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ORIGINAL WORK

Brain Oxygenation Response to Hypercapnia in Patients with Acute Brain Injury

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Abstract

Background: Cerebral hypoxia is a frequent cause of secondary brain damage in patients with acute brain injury. Although hypercapnia can increase intracranial pressure, it may have beneficial effects on tissue oxygenation. We aimed to assess the effects of hypercapnia on brain tissue oxygenation ($PbtO_2$).

Methods: This single-center retrospective study (November 2014 to June 2022) included all patients admitted to the intensive care unit after acute brain injury who required multimodal monitoring, including $PbtO_2$ monitoring, and who underwent induced moderate hypoventilation and hypercapnia according to the decision of the treating physician. Patients with imminent brain death were excluded. Responders to hypercapnia were defined as those with an increase of at least 20% in $PbtO_2$ values when compared to their baseline levels.

Results: On a total of 163 eligible patients, we identified 23 (14%) patients who underwent moderate hypoventilation (arterial partial pressure of carbon dioxide [$PaCO_2$] from 44 [42–45] to 50 [49–53] mm Hg; $p < 0.001$) during the study period at a median of 6 (4–10) days following intensive care unit admission; six patients had traumatic brain injury, and 17 had subarachnoid hemorrhage. A significant overall increase in median $PbtO_2$ values from baseline (21 [19–26] to 24 [22–26] mm Hg; $p = 0.02$) was observed. Eight (35%) patients were considered as responders, with a median increase of 7 (from 4 to 11) mm Hg of $PbtO_2$, whereas nonresponders showed no changes (from − 1 to 2 mm Hg of $PbtO_2$). Because of the small sample size, no variable independently associated with $PbtO_2$ response was identified. No correlation between changes in $PaCO_2$ and in $PbtO_2$ was observed.

Conclusions: In this study, a heterogeneous response of $PbtO_2$ to induced hypercapnia was observed but without any deleterious elevations of intracranial pressure.

Keywords: Brain tissue oxygenation, Cerebral hypoxia, Multimodal monitoring, Brain injury, Hypercapnia

Introduction

Acute brain injury poses a significant challenge to global health; traumatic brain injury (TBI) is the primary cause of mortality and disability in individuals under 45 years of age, whereas subarachnoid hemorrhage (SAH) accounts for more than 27% of life-years lost before 65 years of age, incurring substantial health care expenses and resulting in extensive long-term morbidity as well as high mortality rates [1, 2]. Consequently, contemporary management of acute brain injury patients predominantly focuses on the prevention and treatment of secondary brain injuries given that the primary injury is already present on hospital arrival and that no efficacious pharmacological agents have been discovered to enhance neurological recovery thus far [3–5].

Cerebral hypoxia is indeed a primary and prevalent contributor to secondary brain injury [6–8]; brain tissue oxygen pressure ($PbtO_2$) monitoring serves as an invasive yet effective method for evaluating cerebral

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hypoxia in patients with brain injuries. Low $PbtO_2$ values have been correlated with cerebral anaerobic metabolism and an elevated risk of mortality and poor functional outcomes in this context [9–14]. Low $PbtO_2$ may be observed in various circumstances, including diminished cerebral blood flow (CBF) and/or cerebral perfusion pressure (CPP), intracranial hypertension, hypoxemia due to pulmonary disease, anemia, altered microcirculation, or excessive cellular metabolism and mitochondrial dysfunction [15]. Consequently, multiple therapeutic approaches can be employed to optimize $PbtO_2$, encompassing the use of vasopressors (e.g., to increase CPP), intracranial hypertension treatments (e.g., osmotic therapy), red blood cell transfusions, ventilatory strategies to ameliorate hypoxia, temperature control, and/or sedation (e.g., to decrease cerebral oxygen consumption) [16–18]. Several studies have indeed indicated a favorable impact of $PbtO_2$-based management strategies on mortality and functional outcomes in patients with acute brain injury, particularly in the case of TBI [3, 19].

