CRUCIAL DECISIONS IN SEVERE TRAUMATIC BRAIN INJURY MANAGEMENT: CRITERIA FOR TREATMENT ESCALATION

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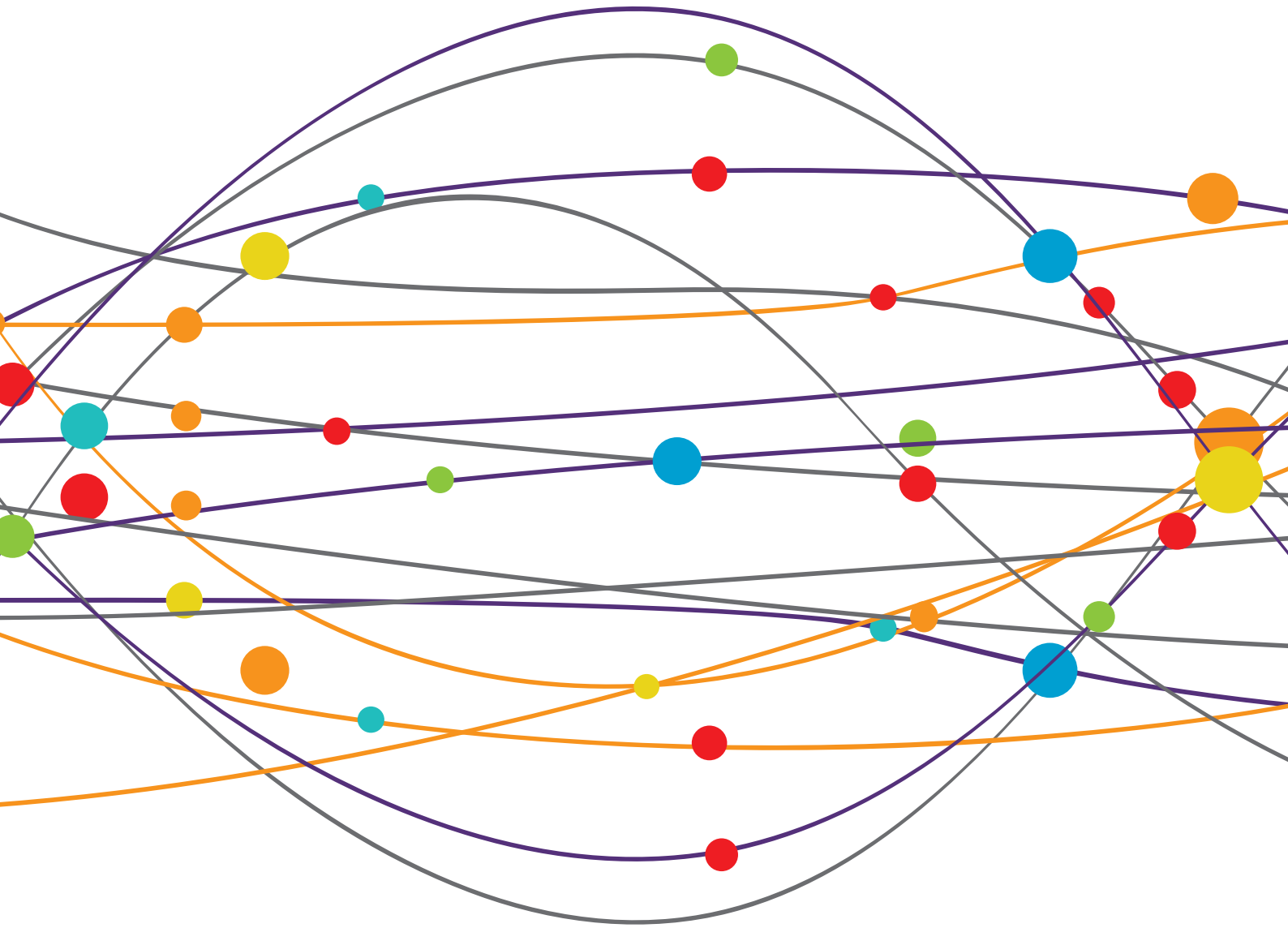

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CRUCIAL DECISIONS IN SEVERE TRAUMATIC BRAIN INJURY MANAGEMENT: CRITERIA FOR TREATMENT ESCALATION

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EDITORIAL
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Editorial: Crucial Decisions in Severe Traumatic Brain Injury Management: Criteria for Treatment Escalation

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Keywords: intracranial hypertension, traumatic brain injury, brain injury, treatment, staircase

Editorial on the Research Topic

Crucial Decisions in Severe Traumatic Brain Injury Management: Criteria for Treatment Escalation

Intracranial hypertension [IH, or too high intercranial pressure (ICP)] is a major cause of secondary brain damage and is associated with poor outcomes in traumatic-brain-injured patients (1–3). For this reason, IH should be promptly and aggressively managed to optimize chances for recovery. Therefore, monitoring and treatment of ICP and cerebral perfusion pressure (CPP) has become the cornerstone of severe TBI management (1, 2).

Several basic and more aggressive interventions are available to treat IH (4, 5). However, increasing level of intensity treatment is associated with higher incidence of adverse events and risks (4, 5). In general, IH management follows a staircase approach, with the higher intensity of treatment being associated with the highest risks.

A recent Delphi-method-based consensus (6) aimed to establish an updated TBI protocol for the management of ICP in adult patients. A panel of 42 experts defined different ICP management protocols, consisting of three tiers of therapies with escalating treatments and risks in order to help clinicians in the management of patients with increased ICP.

Factors that may aggravate IH include not only intracerebral, but also extracerebral issues such as respiratory problems, hypotension, hyponatremia, seizures, obstruction of venous outflow, and fever (5).

Therefore, the maintenance of physiological homeostasis represents the first-line therapeutical tool, and this includes a number of basic measures such as elevation of the head to 30 degrees, hemodynamic stability with maintenance of euvolemia, appropriate comfort and sedation, stabilization of the airways, and mechanical ventilation to maintain appropriate targets of oxygen and carbon dioxide.

Hyperpyrexia should be avoided, and antiepileptic drugs should not be administered as prophylactic measures.

If basic measures are not sufficient to control ICP, a higher level of intensity may be considered (5).

Osmotic agents (such as mannitol and hypertonic saline), for instance, can reduce intracranial pressure and reduce brain volume by creating a gradient across the blood–brain barrier, but they can have several side effects, such as polyuria, alterations of plasma osmolarity, and electrolytes disturbances (4, 5).

In the case of refractory IH, more aggressive second tier therapies can be used, although these present important side effects.

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Hypocapnia consequent to hyperventilation is a potent modulator of pial arterioles, causing cerebral vasoconstriction and therefore reduction of intracranial volume and ICP (7). However, because of the risk of cerebral ischemia, hyperventilation is currently indicated for the reduction of elevated ICP only in patients at risk of imminent cerebral herniation (8).

Therapeutic hypothermia can reduce cerebral metabolism and cerebral blood volume (4). Mild hypothermia (32–34°C) may effectively decrease intracranial pressure (9). However, recent evidence demonstrated that early or prophylactic hypothermia can be detrimental in TBI patients (9, 10).

As another example, decompressive craniectomy, although it can rapidly reduce ICP in cases of refractory IH, can improve mortality, but can also lead to a higher rate of unfavorable neurologic outcome (11).

The increasing risk for treatment-related complications of ICP-reducing therapies increases from basic to higher level of intensity treatment. It is therefore fundamental that the clinicians consider the risks and benefits associated with each strategy for escalation of treatment, and consider patient- specific pathophysiological features (12–15).

In this special issue, we collected articles that focus on the treatment escalation decisions in severe TBI.

Biomarkers and imaging are important in TBI management, as exemplified by the articles by Pinggera et al., Cardim et al., and Lenstra et al. These studies show the feasibility and safety of early MRI, which is informative for clinical practice, assess differences between optic nerve sheath diameter in healthy volunteers compared with TBI patients, and show that ECG abnormalities associated with TBI may represent prognostic biomarkers rather than intrinsic cardiac disease.

Rasulo et al. studied the association of lactate-pyruvate ratio in perilesional areas in intracerebral hemorrhage and cerebral autoregulation in an international multicenter study, showing the interdependence of cerebral metabolism and hemodynamics. This cerebral-systemic interdependence is also shown by Robba et al. who found that pulmonary pathologies impacting on oxygenation impacts on prognosis in TBI patients.

Further, several reviews and an opinion article assess the current insight into treatment escalations in TBI. Lazaridis provides new insights in how to leverage treatment utility and patient preferences in the difficult decision making regarding decompressive craniectomy as a rescue therapy for refractory IH. Finally, Battaglini et al., Gouvea Bogossian et al., and Godoy et al. review treatment escalations en de-escalations for TBI management and recalibrate the current status of hyperventilation as a management option.

The manuscripts included in this collection aim to add important clinical insights and help physicians in decision making for ICP management and escalation of treatment. In our opinion, the collected articles can add important knowledge to current neurocritical care literature and help with "crucial decisions" for TBI management.

AUTHOR CONTRIBUTIONS

All authors served as guest editors for this article collection and contributed equally to this Editorial.

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We would like to convey our gratitude to all authors who have submitted their work for this article collection.

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ORIGINAL RESEARCH
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Safety of Early MRI Examinations in Severe TBI: A Test Battery for Proper Patient Selection

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Introduction: Early magnetic resonance imaging (MRI) provides important information for management and prognosis in patients with severe traumatic brain injury (sTBI). Yet, optimal timing of MRI remains unknown. The aim of our study was to evaluate the safety of early MRI and to identify a method for appropriate patient selection to minimize adverse events related to the intrahospital transport (IHT) and the MRI examination.

