cerebral blood flow. Hence, $PaCO_2$ 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

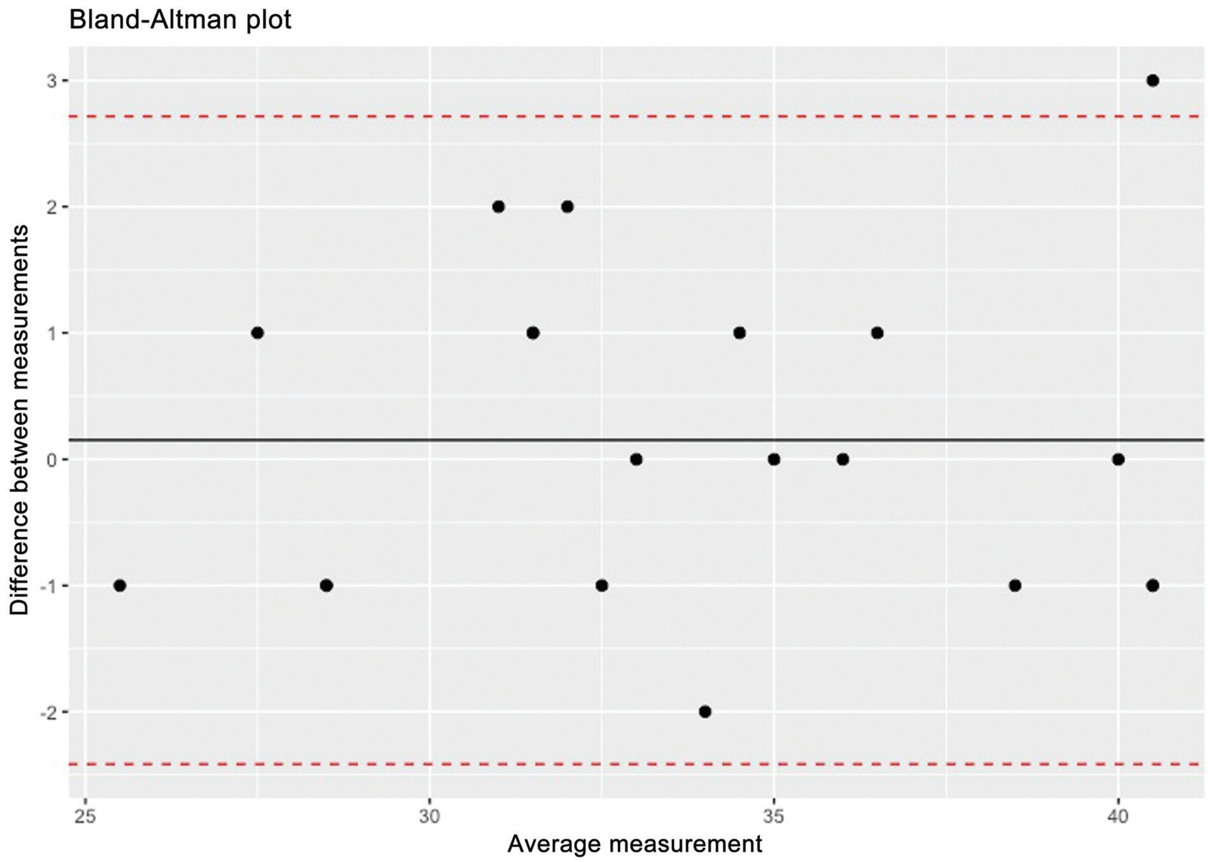

Fig. 3 Bland-Altman plot comparing resting $P_{ET}CO_2$ with PaCO2 in patients with the intracranial steno-occlusive disease. $P_{ET}CO_2$ was measured using the RespirAct machine, whereas P_aCO_2 values were obtained from pre-induction arterial lines. The observed discrepancy between $P_{ET}CO_2$ with P_aCO_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 phenomenon 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 $P_{ET}CO_2$. Though there were no significant differences between preoperative and postoperative resting $P_{ET}CO_2$ values overall, a trend was identified suggesting increasing resting $P_{ET}CO_2$ after revascularization in patients with low preoperative resting $P_{ET}CO_2$ and decreasing resting $P_{ET}CO_2$ after revascularization in patients with high preoperative resting $P_{ET}CO_2$.

The reference standard for measuring PCO_2 is $PaCO_2$, which requires an arterial puncture. However, $P_{ET}CO_2$ is a noninvasive method that is often used to predict $PaCO_2$ values, especially when the arterial to end-tidal gradient is known.[10] The normal $PaCO_2$-$P_{ET}CO_2$ 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 $P_{ET}CO_2$ and the creation of the gradient. In our study, resting $P_{ET}CO_2$ was measured using the sequential gas delivery method and $P_{ET}CO_2$ measured by this system has been shown to be equal to $PaCO_2$.[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 $P_{ET}CO_2$ was measured with the RespirAct during CVR testing and $PaCO_2$ 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 $P_{ET}CO_2$ 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 $P_{ET}CO_2$. Further, in some patients, there was a change in resting $P_{ET}CO_2$ 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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