Because $PbtO_2$ reflects the oxygen content within the cerebral interstitial space, its value relies on the intricate balance between oxygen delivery (dependent on arterial oxygen content, CBF, and tissue diffusion) and oxygen consumption [17, 18]. Many of these interventions aim to augment CBF; a potentially effective intervention in this context involves the manipulation of carbon dioxide (CO_2), a principal regulator of cerebrovascular tone. This phenomenon, known as "cerebral CO_2 reactivity," refers to the capacity of resistance arterioles to dilate or constrict in response to alterations in arterial partial pressure of carbon dioxide [$PaCO_2$]. Notably, this mechanism appears to be preserved even when pressure autoregulation of CBF is disrupted, as demonstrated following aneurysmal SAH [20]. Specifically, it is the fluctuation of perivascular pH, secondary to broad $PaCO_2$ ranges, that regulates vascular smooth muscle tone, fostering vasorelaxation with the elevation of $PaCO_2$ and the subsequent decrease in pH, through various mediators (e.g., nitric oxide or prostaglandins) [21].

Although elevated $PaCO_2$ has been integrated into $PbtO_2$-guided therapy protocols, such as in the brain tissue oxygen monitoring and management in severe traumatic brain injury (BOOST-II) trial [22], and has been recommended in recent guidelines [23], increased $PaCO_2$ may exert adverse effects on intracranial pressure (ICP) by increasing CBF, and its impact on $PbtO_2$ warrants further understanding [24–26]. Consequently, the objective of this study was to evaluate the effects of induced hypercapnia on $PbtO_2$ in patients with acute brain injuries and to determine the proportion of responders to this therapeutic approach.

Methods

Study Design

This retrospective analysis of prospectively collected data encompasses patients with acute brain injury secondary to SAH or TBI who were treated between November 2014 and June 2022 in the Department of Intensive Care at Hôpital Universitaire de Bruxelles, Belgium. All adult patients (>18 years) were eligible if they required ICP and $PbtO_2$ monitoring and underwent moderate hypoventilation and induced hypercapnia in accordance with local protocols [23, 27, 28]. Inclusion criteria were the following: (1) controlled mechanical ventilation; (2) treating physician's decision to induce hypercapnia for at least 60 min ($PaCO_2$ > 45 mm Hg, achieved via an absolute reduction in minute ventilation), with a $PaCO_2$ change of at least 5 mm Hg compared with the baseline value; and (3) documented gas analyses at baseline and within 1 h of induced hypercapnia. The sole exclusion criterion was imminent death, resulting in early limitation of life-sustaining therapies. This study was approved by the Erasme Ethics Committee (P2022/449), which waived the requirement for informed consent.

Data Collection and Definitions

We collected demographic data, including age, sex, and comorbidities. Clinical severity scores on admission, such as the Acute Physiology and Chronic Health Evaluation II [29] score, were calculated for all patients, and neurological assessment was performed using the Glasgow Coma Scale [30]. ICP was continuously measured with intraparenchymal and interventricular probes (Neurovent-P, Raumedic, Helmbrechts, Germany, and IM3.ST_EU, Integra LifeSciences Corporation, Plainsboro, NJ, respectively). Intraparenchymal $PbtO_2$ probes (Licox Integra LifeSciences Corporation, Plainsboro, NJ) were placed, whenever possible, into the hemisphere at the highest risk for secondary brain injury (e.g., near the injured/contused area in patients with TBI or in the area at risk for ischemia in patients with SAH) [28]. Probe location was confirmed via cerebral CT scan after placement. The probe proper functioning was tested with a 100% inspired fraction of oxygen test for a maximum of 5 min.