Methods: Twenty-six patients with sTBI [mean Glasgow Coma Scale (GCS) 6, range 3–8] admitted to our neurosurgical ICU from 03/2015 to 12/2017 and receiving at least one MRI within the first 14 days after initial traumatic event were prospectively included in the study. The following requirements were fulfilled for at least 4 h prior to anticipated MRI: MAP $>$ 70 mmHg, $aPCO_2$ 30–40 mmHg, stable ICP $<$ 25 mmHg. All relevant cardiopulmonary and cerebral parameters and medication were recorded. The following MRI sequences were performed: DWI, FLAIR, 3D T2-space, 3D T1 MPRAGE, 3D SWI, 3D TOF, pASL, and $^{1}H/^{31}P$-MRS.

Results: Four females and 22 males (aged 23–78 years, mean 46.4 years) with a median GCS on admission of 5 (range 3–8) were analyzed. In total, 40 IHTs were performed within the first 14 days (mean 6 days, range 1–14 days). Mean pre-MRI ICP was 14.1 mmHg (range 3–32 mmHg). The mean post-MRI ICP was 14.3 mmHg (range 3–29 mmHg), decreasing to a mean ICP of 13.2 mmHg after 1 h (range 3–29 mmHg). There were no significant differences in ICP measurements before and after MRI ($p = 0.30$). MAP remained stable with no significant changes during the entire IHT and MRI. No other adverse events were observed as well.

Conclusion: Early MRI in acute severe TBI is feasible and safe. Yet, careful patient selection with prior adequate testing of cardiopulmonary and cerebral parameters is crucial to minimize transport- or examination-related morbidity.

Keywords: intrahospital transport, early magnetic resonance imaging, severe traumatic brain injury, intensive care management, critical ill patients

INTRODUCTION

Given the commonly known limitations of structural imaging methods in detecting clinically relevant, yet subtle, intracranial abnormalities after traumatic brain injury, magnetic resonance imaging (MRI) has become integral to neuroimaging diagnostics, especially in severe TBI. Early MRI can provide in-depth analysis of traumatic intracranial lesions, containing not only prognostic information but also potentially for therapeutic management, both with respect to short-term and long-term outcomes (1–4). Albeit early MRI may not dramatically alter initial patient management, it can be decisive for further treatment.

As patients with severe TBI are often on prolonged ventilation, early MRI is challenging as intrahospital transport (IHT) and the time in the scanner requires tedious monitoring. It is known that moving the patient from the NICU for therapeutic or diagnostic reasons is associated with numerous clinical issues such as increase in ICP, hemodynamic complications, or secondary insults (5–8). Especially for head-injured patients, IHT-related adverse events can lead to secondary brain damage, making a selection of possible candidates necessary (5, 9).

Importantly, both optimal timing of initial MRI in severe TBI and IHT-related complications due to early MRI continue to be debated. Thus, we prospectively analyzed 26 patients with severe TBI, who underwent at least one MRI within the first 14 days after the traumatic event, and therefore, an IHT was necessary. The aim of our study was to ensure safety for all patients and reduce adverse events. We established a test battery based on contemporary well-known neurointensive care standards in each patient prior to every anticipated MRI examination.

METHODS

Patients

Consecutive patients between 18 and 85 years of age with severe TBI and an initial Glasgow Coma Scale (GCS) score of eight or less, who required treatment according to the BTF guidelines and underwent an MRI within the first 14 days after the trauma, were prospectively included in the study (10). All patients were monitored with an intraparenchymal ICP probe.

Exclusion criteria were contraindications to MRI (e.g., pacemaker, metal objects, etc.), and/or an unstable clinical condition disqualifying the patient to undergo an MRI examination safely. The study protocol was approved by the local ethics committee of the Medical University Innsbruck (AN2014-0201 339/4.6), and written informed consent was obtained from all included patients and/or from their legal guardians.

Twenty-six patients with severe TBI (mean GCS 6, range 3–8) admitted to our Department from March 2015 to December 2017 met the inclusion criteria and were prospectively included in the study.

Test Battery

In order to ensure the safety of MRI scans, all patients were examined prior to anticipated MRI, needing to meet the following requirements:

- Mean arterial pressure above 70 mmHg for a minimum of 4 h prior to MRI. Vasopressors were allowed as feasible.
- Carbon dioxide levels between 30 and 40 mmHg for at least 4 h prior to MRI.
- Stable intracranial pressure for a minimum of 30 min and more in prone position with no elevation >25 mmHg. Use of osmotic agents was allowed as feasible.

Approval for MRI was given by the senior neurointensivist on duty.

IHT and MRI Examination

Two staff members of the NICU, including one junior or a senior board-certified physician, performed the transport. Each patient was on ventilator support using an Oxylog 3000 (Dräger, Lübeck, Germany) and monitored by a DATEX Omeda Monitor (GE Datex Ohmeda, Helsinki, Finland). During the MRI examination, all patients were under anesthesiological supervision by a board-certified anesthetist. The patients were ventilated and monitored using an Aestiva 5 MRI, DATEX Omeda Monitor (GE, Germany). Standard analgosedation consisted of sufentanyl, propofol, and/or morphium plus midazolam. In some cases, ketanest was additionally administered. No patients received barbiturates. Medication and cardiopulmonary parameters were recorded at an interval of 15 min. Intracranial pressure was obtained at the NICU 1 h before the scheduled IHT, immediately before and after IHT, and 1 h afterward.

In the NICU and during IHT, the head was elevated 30° head-of-bed position. During the MRI scan, the patient was in a prone position with a 0° head-of-bed position, due to the standard spatial and technical circumstances. Repositioning on the MRI table was performed by at least four hospital staff members. Given the site characteristics, transporting the patient from the NICU to the MRI required a double floor change, i.e., taking the elevator twice.

Magnetic Resonance Imaging

All patients underwent standard MRI including the following sequences: DWI, FLAIR, 3D T2-space, 3D T1 MPRAGE, 3D SWI, 3D TOF, and pASL. MRI was performed on a 3T whole-body system (Verio, Siemens Medical AG, Erlangen, Germany). MR spectroscopy was performed on the same MRI unit with a double-tuned 1H/31P volume head coil (Rapid Biomedical, Würzburg, Germany). For each patient, a scan time of 60 min was planned, not including the time of repositioning the patient and change of the head coils.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics (V.21, version 21, SPSS Inc., IBM, Chicago, IL, USA). Continuous variables were reported as mean ± standard deviation (SD). To detect differences between time points, the pairwise Wilcoxon test was used. Differences with a value of $p < 0.05$ were considered statistically significant. Graphs were created using GraphPad Prism (version 6.0c; for Mac; GraphPad Software, La Jolla California USA).

RESULTS

Patients

A total of 26 patients (aged 23–78 years, mean 46.4 years; four female and 22 male patients) with severe TBI were enrolled in the analysis. Median GCS on admission was five (range 3–8).

Imaging

Sixty-five MRI examinations were scheduled, 19 (29.2%) were not pursued due to the following reasons: three patients (4.6%) died prior to the first MRI, and in 16 patients (24.6%) MRI slots and/or any anesthesia teams were not available. In total, the pre-MRI test battery was performed 46 times. Of these, six patients (13.0%) failed due to increased ICP, and therefore, no MRI was performed. Finally, 40 IHT for MRI were performed within the first 14 days after the trauma with a mean of 6 days (range 1–14). A single MRI examination was performed in 13 patients, two MRI scans in 12 patients, and three MRI examinations in one patient. One patient passed the test, but showed an increase in the ICP prior to the MRI, which was therefore canceled (2.2%).

Mean duration of the MRI scan including positioning the patient on the MRI table and installing the monitoring was 82 min (range 45–120 min).

Intracranial Pressure

Mean pre-examination ICP ranged from 3 to 32 mmHg 1 h before the scheduled MRI (mean: 14.1 mmHg) and remained stable ranging between 3 and 25 mmHg (mean 12.8 mmHg) directly before the IHT to the examination. Being back at the NICU, the mean ICP was 14.3 mmHg (range 3 to 29 mmHg), slightly decreasing to a mean ICP of 13.2 mmHg after 1 h (range 3 to 29 mmHg). Values above 25 mmHg were seen 1 h before MRI and after MRI in two patients, respectively. There were no significant differences between the measurements in any time point during the MRI examination (**Figure 1**). The canceling of anticipated MRI was necessary only in one patient who passed the test battery, yet developed an increased ICP shortly before imaging. Noteworthy, the same patient underwent testing again the other day, passed the test battery, and MRI was performed without any issues.

Cardiopulmonary Parameters

Pressure-controlled ventilation was used in 36 patients (90%) and volume-controlled ventilation in four cases (10%). MAP remained stable throughout the entire course with no significant changes. $EtCO_2$ differed before, during, and after the MRI examination, yet clinically not relevant. All data are listed in **Table 1** and **Figure 2**.

Medication

Neosynephrine was administered during 38 intrahospital transports/MRI examinations, in a concentration of 10 mg/50 ml in 31 cases and of 50 mg/50 ml in seven patients. Dobutamine was applied in one patient (concentration 250 mg/50 ml). Eight patients required no catecholamine support.

The utilization of sedatives and analgesics is listed in **Table 2**. The most commonly used analgesic was sufentanyl (85%), and the most common sedative medication was midazolam (92.5%).