For each patient, we recorded $PbtO_2$, pH, $PaCO_2$, ICP, CPP, and minute ventilation at baseline and after induced hypercapnia. Baseline values were considered before minute ventilation was modified; average $PbtO_2$, ICP, and CPP values over the 20 min preceding this time point were used. Patients underwent moderate hypoventilation for at least 60 min. To assess the effects of induced

hypercapnia, the following arterial blood gas analysis (ABG) was performed within 45 and 60 min thereafter to exclude additional confounders on $PbtO_2$ values; average $PbtO_2$, ICP, and CPP values over the 20 min following this time point were used. No other therapeutic interventions were permitted during this period. Responders to induced hypercapnia were patients who exhibited a $PbtO_2$ value increase of at least 20% compared with baseline values [31, 32]. Intracranial hypertension was defined as an ICP > 20 mm Hg for at least 5 min. Neurological outcomes were assessed using the Glasgow Outcome Scale at 6 months, and mortality was evaluated at intensive care unit (ICU) and hospital discharge.

Study Outcomes

The primary outcome was the absolute change in $PbtO_2$ after induced hypercapnia compared with baseline. Secondary outcomes included the proportion of $PbtO_2$ responders in the study cohort, the correlation between $PaCO_2$ and $PbtO_2$ changes, and different responses according to the type of brain injury and outcome.

Statistical Analysis

Descriptive statistics were computed for all variables. Numeric variables were described either as median and interquartile intervals (25–75%) or mean and standard deviation. Categorical variables were described as proportions. Normally distributed continuous variables were compared using Student's *t*-test, and asymmetrically distributed variables were compared using the Mann–Whitney *U*-test. For comparing paired measurements, normally distributed continuous variables were compared using paired *t*-tests, and asymmetrically distributed variables were compared using the Wilcoxon rank-sum test. For comparing and evaluating the differences in variation before and after an intervention in different subgroups, we used a generalized mixed model for repeated measures; generalized mixed linear models describe the relationship between a dependent variable (responders) and independent variables (e.g., $PbtO_2$ and other physiological variables) using coefficients that can vary with respect to one or more time points (e.g., baseline and after moderate hypoventilation) and using nonnormal data distribution. To investigate possible baseline variables associated with $PbtO_2$ responders, we performed a univariable logistic regression analysis according to Firth's method because of the small sample size. The Firth method is a penalized log-likelihood function that mitigates bias introduced by rare events on a data set or small sample size [33]. The chosen baseline variables in the univariate logistic regression were selected according to clinical and physiological relevance. Odds ratios and 95% confidence intervals (CIs) were computed for each variable; a p value < 0.05 was considered statistically significant. Similarly, we performed a univariable linear regression model to investigate the association of baseline line physiological and clinical variables with absolute delta $PbtO_2$ (difference between $PbtO_2$ after hyperventilation and $PbtO_2$ at baseline). For the statistical analysis, we used Prism 9.5.0 by GraphPad Software, LLC.

Results

Study Population

In a cohort of 163 patients with acute brain injury with TBI or SAH who were monitored with ICP and $PbtO_2$, 23 (14%) underwent induced hypercapnia during the study period and were included in the analysis; among these, six had TBI and 17 had SAH. The median age was 52 years (interquartile range: 40–62 years), with arterial hypertension and alcohol consumption being the most common comorbidities. The median Glasgow Coma Scale and Acute Physiology and Chronic Health Evaluation II scores on admission were 7 (3–11) and 16 (14–21), respectively. Intracranial hypertension at any point during the ICU stay was observed in 11 of 23 (48%) patients. The primary characteristics of the study population are detailed in Table 1.

Induced Hypercapnia and $PbtO_2$

Induced hypercapnia was initiated at a median of 6 (4–10) days following ICU admission. Table 2 presents the alterations in primary collected variables before and after induced hypercapnia. As anticipated, $PaCO_2$ significantly rose from baseline (44 [42–45] to 50 [49–53] mm Hg; $p < 0.001$) following the reduction in minute ventilation, resulting in a significant decrease in pH (from 7.40 [7.36–7.45] to 7.35 [7.31–7.39]; $p < 0.001$).

A significant overall increase in median $PbtO_2$ values from baseline (21 [19–26] to 24 [22–26] mm Hg; $p = 0.02$) was observed after reducing minute ventilation (Fig. 1 and Table 2). However, there was no linear correlation between changes in $PaCO_2$ and changes in $PbtO_2$ in the overall population, as shown in Supplemental Fig. S1 ($r = -0.028$ [95% CI −0.45 to 0.40]). In a univariable linear regression, baseline CPP was associated with changes in $PbtO_2$ after induced hypercapnia (β 0.138 [95% CI 0.012 to 0.263], $p = 0.03$). No multivariable linear regression was possible because of the limited sample size (Supplemental Table S1).

We identified eight (35%) responders to induced hypercapnia, with a median $PbtO_2$ increase of 7 (5–11) mm Hg (from 19 [18–21] to 25 [24–30] mm Hg; $p = 0.014$), in comparison with nonresponders ($n = 15$; changes in $PbtO_2$ from −1 to 2 mm Hg and absolute $PbtO_2$ values from 24 [21–27] to 23 [21–27] mm Hg; $p = 0.64$; Fig. 1).

Table 1 Characteristics of the study population, according to $PbtO_2$ response

	All ($N=23$)	Responders ($n=8$)	Nonresponders ($n=15$)	*p* value
APACHE II score, median (IQR)	16 (14–21)	14 (13–16)	18 (15–21)	0.46
GCS admission, median (IQR)	7 (3–11)	6 (3–7)	7 (3–13)	0.25
Age, median (IQR), y	52 (40–62)	52 (40–60)	52 (40–63)	0.78
Male sex, *n* (%)	13 (56)	7 (88)	6 (40)	0.03
Hypertension, *n* (%)	10 (44)	4 (50)	6 (40)	0.66
Diabetes, *n* (%)	2 (9)	1 (13)	1 (7)	0.65
Heart disease, *n* (%)	2 (9)	2 (25)	0 (0)	0.045
Previous neurological diseases, *n* (%)	1 (4)	0	1 (7)	0.48
Chronic kidney disease, *n* (%)	1 (4)	1 (13)	0 (0)	0.17
Asthma/COPD, *n* (%)	3 (13)	2 (25)	1 (7)	0.23
Cirrhosis, *n* (%)	2 (9)	2 (25)	0 (0)	0.045
Alcohol, *n* (%)	8 (35)	3 (38)	5 (33)	0.85
Smoking, *n* (%)	7 (30)	2 (25)	5 (33)	0.69
Intracranial hypertension, *n* (%)	11 (48)	4 (50)	7(47)	0.91
SAH, *n* (%)	17 (74)	5 (63)	12 (80)	0.39
TBI, *n* (%)	6 (26)	3 (38)	3 (20)	0.39
GOS at 6 months, median (IQR)	3 (1–4)	3 (1–3)	3 (1–4)	0.40
ICU death, *n* (%)	7 (30)	3 (38)	4 (27)	0.63
Hospital death, *n* (%)	7 (30)	3 (38)	4 (27)	0.63

Responders experienced an increase in $PbtO_2$ after induced hypercapnia of at least 20% from baseline. Data are presented as median (IQR) and count (%)

APACHE, Acute Physiology and Chronic Health Evaluation, COPD, chronic obstructive pulmonary disease, GCS, Glasgow Coma Scale, GOS, Glasgow Outcome Scale, ICU, intensive care unit, IQR, interquartile range, $PbtO_2$, brain tissue partial pressure of oxygen, SAH, subarachnoid hemorrhage, TBI, traumatic brain injury

Table 2 Changes in main physiological variables before and after induced hypercapnia