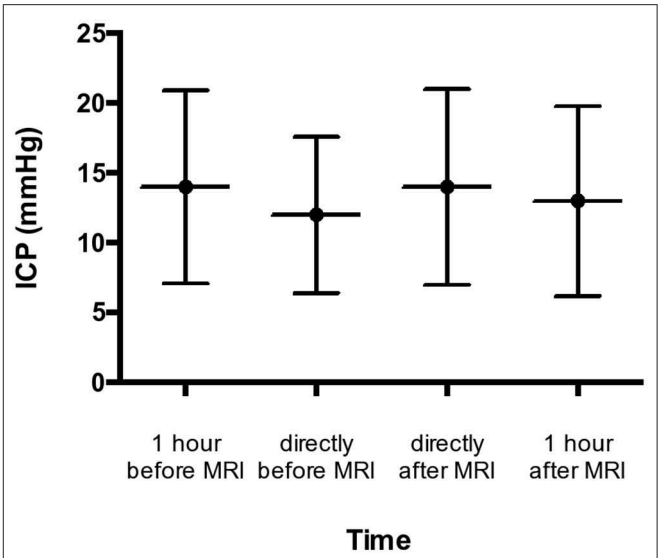

FIGURE 1 | Pre- and post-examination ICP courses.

TABLE 1 | Pre- and post-examination MAP and $etCO_2$ courses.

	$EtCO_2$	MAP
Pre transport (NICU)	36.0 (27–47)	90.6 (70–119)
Start MRI (0min)	36.7 (27–46)	91.3 (72–113)
After 15min	35.6 (29–44)	90.9 (73–112)
After 30min	34.9 (27–40)	90.6 (73–113)
After 45min	34.6 (27–40)	91.0 (73–110)
After 60min	34.7 (30–40)	91.4 (73–113)
After 75min	35.3 (30–40)	92.3(70–113)
After 90min	35.1 (30–39)	95.4(73–112)
After 105min	34.9 (32–38)	95.4(78–110)
After 120 min	33.5 (32–35)	92.1(77–105)
Post transport (NICU)	39.3 (33–48)	90.6 (50–140)

Additionally, procuronium was administered during 18 MRI examinations (ranging from 30 to 100 mg adapted to patient's body weight). Ephedrine was administered as a bolus to maintain/optimize MAP in two examinations.

DISCUSSION

Our study of sTBI patients who received MRI within 14 days after trauma provides representative comprehensive data on the feasibility and safety of MRI in the acute phase after severe TBI.

Overall, we have demonstrated that with proper preparation and accurate patient selection, MRI is possible in the vast majority of these severely injured patients with neither significant changes in cardiac/pulmonary parameters nor ICP. To our best knowledge, this is the first clinical prospective study showing the safety and feasibility of early MRI examination in these patients.

Diffuse axonal injuries (DAI), frequently occurring after TBI often leads to cognitive and behavioral impairment.

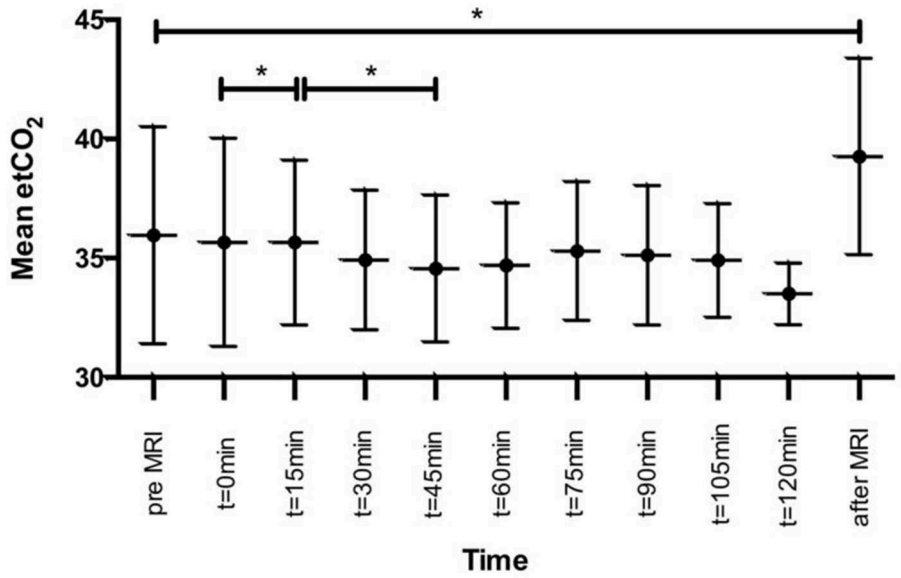

FIGURE 2 | Pre- and post-examination $etCO_2$ courses. *statistically significant.

TABLE 2 | Utilization of sedatives and analgetics.

Combination	Number	Percentage
Midazolam + Sufentanyl + Ketanest	16	40%
Midazolam + Sufentanyl	18	45%
Midazolam + Vendal	3	7.5 %
Propofol alone	3	7.5 %

Structural neuroimaging methods are insensitive in detecting such alterations. Thus, there has been a rapidly increasing interest in MRI that can provide a more detailed analysis of all intracranial lesions, giving an objective assessment of the degree of diffuse tissue injury, microhemorrhages, and posttraumatic "tissue at risk." This is normally seen in the pericontusional region, where diffuse tensor imaging (DTI) can detect areas with vasogenic or cytotoxic edema, while the area of decreased ADC represents edema. Prevention of contusion growth represents a potential therapeutic target in the prevention of secondary injury in TBI (11). MRI after TBI yields essential prognostic information and offers a high potential to determine the degree of injury, and to improve stratification, in order to identify patients who require an extended period of intubation and intensive care management and to provide guidance in early decision making (2, 3, 12–14).

The proper timing of MRI continues to be debated, as MRI in ventilated patients in an early stage is highly challenging and related to numerous critical care issues. Manolakaki et al. suggested that early MRI is of limited usefulness in patients with TBI since it hardly changed patient management in the acute phase (15). This can be debated as "tissue at risk" may well be identified. Nevertheless, MRI is seen as very useful in predicting short-term and long-term functional outcome (16, 17). Neurointensivists, nowadays, are confronted with the dilemma when to perform MRI in critically ill patients. It is known that transferring these patients from the NICU is associated with a variety of medical complications or technical equipment failure. In general, IHT is deemed hazardous in critically ill patients with common complications such as thrombosis, bleeding, or decline in pulmonary function (18). Bergman et al. also reported technical hazards and equipment failure (19). Similar to our study, Martin et al. focused on severe TBI patients. In their cohort of 31 patients, a significant risk for secondary insults and adverse events was demonstrated in IHT to perform computed tomography (CT) scan. However, all documented events may have resulted in a change in medical therapy, but did not significantly alter outcome (9). Similar findings have been reported by Kleffmann et al. who observed a significant ICP increase during transport and CT scans (7). Notably, in their series of 14 patients with TBI, no GCS was provided, rendering comparison to our cohort difficult. Picetti et al. also demonstrated a higher risk for intracranial hypertension during IHT, but their cutoff value of 20 mmHg was fairly low for sufficient comparison with our findings (8). Partially corresponding to our results, they reported an elevated $etCO_2$ after the imaging (8). Likewise, we also consider this to be of little clinical significance as $etCO_2$ values were substantially lower during the time of MRI examinations.

It is our firm belief that the very low rate of failed MRI (2.2%) in our study results from our standardized preparation for MRI including the test battery and consistent patient selection. Of note, Tobin et al. reported a rate of 87% successful MRI in critically ill children, among them 10% with TBI (20). Our aforementioned standard operating procedure with the careful

patient selection is in line with other studies. Both Cuschieri et al. and Berkow et al. suggested an implementation of standardized operating procedures in critically ill patients to improve patient outcome and morbidity (21, 22). A recent review on IHT stated that proper stabilization of the patient before anticipated intervention prevents directly IHT-related adverse events or complications (23). Importantly, as previous reports dealing with MRI in critically ill patients described, coordination with the MR facility is mandatory to decrease delay and minimize the length of the IHT (24).

We acknowledge that our study has several limitations. Certainly, our results must be interpreted carefully in light of the small sample size, even though similar to other studies (5, 9). Also, given the possible adverse effects of ICP probes in surrounding brain tissue during the MRI examination, continuous measurements of intracranial pressure was not possible during MRI as the intraparenchymal probes have not been approved/eligible for this purpose (25). It is therefore possible that episodes of high intracranial pressure may have gone unnoticed. However, relevant intracranial hypertension during MRI would have very likely provoked accompanying significant changes in other recorded parameters, or even ICP decompensation immediately after imaging, which was not the case in any of the included patients. Additionally, our analysis focused primarily neither on complications during IHT directly nor on therapeutic decision changes due to findings in the MRI.

To the best of our knowledge, this is the largest series regarding early MRI in ventilated patients with severe TBI. Despite the very challenging character of early MRI in critically ill patients and possible technical difficulties associated with required MR compatibility, we have demonstrated that early magnetic resonance after severe TBI is technically feasible, representing a promising non-invasive tool for comprehensive assessment of brain damage and posttraumatic "tissue at risk," with an obvious potential to provide better guidance of clinical therapy and prediction of overall neurological outcome. Proper testing of relevant clinical parameters confirming the stable clinical condition of patients in a standardized manner plays a crucial role in avoiding related complications in these patients. Furthermore, IHT of critically ill and/or ventilated patients should not limit further meaningful clinical trials in these patients that are indisputable for better decision making in a daily clinical practice.

CONCLUSION

Early MRI is feasible and safe in acute severe TBI when patients are carefully selected and properly tested in a standardized manner. To minimize MRI- and IHT-related risks and complications in these patients, consistent intensive monitoring and management of critically ill patients should be performed in close cooperation with anesthesiologists and neurointensivists.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study protocol was approved by the local ethics committee of the Medical University Innsbruck (AN2014-0201 339/4.6).

Consent for Publication

Written informed consent was obtained from all included patients and/or from their legal guardians.

AUTHOR CONTRIBUTIONS

DP: acquisition, analysis of data, and interpretation of data. ML: acquisition and interpretation of data. IB and MB: acquisition and analysis of data. CT: design of the study and revisions. OP: conception/design of the study, acquisition, analysis of data, and interpretation of data. All authors have approved the submitted version and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, have been appropriately investigated, resolved, and the resolution documented in the literature.