	Before	After	*p* value
$PbtO_2$, mm Hg	21 (19–26)	24 (22–26)	0.03
pH	7.40 (7.36–7.45)	7.35 (7.31–7.39)	< 0.001
Hb, g/dL	9.6 (8.9–11.2)	9.5 (8.7–11.0)	0.24
$PaCO_2$, mm Hg	44 (42–45)	50 (49–53)	< 0.001
PaO_2, mm Hg	128 (98–147)	118 (106–138)	0.38
Glucose, mg/dL	150 (131–162)	158 (135–194)	0.12
Lactate, mmol/L	1.1 (0.9–1.4)	1.1 (0.8–1.3)	0.39
ICP, mm Hg	8 (7–18)	10 (8–20)	0.63
CPP, mm Hg	113 (99–121)	106 (88–118)	0.39
Temperature, °C	36.1 (35.7–36.9)	36.4 (35.6–37.1)	0.70
FiO_2, %	45 (35–50)	45 (35–50)	0.89
PEEP, cm H_2O	7 (5–10)	8 (5–11)	0.99
MV, mL/min	9,000 (7,480–11,130)	8,000 (6,450–10,580)	0.01

Data are presented as median (interquartile range)

CPP, cerebral perfusion pressure, FiO_2, inspired fraction of oxygen, Hb, hemoglobin, ICP, intracranial pressure, MV, minute ventilation, $PaCO_2$, arterial partial pressure of carbon dioxide, PaO_2, arterial partial pressure of oxygen, $PbtO_2$, brain tissue partial pressure of oxygen, PEEP, positive end expiratory pressure

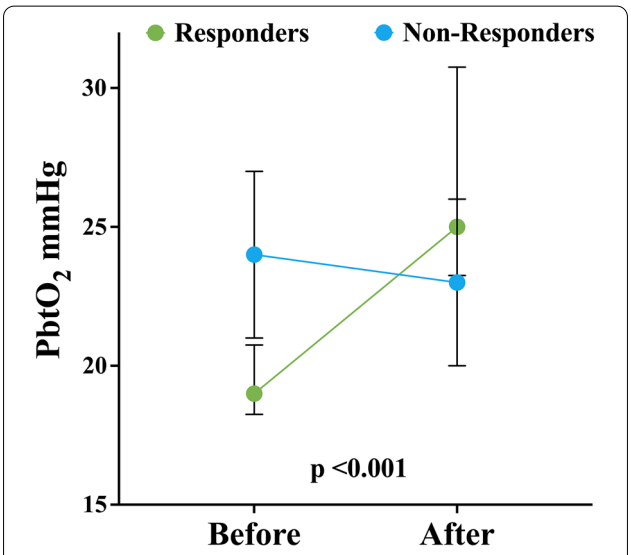

Fig. 1 Changes in brain oxygenation ($PbtO_2$) before and after induced hypercapnia, according to $PbtO_2$ response. Differences between groups were assessed using a generalized mixed model. Data are presented as median and interquartile range

Responders more frequently had preexisting heart disease and liver cirrhosis than others (Table 1); no other significant differences in baseline physiological values were observed between groups, as shown in Supplemental Table S2. In the univariable analysis, no baseline physiological variables were associated with $PbtO_2$ responders (Supplemental Table S3). No multivariable analysis was performed because of the limited sample size. Also, no correlation between the change in $PaCO_2$ and the change in $PbtO_2$ was observed (Fig. 2).

Supplemental Table S4 displays alterations in $PaCO_2$ and $PbtO_2$ response according to various subgroups. We observed a significant $PbtO_2$ increase at hypercapnia in patients with SAH and in those with unfavorable neurological outcome when compared with others. The changes in $PaCO_2$, ICP, and CPP before and after induced hypercapnia, according to $PbtO_2$ response, are reported in Fig. 3. In all nonresponders, ICP remained below 20 mm Hg, whereas among $PbtO_2$ responders, three patients had an ICP > 20 mm Hg at hypercapnia (the maximum level of ICP was 30 mm Hg). However, this did not result in a CPP < 60 mm Hg or a $PbtO_2$ < 20 mm Hg.

Discussion

In this single-center retrospective physiological study, the response to therapeutic hypoventilation was heterogeneous, leading to a significant increase in $PbtO_2$ in one third of patients. Overall, ICP remained within the normal ranges but increased in responders, accompanied by a decrease in CPP, although the difference before and after hypoventilation was not statistically significant. There was no correlation between the change in $PaCO_2$ and the change in $PbtO_2$. Because of the small cohort, we were unable to identify baseline characteristics associated with

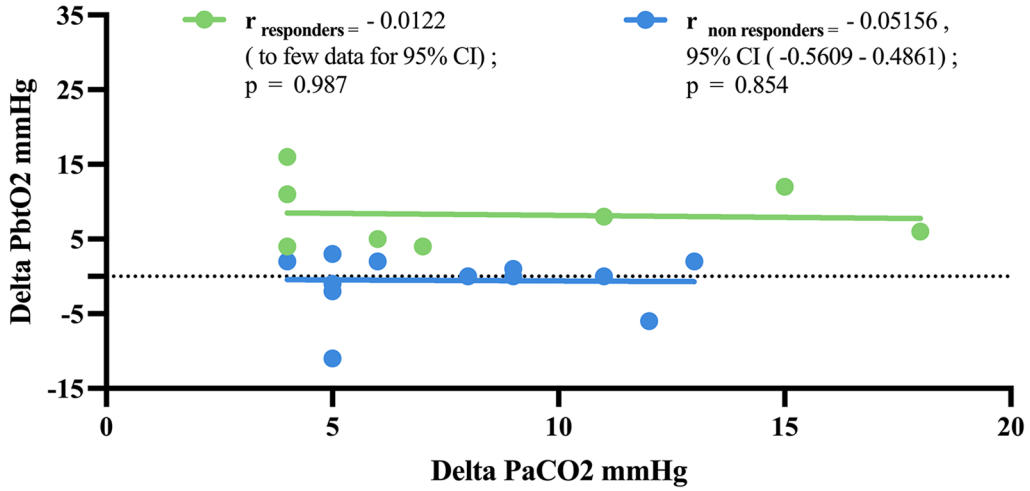

Fig. 2 Spearman correlation of changes in $PaCO_2$ (delta $PaCO_2$) due to a decrease in minute ventilation and changes in brain oxygenation (delta $PbtO_2$) in responders (in green) and nonresponders (in light blue). CI confidence interval, $PaCO_2$ arterial partial pressure of carbon dioxide, $PbtO_2$ brain tissue partial pressure of oxygen

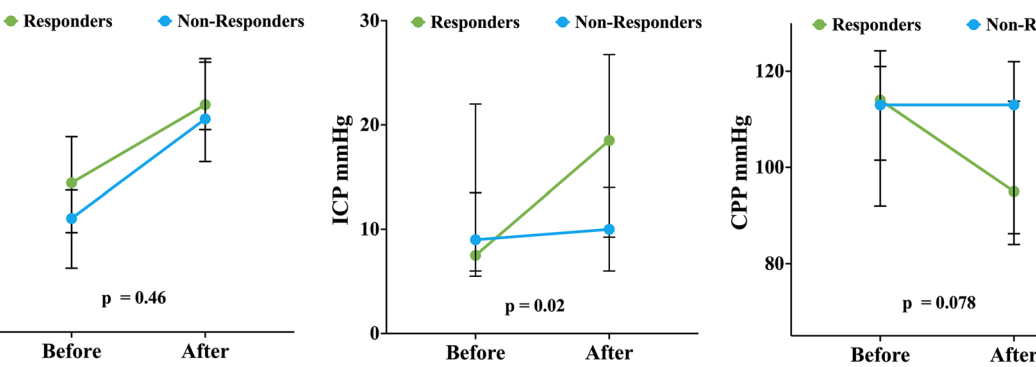

Fig. 3 Changes in arterial partial pressure of carbon dioxide ($PaCO_2$), intracranial pressure (ICP) and cerebral perfusion pressure (CCP) before and after induced hypercapnia, according to brain oxygen pressure ($PbtO_2$) response. Differences between groups were assessed using a generalized mixed model. Data are presented as median and interquartile range

a significant $PbtO_2$ response to hypercapnia. However, baseline CPP was directly associated with changes in $PbtO_2$ after induced hypercapnia.