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Lung Injury Is a Predictor of Cerebral Hypoxia and Mortality in Traumatic Brain Injury

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Background: A major contributor to unfavorable outcome after traumatic brain injury (TBI) is secondary brain injury. Low brain tissue oxygen tension (PbtO2) has shown to be an independent predictor of unfavorable outcome. Although PbtO2 provides clinicians with an understanding of the ischemic and non-ischemic derangements of brain physiology, its value does not take into consideration systemic oxygenation that can influence patients' outcomes. This study analyses brain and systemic oxygenation and a number of related indices in TBI patients: PbtO2, partial arterial oxygenation pressure (PaO2), PbtO2/PaO2, ratio of PbtO2 to fraction of inspired oxygen (FiO2), and PaO2/FiO2. The primary aim of this study was to identify independent risk factors for cerebral hypoxia. Secondary goal was to determine whether any of these indices are predictors of mortality outcome in TBI patients.

Materials and Methods: A single-centre retrospective cohort study of 70 TBI patients admitted to the Neurocritical Care Unit (NCCU) at Cambridge University Hospital in 2014–2018 and undergoing advanced neuromonitoring including invasive PbtO2 was conducted. Three hundred and three simultaneous measurements of PbtO2, PaO2, PbtO2/PaO2, PbtO2/FiO2, PaO2/FiO2 were collected and mortality at discharge from NCCU was considered as outcome. Generalized estimating equations were used to analyse the longitudinal data.

Results: Our results showed PbtO2 of 28 mmHg as threshold to define cerebral hypoxia. PaO2/FiO2 found to be a strong and independent risk factor for cerebral hypoxia when adjusting for confounding factor of intracranial pressure (ICP) with adjusted odds ratio of 1.78, 95% confidence interval of (1.10–2.87) and p-value = 0.019. With respect to TBI outcome, compromised values of PbtO2, PbtO2/PaO2, PbtO2/FiO2, and PaO2/FiO2 were all independent predictors of mortality while considered individually and adjusting for confounding factors of ICP, age, gender, and cerebral perfusion pressure (CPP).

However, when considering all the compromised values together, only PaO2/FiO2 became an independent predictor of mortality with adjusted odds ratio of 3.47 (1.20–10.04) and p-value = 0.022.

Conclusions: Brain and Lung interaction in TBI patients is a complex interrelationship. PaO2/FiO2 seems to be a major determinant of cerebral hypoxia and mortality. These results confirm the importance of employing ventilator strategies to prevent cerebral hypoxia and improve the outcome in TBI patients.

Keywords: mortality outcome, traumatic brain injury, cerebral oxygenation, partial arterial oxygen pressure, lung injury, hypoxia threshold

INTRODUCTION

Traumatic brain injury (TBI) is a leading cause of death and disability (1). A characteristic feature of TBI is a wide variation in functional outcome (2). Clinicians treating patients with TBI often make therapeutic decisions based on the assessment of prognosis (3). Several studies have attempted to find parameters that allow the clinicians to assess the risks and outcomes of the patient after TBI. These include clinical and demographic variables such as age, gender, race, Glasgow Coma Score (GCS), which includes motor score and pupil reactivity, and cause of injury (4).

A major contributor to unfavorable outcomes is secondary brain damage which progresses hours or days after TBI (5). It is widely accepted that causes of secondary injury include impaired cerebral metabolism, hypoxia, and ischemia (5). Currently, severe TBI care is centered on control of intracranial pressure (ICP) and cerebral perfusion pressure (CPP), where invasive ICP monitoring is the gold standard monitor (6). However, studies have shown that cerebral hypoxia after severe TBI can occur despite ICP and CPP being within normal ranges, and this note should be taken into consideration when making a decision to enhance treatment for ICP management (5–7). Furthermore, cerebral hypoxia causing cellular metabolic dysfunction may precede a rise in ICP, implying diffusion abnormalities rather than abnormalities with perfusion (5).

Several studies suggested that cerebral hypoxia is also an independent factor associated with unfavorable outcome (7–9). Subsequently, brain tissue oxygen tension (PbtO2) and microdialysis have been introduced in some institutions as advanced brain monitoring methods to complement ICP monitoring.

Although PbtO2 provides clinicians with an understanding of the ischemic and non-ischemic derangements of brain physiology (9, 10), there are some unanswered questions. Firstly, it is not exactly known which parameters are the major determinants of PbtO2. Hemoglobin, cerebral perfusion pressure, and systemic oxygenation seem to have an important role (10, 11); however, it is not clear which specific variable has the predominant role in the occurrence of cerebral hypoxia. Secondly, uncertainty exists regarding the critical threshold that defines poor outcome and whether monitoring of PbtO2 influence the treatment and hence the outcome (12).

The most recent brain trauma foundation guidelines suggest that "hypoxia detected by monitors is associated with worse outcomes" (13). However, PbtO2 value alone does not take into consideration systemic and ventilator parameters such as partial arterial oxygen tension (PaO2), which are often crucial in the neurocritical care population (14). We therefore conducted a retrospective study, with the primary aim of indicating the threshold of cerebral hypoxia and parameters that are determinants of cerebral hypoxia. Our secondary goal was to assess whether any of these indices (PbtO2, partial arterial oxygenation pressure (PaO2), PbtO2/PaO2, ratio of PbtO2 to fraction of inspired oxygen (FiO2), and PaO2/FiO2) based on the relationship between cerebral tissue oxygenation and systemic arterial oxygenation and the fraction of inspired oxygen, can be useful for prognostication of mortality in TBI patients.

MATERIALS AND METHODS

This is a single-centre retrospective cohort study. The study was approved by the relevant research ethic committee (30REC97/291) for anonymized data recording.

Patient Inclusion, Data Collection, and Management

Patients were identified using the EPIC system® which contains a database of all patients admitted to NCCU at Cambridge University Hospitals between November 2014 and October 2018. The patients included in this study were adult TBI requiring advanced neuromonitoring with invasive ICP and PbtO2 captured using ICM +® brain monitoring software (Cambridge Enterprise Ltd, Cambridge, UK; http://www.neurosurg.cam.ac.uk/icmplus). ICP was monitored with an intraparenchymal sensor (Codman ICP Micro-Sensor; Codman & Shurtleff, Raynham, MA). Licox sensors (Codman Raynham, MA) were inserted through a cranial access device (Technicam, Newton Abbot, UK). The probe was inserted in the perilesional areas. Arterial blood pressure (ABP) was zeroed at the level of the middle cranial fossa (Baxter Healthcare Health Care Corp. Cardio-Vascular Group, Irvine, CA). Arterial blood gases were obtained through an invasive catheter in the radial artery and concomitant PaO2 and PbtO2 values were recorded along with fraction of inspired oxygen. The collected data was saved

into a standardized and secure electronic spreadsheet using Microsoft Excel 2013® (Redmond, WA, USA). The following characteristics were manually collected and added to the dataset: demographics of the patients, hemoglobin level (Hb), Glasgow Coma Scale (GCS) at admission and mortality at discharge from NCCU.

Patients were managed according to current TBI guidelines and management protocol (15), based on a staircase approach with increasing level of therapy including intravenous sedation, neuromuscular paralysis, therapeutic hypothermia, hyperosmolar therapy, cerebral spinal fluid diversion using external ventricular drains, and surgical decompression. In general, management endpoints include maintaining CPP >60 mmHg and PbO2>20 mmHg in our unit (13, 15–17). No withdrawal of life sustaining therapies was applied in the study population.

Statistical Analysis

Our dataset consisted of instantaneous values of several variables (ICP, CPP, Hb, FiO2) at time instances when measured values for both PbtO2 and PaO2 were available. Due to repeated simultaneous measurements of variables at different time points and for different subjects (longitudinal data), generalized estimating equations (an extension of generalized linear models) with a covariance matrix structured by an autoregressive model were employed (11). A *p*-value smaller than 0.05 was considered as statistically significant. All the analyses were conducted in Matlab R2017b (Mathworks, Natick, MA). Throughout this paper, the term "episode" refers to each simultaneous measurement of all variables. If PbtO2<Threshold for an episode, then that episode is referred as "an episode with compromised PbtO2" or "hypoxic."

PbtO2 Threshold for Cerebral Hypoxia

In our study, we conducted two analyses to further investigate the PbtO2 threshold: (A) We calculated the correlation of the percentage of hypoxic episodes (defined as Pbto2<Threshold) and the mortality outcome when Threshold value was changed from 7 to 40 mmHg. (B) We also obtained the odds ratio (OR) and its 95% confidence interval (CI) for mortality detection by applying generalized estimating equations when the compromised PbtO2 (dichotomized PbtO2<Threshold or PbtO2≥Threshold) were entered to the model as input, mortality outcome was considered as the response variable while adjusting for confounding factors such as ICP, CPP, age and gender by considering them as covariates (11).

Determinant of Cerebral Hypoxia

Our goal was to determine whether PaO2/FiO2 can be used as a surrogate of PbtO2 and consequently as a predictor of hypoxia. For this purpose, PbtO2 was considered as the response variable. PaO2/FiO2 was entered into the model as continuous input variable while adjusting for confounding factors such as PaO2, CPP, and Hb by considering them as covariates in the model. To find an optimal threshold on PaO2/FiO2 value to indicate cerebral hypoxia, we plotted the mean and 95% CI of PaO2/FiO2 values over dichotomized group of episodes: those with compromised PbtO2 (PbtO2<Threshold), and those with normal PbtO2 values (PbtO2≥Threshold) when Threshold was changed over a range of 10–32 mmHg. We also calculated the probability of the two-sample *t*-test that the difference between average of compromised and normal PbtO2 episodes is significant.