In patients with TBI, Okonkwo et al. demonstrated that the use of $PbtO_2$-guided therapy, employing a specific and intricate protocol, reduced the incidence of brain hypoxia compared with patients who underwent ICP-guided therapy alone [22]. Furthermore, two meta-analyses reported that combined ICP/$PbtO_2$-guided therapy was associated with improved neurological outcomes when compared to standard ICP-guided therapy in this setting [34, 35]. In SAH, low $PbtO_2$ levels have been linked to various pathological pathways, such as reduced CBF, lung injury with hypoxemia, and/or anemia [28]; consequently, strategies aimed at increasing brain perfusion can elevate $PbtO_2$ levels in some of these patients [17].

One possible strategy to increase $PbtO_2$ is to promote vasodilation by inducing hypercapnia [25, 26]. Increased $PaCO_2$ results in vasodilation of cerebral arterioles, leading to increased CBF. This response, known as cerebrovascular reactivity, is a crucial mechanism to maintain appropriate oxygen delivery to brain tissue in response to metabolic demands. The underlying mechanism for CO_2-induced vasodilation involves changes in the pH of the cerebrospinal fluid and the release of various vasodilatory mediators, such as nitric oxide (NO), adenosine, and prostaglandins [21, 36]. Interestingly, this phenomenon is heterogeneous and varies in different areas of the brain and in different individuals [37–39]. By increasing CBF, mild hypercapnia could improve cerebral oxygenation, as shown in animal models of acute brain injury [40]. In a study including patients with SAH, Stetter et al. showed that temporary mild hypercapnia can increase CBF and brain tissue oxygen saturation with no relevant adverse effects, especially on ICP [25]. In our study, responders to hypercapnia concomitantly showed an increase in ICP, probably because of an increased cerebral blood volume [24, 41, 42]. Hypercapnia also influences blood flow in other organs; in pulmonary circulation, it induces vasoconstriction, which is known as the "hypoxic pulmonary vasoconstriction response" [43]. This response serves to divert blood flow away from poorly ventilated lung areas with high CO_2 levels, thus optimizing oxygenation; no significant drop in PaO_2 values was observed in our study. In systemic circulation, hypercapnia typically causes vasodilation, enhancing blood flow to tissues [44], with some notable exception regarding kidneys and to some extension the skeletal muscle [45, 46]; nonetheless, no changes in CPP were observed in our study. As such, our findings suggest that hypercapnia may affect cerebral perfusion and oxygenation in patients with brain injury without detrimental effects or adverse consequences for other organs.

Notably, a significant $PbtO_2$ response was observed in only one third of the patients. One possible explanation for these findings is the loss of cerebrovascular reactivity following an acute brain injury [47, 48]. Several mechanisms contribute to the loss of cerebrovascular reactivity, such as endothelial dysfunction (resulting from an imbalance in the production of vasodilatory and vasoconstrictive mediators), smooth muscle cell dysfunction (stemming from structural and functional changes in these cells, impairing their ability to respond to vasodilatory stimuli), neural dysregulation (arising from alterations in perivascular nerves that modulate cerebral vascular tone through the release of vasoactive neurotransmitters), or altered metabolic coupling (pertaining to the relationship between neuronal activity and CBF) [49–52]. Unfortunately, our study did not specifically assess which of these mechanisms might be present in nonresponder patients. Although we observed a more substantial $PbtO_2$ response in patients with SAH in an exploratory descriptive analysis, it remains unknown whether the underlying brain injury may have different effects on cerebrovascular reactivity. Moreover, a larger $PbtO_2$ response was observed in patients with unfavorable neurological outcome, who might have also exhibited a higher probability of neural dysfunction or altered metabolic coupling. This observation may contradict our hypothesis that the loss of cerebrovascular reactivity is the primary factor behind the varying $PbtO_2$ responses, although it remains an exploratory analysis. Further research is needed to explore the potential mechanisms and their impact on the response of $PbtO_2$ to induced hypercapnia in this setting.