Predictors of Mortality

We aimed to identify those variables (among PaO2, PbtO2, PbtO2/PaO2, PbtO2/FiO2, PaO2/FiO2) that were strong and independent predictors of mortality. For this purpose, we found the threshold value for each variable that can distinguish death from survival outcomes by calculating the percentage of episodes where the variable was smaller than the threshold value for each patient. The mean and 95% CI of these percentages were obtained and compared between patients who died and those who survived. Then the most predictive (optimal) threshold of mortality was identified as the threshold value where the difference between the death and survival plots are maximized in a statistically significant manner (when probability of *t*-test is smaller than 0.05). Each variable was then dichotomized using the obtained threshold value (variable< Threshold vs. variable ≥ Threshold) and entered into the model as input whereas the mortality outcome was considered as the response variable. The association of each dichotomized variable and mortality was also adjusted for confounding factors ICP, CPP, age, and gender.

RESULTS

During the period of study, a total of 303 measurements from 70 patients fulfilled the inclusion criteria outlined previously.

TABLE 1 | Baseline data of study cohort.

	Dead	Survived	*P*-value
N	13	57	
Age (years)	63 ± 17	39 ± 18	<0.001*
Male (%)	76.9	70.2	0.608
GCS	4 (3–7.5)	14 (10.5–15)	<0.001*
PaO2	112.0 ± 36.9	116.8 ± 30.3	0.328
FiO2	0.5 ± 0.2	0.4 ± 0.1	<0.001*
Pbto2	18.8 ± 8.8	26.0 ± 11.3	<0.001*
Pbto2/PaO2	0.18 ± 0.09	0.23 ± 0.11	<0.001*
Pbto2/FiO2	42.2 ± 25.2	75.6 ± 42.2	<0.001*
PaO2/Fio2	242.3 ± 85.2	326.0 ± 99.0	<0.001*
ICP	14.6 ± 7.9	9.6 ± 5.0	<0.001*
CPP	72.4 ± 12.7	76.5 ± 8.2	0.004*
Hb	9.56 ± 0.24	9.63 ± 0.11	0.002*
Number of measurements per patient	3 (1–6)	4 (2.75–6)	0.535

*Numerical data are expressed as mean ± SD and compared with one-way ANOVA with repeated measurements. Categorical data are expressed as number (percentage) or median (IQR) and compared with chi-square test. N, number; GCS, Glasgow Coma Scale; PaO2, partial pressure of oxygen; FiO2, inspired fraction of oxygen; PbtO2, brain tissue oxygen tension; ICP, intracranial pressure; CPP, cerebral perfusion pressure; Hb, Hemoglobin. *Statistically significant.*

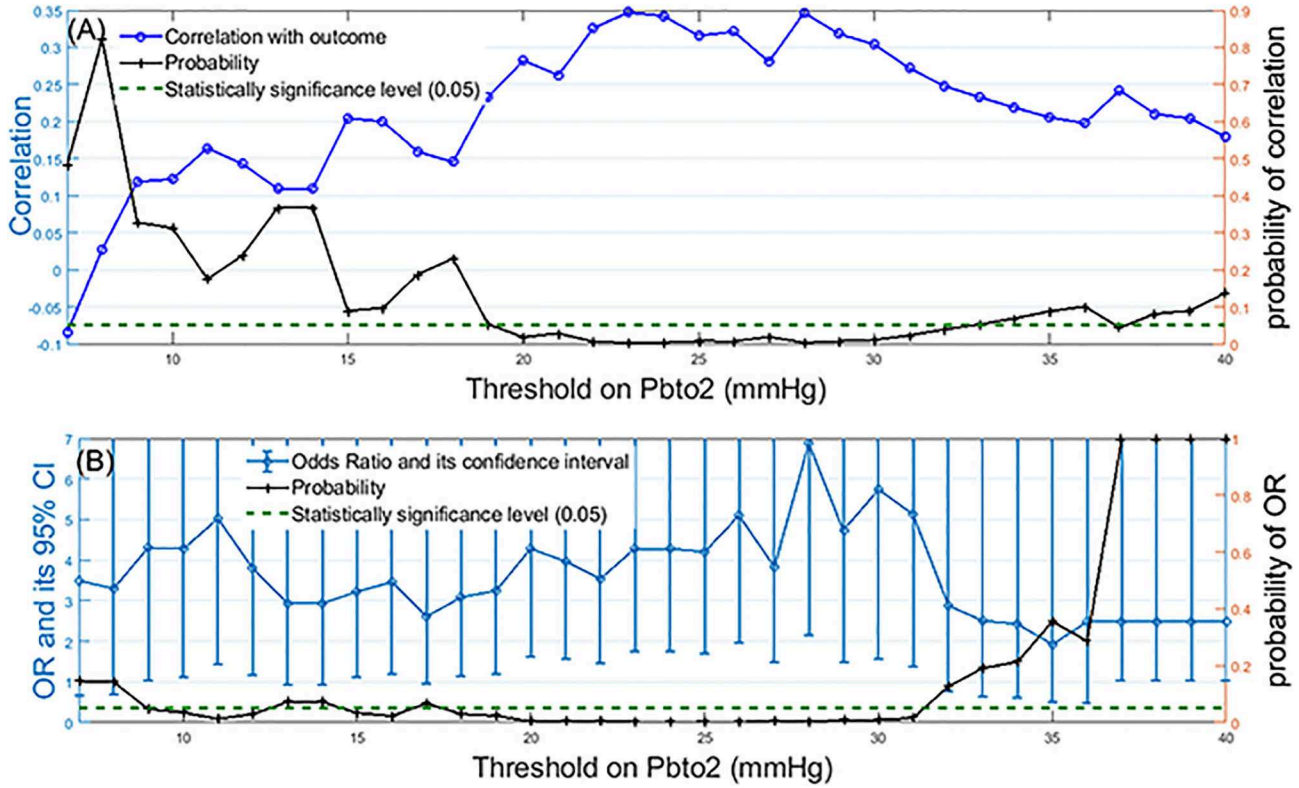

FIGURE 1 | Identification of the optimal threshold on PbtO2 to define hypoxia: **(A)** Left-side vertical axis shows correlation values between the percentage of episodes with compromised PbtO2 and the mortality outcome over all patients when the PbtO2 threshold (shown as horizontal axis) changed from 7 to 40 mmHg. Right-side vertical axis displays the probability of the significance of the calculated correlation for each threshold value. **(B)** Left-side vertical axis displays odds ratio and its 95% confidence interval for mortality detection by using dichotomized PbtO2 (PbtO2< Threshold or ≥Threshold) as the input of generalized estimating equations while adjusting for confounding factors such as intracranial pressure (ICP), cerebral perfusion pressure (CPP), age and gender. The right-side vertical axis displays the probability associated with calculated OR. The dashed green line represents the probability significance level of 0.05. So, any probability below the dashed green line is statistically significant.

Table 1 summarizes the baseline data of the study cohort. The mean age of the cohort was 43 ± 20. The average number of repeated measurements per subject was 4.

Median admission GCS was 12.5 (6–15). Median number of measurements per patient was 4 (2–6) and not significantly different between those who survived and died. All other variables except gender and PaO2 values were significantly different between the two outcomes.

PbtO2 Threshold for Cerebral Hypoxia

Figure 1A presents the correlation plot along with probability of its significance (right vertical axis) for when threshold value changes from 7 to 40 mmHg. We observe that the statistically significant correlation (p-value < 0.05) becomes more than 0.25 when hypoxic threshold is defined in the range of 20–31 mmHg. **Figure 1B** presents Odds Ratio (OR) and its 95% Confidence Interval (CI) for mortality detection along with its statistical significance (probability on the right vertical axis). We observe that the statistically significant odds ratio becomes equal or more than 4 when PbtO2 threshold (and therefore to define hypoxia) is in the range of 20–31 mmHg.

In our dataset both correlation and OR were maximized at the threshold of 28 mmHg. Further grouping of the patients into two age categories (those with age of ≥60 years old vs. those younger than 60 years old) revealed that although the maximum correlation for older subjects occurs at PbtO2 threshold of 28, this threshold value decreases to 20 mmHg for the younger patients (**Figure 2**).

From a total of 303 episodes of measurements, 186 episodes had Pbto2<28. Among these, only 12 had ICP>20 and 6 episodes had CPP<60. Thus, prevalence of ICP elevation among hypoxic episodes (12/186 or 6.1%) was comparable with general prevalence of ICP elevation over all episodes (18/303 or 5.9%) (9). Also, 60.6% of the hypoxic episodes (Pbto2 ≤ 28) had ICP value lower than 20 and CPP value more than 60 mmHg.

Determinants of Cerebral Hypoxia

CPP and PbtO2 had a non-statistically significant correlation of 0.1 ($p = 0.063$) considering the overall population. Hb and PbtO2 had a statistically non-significant correlation of 0.14 ($p = 0.084$). PaO2/FiO2 revealed a statistically significant correlation of 0.22 ($p < 0.001$) with brain tissue oxygenation. The results

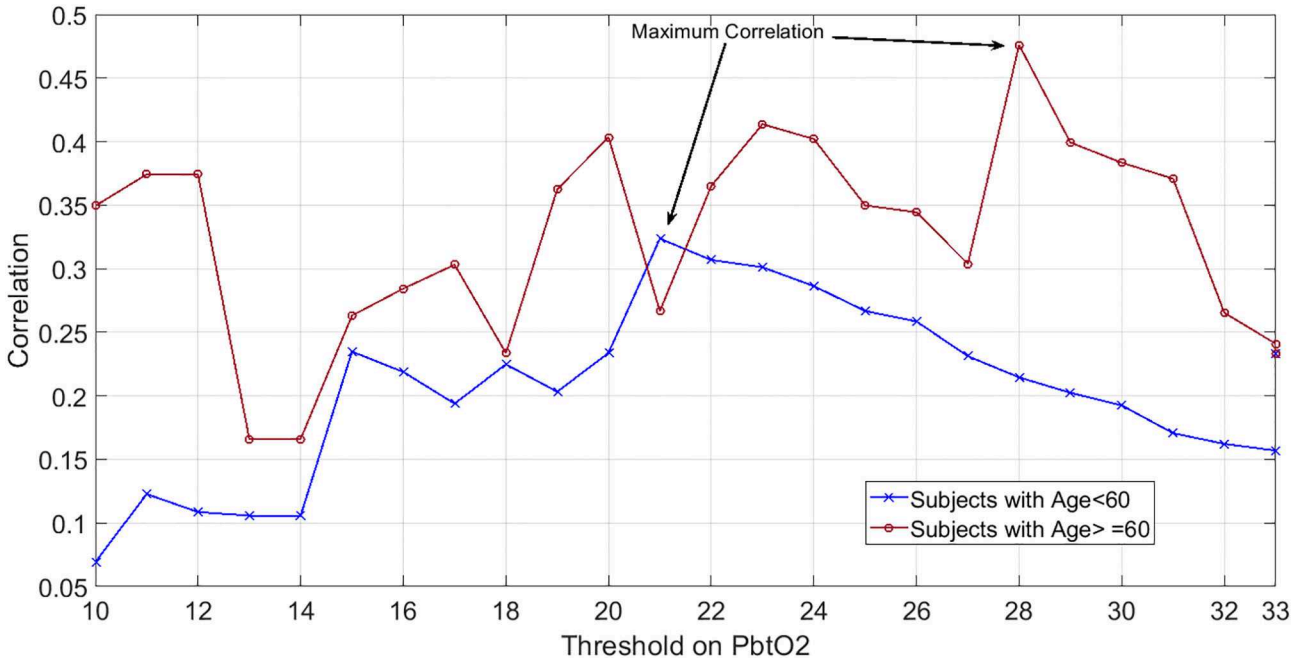

FIGURE 2 | Showcasing dependency of hypoxic PbtO2 threshold to subjects' age: Correlation values between the percentage of episodes with compromised PbtO2 and the mortality outcome over patients when PbtO2 threshold (shown as horizontal axis) changed from 7 to 40 mmHg. Blue plot indicates the patients younger than 60 years old while red plot shows the correlation results for those who are 60 years old or older.

of generalized estimating equations revealed an independent and strong linear correlation between brain oxygenation and PaO2/FiO2 (adjusted $p < 0.001$).

Figure 3 shows the mean and 95% CI of PaO2/FiO2 over dichotomized group of episodes based on PbtO2 threshold. The right axis displays probability of two-sample *t*-test that the difference between average of compromised and normal PbtO2 episodes is significant. We observe that if the hypoxia threshold is defined in the acceptable range of 20–30 mmHg as discussed before, then a PaO2/FiO2 in the range of 300–320 can result in reasonable separation between compromised and normal Pbto2 episodes and consequently in identifying cerebral hypoxia. For simplicity, in this work, we choose the middle of the range as the optimal threshold of PaO2/FiO2 (PaO2/FiO2<310) to indicate hypoxia for our dataset. Finally, analyzing independent association between dichotomized PaO2/FiO2 (PaO2/FiO2< or $\geq$ 310) and hypoxia (defined as PbtO2 < 28) results revealed that in fact, PaO2/FiO2 < 310 is an independent risk factor for compromised PbtO2 in our dataset with adjusted odds ratio of 1.78, 95% confidence interval of (1.10–2.87) and p-value = 0.019 (**Figure 3**).

Predictors of Mortality

All variables except PaO2 showed statistically significant correlation with mortality: PbtO2 (correlation = −0.24, p-value < 0.001), PbtO2/PaO2 (correlation = −0.20, p-value < 0.001), PbtO2/FiO2 (correlation = −0.30, p-value < 0.001), PaO2/FiO2 (correlation = −0.31, p-value < 0.001). Correlation value of PaO2 with outcome was non-significant (correlation = −0.06, p-value = 0.328).

Figure 4 displays the mean and 95% CI of the percentages of compromised episodes for both death and survival outcomes. Using these plots, for each variable, we identified the most predictive (optimal) threshold of mortality as the threshold value where the difference or separation between the death and survival plots are maximized in a statistically significant manner. The most predictive threshold on Pbto2, Pbto2/Pao2, Pbto2/Fio2, and PaO2/FiO2 are 28, 0.27, 60, and 310, respectively.

Table 2 presents the adjusted odds ratios, its 95% CI and p-values of death detection using the dichotomized version of each variable by applying the optimal threshold we just obtained. We observe that PbtO2<28, PbtO2/PaO2<0.27, PbtO2/FiO2<60, and PaO2/FiO2<310 are each independent predictor of mortality when considered individually.

Finally, entering all these dichotomized variables as the inputs of the model and mortality outcome as the output while adjusting for confounding factors revealed that while each of these dichotomized variables were individually an independent predictor of mortality, when one considered all compromised values together, then PaO2/FiO2 became the independent predictor of mortality with adjusted odds ratio of 3.47 (1.20–10.04) and p-value = 0.022.

DISCUSSION

Our results demonstrated that: (1) Cerebral hypoxic threshold ranges from 20 to 31 mmHg; the optimal hypoxic threshold

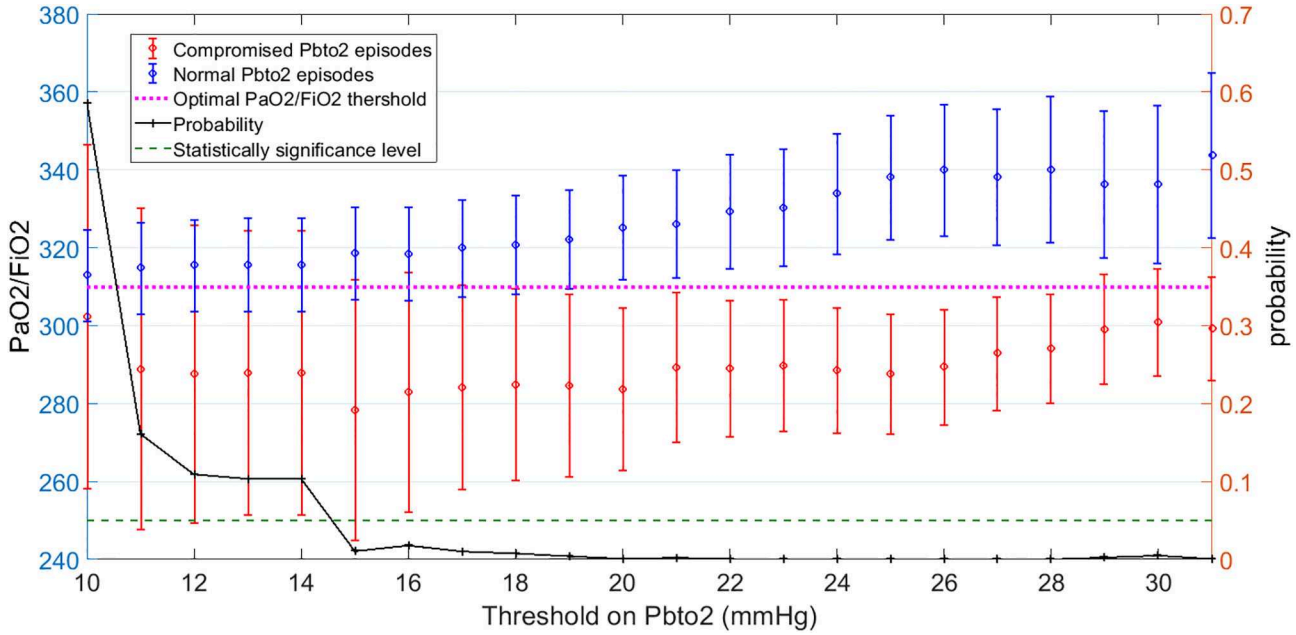

FIGURE 3 | Left-side vertical axis shows the average and 95% Confidence Interval (CI) of PaO2/FiO2 values for two groups of episodes: Those with compromised PbtO2 values of PbtO2<Threshold (in red) and those with normal PbtO2 values of PbtO2≥Threshold (in blue). Right-side vertical axis indicates the probability of the *t*-test that the average of PaO2/FiO2 values are significantly different between the normal (blue) and compromised episodes (red). The vertical axis displays the Threshold values on PbtO2. The dashed green line represents the probability significance level of 0.05. So, whenever probability of the *t*-test (in black) is below the dashed green line, PaO2/FiO2 values are significantly different between those episodes with compromised and normal PbtO2 values: This happened when PbtO2 Threshold is within the range of 20–30 mmHg. The average value of PaO2/FiO2 for when PbtO2 Threshold is within the range of 20–30 corresponds to 310 (The dashed pink line). Thus, PaO2/FiO2 = 310 can be employed as the optimal threshold value on PaO2/FiO2 to define a hypoxic episode.

for patients older than or equal to 60 years old is 28 mmHg, while this threshold decreases to 21 mmHg for those younger. (2) PaO2/FiO2 is significantly correlated with PbtO2, whereas CPP and Hb have a statistically non-significant correlation with PbtO2. PaO2/FiO2<310 is an independent risk factor for cerebral hypoxia. (3) PbtO2, PbtO2/PaO2, PbtO2/FiO2, and PaO2/FiO2 are each independent predictor of mortality. When considering all these compromised values together PaO2/FiO2 becomes the most independent predictor of morality.