This study has inherent limitations. First, it is important to acknowledge that our study relied on the accuracy of the medical records, and it is possible that relevant data may not have been consistently reported because of its retrospective design. Second, as a single-center study, the generalizability of our results to other centers may be limited. Furthermore, the decision to induce hypercapnia was determined by the treating physician and not protocolized, which could impact the generalizability of our findings. However, it is worth noting that this decision was typically made in cases in which ICP was within normal limits and $PbtO_2$ was low. Third, we had a small patient cohort, which limited our analysis and statistical inference; therefore, our results should be interpreted with caution. The small sample size of this study limits the generalizability of its findings and impacts their applicability in the clinical domain. Studies with a limited number of participants may not adequately represent the broader population or patient groups, leading to potential biases and reduced external validity. Clinicians need robust evidence from additional studies with larger and

diverse cohorts to confidently implement the routine use of induced hypercapnia as a valid tool to increase $PbtO_2$. Moreover, additional research is required to understand the heterogeneous effect of such therapy on tissue oxygenation after an acute brain injury. Fourth, we did not evaluate the probe position, which may have impacted our results, as cerebrovascular reactivity is not uniform throughout the brain. Fifth, the threshold used to define "$PbtO_2$ responders" is somewhat arbitrary, although it has been used in previous studies. The decision to use a relative increase in $PbtO_2$, rather than an absolute increase, was based on the understanding that areas with reduced CBF and impending ischemia may exhibit a lower increase in $PbtO_2$ in response to specific challenges (e.g., an increase in mean arterial pressure, inspired fraction of oxygen, red blood cells transfusions, or $PaCO_2$) as compared to normally perfused areas [53]. Therefore, assessing the relative increase in $PbtO_2$ would provide a more accurate evaluation of the response to therapies. Lastly, it is important to consider that the effect of $PaCO_2$ on $PbtO_2$ may not follow a linear relationship, which could have influenced our results. Additionally, because we did not have continuous measures of CO_2, we were unable to assess whether there is a threshold effect associated with the $PbtO_2$ response to hypercapnia. Furthermore, it is worth noting that practices might have changed during the study period, and these changes could have influenced our subgroup analyses.

Conclusions

In this study, patients exhibited a heterogeneous $PbtO_2$ response to moderate hypoventilation and induced hypercapnia. Future studies should focus on identifying which patients may benefit from this approach and the optimal strategy for implementing induced mild hypercapnia.

Supplementary Information
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Author Contributions
MA, EGB, and FST contributed to conception and design of the study. MA, MS, LP, and FA collected data. EGB and MA performed data curation. EGB, MA, and FST performed the statistical analysis. MA, EGB, and FST wrote the first draft of the manuscript. KD and SS revised the manuscript for intellectual content and English editing. All authors contributed to manuscript revision and read and approved the submitted version.

Source of Support
None.

Data Availability
Because of ethical restrictions, the data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request. All data generated after the analysis during this study are included in this published article and in its supplementary material.

Conflicts of interest
The authors declare that they have no competing interests regarding this article.

Ethical Approval/Informed Consent
The study followed ethical guidelines, and the Erasme Hospital Ethics Committee approved this study (P2022/449). Written informed consent for study participation was waived by the ethics committee.

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