Pathophysiology of brain tissue oxygenation is complicated and dependent on several factors including oxygen delivery (cerebral blood flow), arterial oxygen content, oxygen diffusion from the capillary into the mitochondria and mitochondrial oxygen consumption. Brain tissue oxygen is a good clinical marker to identify ischemic and non-ischemic derangements of brain physiology (12). Some studies showed that TBI patients who did not survive, had lower PbtO2 values than those who did survive (11, 12, 18, 19).

Although many have suggested PbtO2 of 20 mmHg as a threshold associated with unfavorable outcome in brain injured patients (8, 18), the optimal threshold of PbtO2 that correlates with bad outcome is not clear and widely varies between studies (20, 21). Meixensberg et al. (20) found no statistical improvement in outcome at 6 months, when PbtO2 was targeted above 10 mmHg. In a prospective study including TBI patients (22), patients treated with ICP and brain tissue PbtO2 monitoring were compared with controls who had undergone ICP monitoring alone, using a PbtO2 target of 25 mmHg. The authors found a significantly reduced mortality rate (44 vs. 25%, $p < 0.05$) in the group monitored with PbtO2. The recently published BOOST-II study (23)-a randomized controlled trial comparing patients undergoing treatment protocol based on ICP+PbtO2 monitoring vs. ICP monitoring alone- found that a management protocol based on PbtO2 (target 20 mmHg) and ICP monitoring reduced the proportion of time with brain tissue hypoxia after severe TBI (0.45 in ICP-only group, 0.16 in ICP+PbtO2 group; $p < 0.0001$) and had a trend toward lower mortality and more favorable outcomes than ICP-only treatment. The ongoing BOOST-III study (ClinicalTrials.gov: NCT03754114) will aim to further clarify this issue.

Our results showed a higher threshold compared to the aforementioned literature, but were in agreement with Eriksson et al. (24), who found that the first 72 h of PbtO2<29 mmHg were associated with higher mortality. These results challenge the brain oxygenation threshold of 20 mmHg that has been used conventionally and delineates a time for monitoring PbtO2 that is predictive of outcome (5). However, we also found that hypoxic PbtO2 threshold changes with age. Recent evidence suggests that cerebrovascular autoregulation and ICP are profoundly dependent on age (25). For example, cerebral atrophy could buffer new pathological intracranial masses, which can be linked to a lower incidence of intracranial hypertension

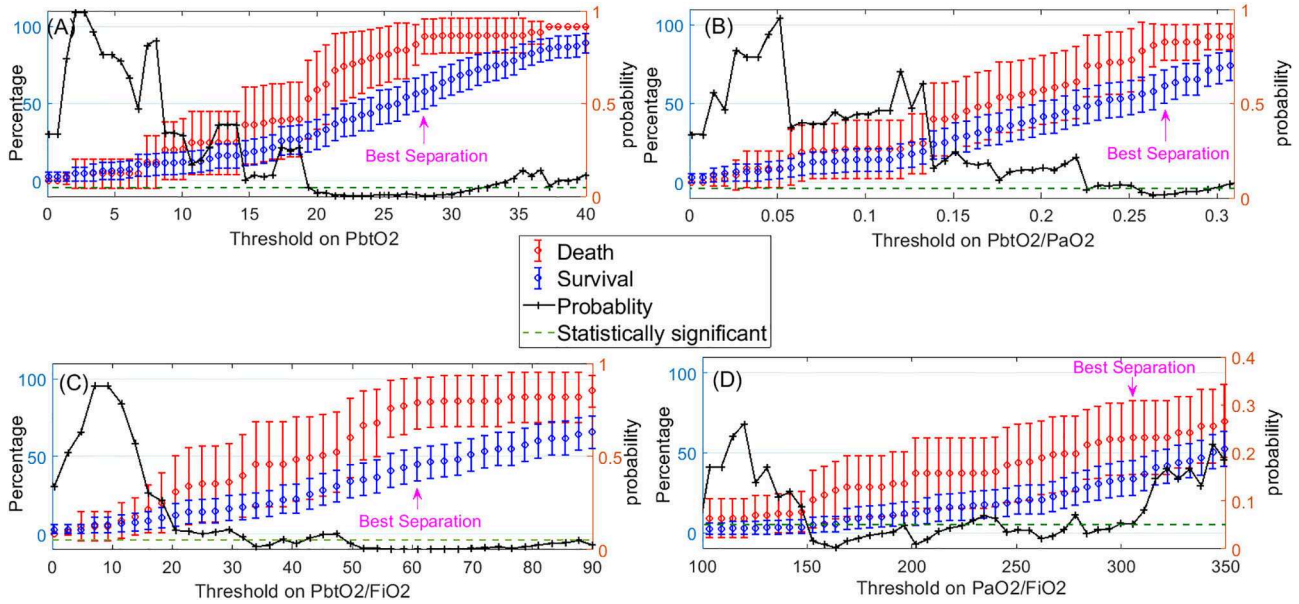

FIGURE 4 | Left-side vertical axis shows the average and 95% confidence interval for the percentages of compromised episodes of a variable (when the variable< Threshold) for two groups of patients: those who died (in red) and those who survived (in blue). The right-side vertical axis indicates the probability of the *t*-test that percentage of compromised episodes is significantly different between those who died and survived. The dashed green line represents the probability significance level of 0.05. So, whenever probability of the *t*-test (in black) is below the dashed green line, difference between death and survival is statistically significant. The pink arrow displays where the best separation between the death and survival outcomes is achieved. This point can be used to obtain the optimal threshold value on each of the following variables to indicate a hypoxic episode: **(A)** PbtO2, **(B)** PbtO2/PaO2, **(C)** PbtO2/FiO2, **(D)** PaO2/FiO2.

(26). Similarly, it is plausible that the need for higher target of PbtO2 in the elderly population could be due to a lower cerebrovascular reserve.

There are numerous factors that may affect PaO2 including pH, temperature and the oxygen saturation of Hb (27). Among these, CPP increase and consequent cerebral blood flow (CBF) optimization seem to be one of the major determinants (28).

Rosenthal et al. (27) explored whether PbtO2 more closely reflects variables related to cerebral oxygen diffusion or cerebral oxygen delivery and metabolism. In this study, patients underwent oxygen challenge (increase FiO2 100%), pressure challenge (increase arterial blood pressure) and carbon dioxide (CO2) challenge (hyperventilation). In multivariable analysis adjusting for various variables of cerebral oxygen delivery and metabolism, the only statistically significant relationship was that between PbtO2 and the product of CBF and cerebral arteriovenous oxygen tension difference (AVTO2), suggesting a strong association between brain tissue oxygen tension and diffusion of dissolved plasma oxygen across the blood-brain barrier. In our cohort, all hypoxic episodes had low CPP, although CPP< 60 did not prove to be an independent predictor of hypoxia. The prevalence of ICP elevation among hypoxic episodes (12/186, 6.1%) was comparable with general prevalence of ICP elevation over all episodes (18/303, 5.9%). 60.6% of the hypoxic episodes (PbtO2≤ 28) had ICP value lower than 20 and CPP value more than 60 mmHg, thus suggesting that normal values of ICP and CPP do not necessarily prevent hypoxia (22).

PbtO2 also depends on systemic oxygenation and ventilator parameters (10). Assuming normal alveolar function, PaO2 has a linear relationship with inspired oxygen (FiO2) (29). In patients with acute respiratory distress syndrome (ARDS), the PaO2/FiO2 ratio whilst on standard ventilator settings, is an appropriate tool to ensure correct categorization of patients with ARDS by disease severity (30). There is further evidence showing strong correlation between PbtO2 and FiO2 and a relationship between PbtO2 and PaO2 (31–33).

In these settings, FiO2 can be easily controlled, but PaO2 may be variable, therefore variations in PaO2 with FiO2 (as a result of the various dependent factors described above) will have an effect on the PbtO2, hence it will be dependent upon PaO2 fluctuations. As a result, the absolute PbtO2 value may be better interpreted whilst also considering the PaO2.

In the context of head injury, conventional physiology states that if CBF is reduced below a defined ischaemic threshold the affected areas of the brain must extract more oxygen from the limited blood supply to maintain cerebral metabolism (34). Through the use of oxygen-15 (15O) positron emission tomography (PET), authors show that the mean oxygen fraction (OEF) achieved significantly smaller OEF increases in hypoxic regions compared with normoxic regions, with similar falls in CBF (34). These findings imply that there may be other mechanisms contributing to tissue hypoxia that cannot be explained by classical physiological concepts relating to macrovascular brain ischemia (34). Menon et al. used an end-capillary oxygen tension (PvO2)—PbtO2 gradient in normoxic

TABLE 2 | Odds Ratio (95% confidence interval) and *p*-value of death detection using the dichotomized version of each variable (variable< Optimal Threshold).

Compromised value of the variable	Odds ratio (95% CI)	*p*-value
PbtO2<28	6.88 (2.13–22.23)	0.001*
PbtO2/PaO2<0.27	6.73 (2.14–21.14)	0.001*
PbtO2/FiO2<60	10.20 (3.64–28.61)	<0.001*
PaO2/FiO2<310	4.54 (1.83–11.29)	0.001*

**Statistically significant.*

and hypoxic areas of brain tissue in patients with TBI to provide a measure of efficiency of microvascular oxygen delivery. The authors found that hypoxic areas of brain exhibited large diffusion gradients between tissue and end-capillary compared to normoxic regions, despite similar reductions in CBF (34). This can be explained by an increase in diffusion distance (increased tissue path lengths for oxygen) due to endothelial swelling, patchy microvascular collapse and peri-vascular edema. It is possible that based on these findings, PbtO2/PaO2 and PbtO2/FiO2 ratio may be a better indicator to severity of brain injury than absolute PbtO2.

The limitations of standalone PbtO2 monitoring was recognized by Arikan et al. (35) who were able to calculate a hypoxic threshold using a ratio of PbtO2/PaO2 suggesting that in the absence of hypoxemia (low PaO2) and at a constant cerebral metabolic rate of oxygen (CMRO2), ratios <0.10 indicated covert hypoxia and a deficient delivery of oxygen into the brain.

PbtO2/PaO2 ratio was applied to investigate the oxygenation status in tissue surrounding arterio-venous malformations (AVMs) and in the distant brain during surgery to better understand the perfusion pressure breakthrough phenomenon (36). In a cohort of 22 patients with supratentorial AVMs and 16 patients with cerebral aneurysm as controls, PbtO2/PaO2 ratio showed to be a better indicator than absolute PbtO2 in detecting intraoperative hypoxia in the margins of AVMs and in the distal ipsilateral brain. In our study, we found that PbtO2/PaO2<0.27 is an independent predictor of mortality. Our results confirm previous results but they also add new insight because of the higher number of patients and for the application of this index in traumatic brain injured patients and its correlation with outcome.

PbtO2/FiO2 ratio has never been studied so far, but- for the above mentioned reasons- it is plausible that it could be able to predict the severity of systemic and cerebral oxygenation impairment and could be potentially useful as part of the decision making for escalation of treatment after TBI (6). Finally, the PaO2/FiO2 threshold for mortality is consistent with the PaO2/FiO2 definition of ARDS and seems to be the most independent predictor of mortality comparing to other ratio, thus suggesting that the role of systemic oxygenation and mechanical ventilation is fundamental in brain injured patients (37–39).

Limitations of the Study

The present study has several limitations that can interfere with the generalization of the results. First, this is a retrospective study and thus, some clinical data regarding the specific type of TBI injury and neurosurgical interventions were lacking. Second, the population studied is heterogeneous with different clinical presentations (as for GCS). Third, the study sample size is small both in terms of number of subjects and number of measurements per patient. Fourth, our dataset consisted of variable values at when the Pbto2 and Pao2 measurements were available. Conducting a prospective study while addressing these issues are needed for further validation of our findings.

CONCLUSION

Among the determinants of cerebral oxygenation, systemic oxygenation seems to have the greater role. Therefore, appropriate mechanical ventilation to achieve appropriate oxygen targets is fundamental for the management of TBI patients. The critical threshold of PbtO2 could be related to patient's age; therefore, the threshold of cerebral oxygenation to consider treatment escalation should be made considering patients' specific and individualized need.

Indices such as the PbtO2/PaO2, PbtO2/FiO2, and PaO2/FiO2 ratios can be potentially used to discriminate patients at risk of mortality in TBI patients. We therefore believe that the inclusion of these indices may reflect the interrelationship between pathologies in the brain and lung in a more comprehensive fashion. The future work can include further validations of these findings in a prospective study.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The study was approved by the Cambridge University Hospital Ethical Committee (30REC97/291) for anonymized data recording. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

CR, AG, SA, RB, and PH contributed to the conception and design of the study. AG, CR, EB, MS, RB, and PH contributed to the acquisition of data for the work. SA and CR performed the statistical analysis with the collaboration of AG and PP. CR, SA, PP, and AG wrote the first draft of the manuscript. All authors revised and approved the final version of the manuscript.

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Effects of Age and Sex on Optic Nerve Sheath Diameter in Healthy Volunteers and Patients With Traumatic Brain Injury

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The measurement of optic nerve sheath diameter (ONSD) has been reported as a non-invasive marker for intracranial pressure (ICP). Nevertheless, it is uncertain whether possible ONSD differences occur with age and sex in healthy and brain-injured populations. The aim of this study was to investigate the effects of sex and age on ONSD in healthy volunteers and patients with traumatic brain injury. We prospectively included 122 healthy adult volunteers (Galliera Hospital, Genova, Italy), and compared age/sex dependence of ONSD to 95 adult patients (Addenbrooke's Hospital, Cambridge, UK) with severe traumatic brain injury (TBI) requiring intubation and invasive ICP monitoring. The two groups were stratified for sex and age. Age was divided into 3 subgroups: (1) young adults: 18–44 years; (2) middle-aged adults: 45–64 years; (3) old adults: >65 years. In healthy volunteers, ONSD was significantly different between males and females [median (interquartile range): 4.2 (3.9–4.6) mm vs. 4.1 (3.6–4.2) mm ($p = 0.01$), respectively] and was correlated with age ($R = 0.50$, $p < 0.0001$). ONSD was significantly increased in group 3 compared to groups 2 and 1, indicating that ONSD values are higher in elderly subjects. In TBI patients, no differences in ONSD were found for sex and the correlation between ONSD and age was non-significant ($R = 0.13$, $p = 0.20$). ONSD increases with age and is significantly larger for males in healthy volunteers but not in TBI patients. Different ONSD cut-off values need not be age- or sex-adjusted for the assessment of increased ICP in TBI patients.

Keywords: optic nerve sheath diameter, ultrasonography, traumatic brain injury, intracranial pressure, healthy volunteers

INTRODUCTION

Elevated intracranial pressure (ICP) is a harmful condition resulting from many neurological and non-neurological diseases (1) and is associated with poor outcome (2). The gold standard techniques to measure intracranial pressure (ICP) are all invasive, such as intraventricular catheterization and intraparenchymal probes. They carry several risks including infection, hemorrhage and therefore, are precluded in patients in need of monitoring over long time or susceptible to coagulopathy or platelet disorders (3).

In this scenario, several alternative non-invasive methods to assess ICP have been developed over the past years (4). Among these, the ultrasonographic measurement of optic nerve sheath diameter (ONSD) has gained popularity given its feasibility, repeatability, safety and absence of radiation hazard or known side effects. The sheath around the optic nerve is an extension of the dura-mater and is filled with cerebrospinal fluid (CSF), so increases of intracranial pressure are detectable as rises of ONSD in the anterior, retrobulbar compartment ∼3 mm behind the globe (5). However, there are potential challenges: the extension of optic sheath is most probably a non-linear function of ICP, its elasticity is unknown and may vary from person-to-person and many variables may affect the relationship between diameter and ICP.

This technique has demonstrated low intra- and inter-observer variability (6) and according to several studies, ICP and ONSD are linearly associated in conditions of intracranial hypertension (4, 7–9). A recent meta-analysis (10) indicated that ultrasonographic ONSD may be a potentially useful approach to assess intracranial hypertension when invasive devices are not indicated or available. However, the threshold of ONSD related to elevated ICP in brain-injured patients is still debatable (10). More information is needed about the variability of ONSD in pathological conditions and the range of normality. Furthermore, it is not clear whether non-invasive ICP assessment with ONSD in TBI patients is affected by age and sex.

The aim of this study was to investigate the effects of sex and age on optic nerve sheath diameter in healthy volunteers and patients with traumatic brain injury.

MATERIALS AND METHODS

This article fulfills the "Strengthening the reporting of observational studies in epidemiology (STROBE)" guidelines (11).

Healthy Population

The study protocol was approved by the Research Ethics Boards of Genova, Italy (REC 031R8G2015) and observed the principles of the Declaration of Helsinki. One-hundred twenty-two healthy volunteers were prospectively recruited between 1st September 2015 and 1st January 2018 at Galliera Hospital, Genova, Italy. We prospectively recruited adult (>18 years-old) Italian healthy volunteers [American Society of Anesthesiologists (ASA) 1–2] undergoing pre-surgery examination for low risk surgical interventions at Galliera Hospital. Inclusion criteria included the absence of any cardiovascular, respiratory neurological and systemic pathology and the absence of any chronic diseases and any acute illnesses in the preceding 4 weeks from the assessment. Written informed consent was obtained from all participants before enrollment. Patients with a history of head injury, history of optic nerve lesion or previous optic nerve trauma, as well as pregnant women (excluded by anamneses and/or laboratory test) were excluded. Eligible patients were screened, their demographic data recorded, as well as non-invasive arterial blood pressure (ABP) measured using a conventional arm cuff.

TBI Patients

Ninety-five TBI patients were recruited between the 20th December 2015 and the 1st September 2017 at the Neurosciences and Trauma Critical Care Unit, Addenbrooke's Hospital, Cambridge, UK. The protocol was approved by the Research Ethics Boards at the University of Cambridge (REC 15/lo/1918). Written consent was obtained from all participants' next of kin. We included patients aged >18 years old with severe traumatic brain injury [Glasgow Coma Scale (GCS) 3–8], requiring intubation and invasive ICP monitoring.

Exclusion criteria were the absence of an informed consent, skull base fracture with cerebrospinal fluid leaking and a known history of ocular pathology or optic nerve trauma. Demographic data including sex, age, ABP measured invasively at the radial artery (Baxter Healthcare Health Care Corp., Cardio Vascular Group, Irvine, CA, USA), ICP [via an intraparenchymal probe (Codman & Shurtleff, Raynham, MS, USA)] and ONSD were recorded after the ICP probe insertion on admission day 1 at variable times across individuals according to the patients logistic availability.

Endpoints

The primary endpoint was to evaluate ONSD measured by ultrasound in healthy volunteers. We aimed to assess the difference in ONSD between sex (male vs. female) and in different age groups [group 1: young adults (18–44 years); group 2: middle-aged adults (45–64 years); group 3: old adults (>65 years)]. The secondary endpoint was to assess the differences in ONSD stratified for age and sex patients with traumatic brain injury and compare these findings with the healthy volunteers population.

ONSD Measurement

In healthy volunteers and TBI patients, ONSD was measured 3 mm behind the retina. Two trained investigators with more than 30 examinations of experience as previously described (5) (CR, FC in Genova and CR, DC in Cambridge) used a 7.5 MHz linear ultrasound probe oriented perpendicularly in the vertical plane and at around 30 degrees in the horizontal plane on the closed eyelids of both eyes from supine subjects (Cambridge, UK: 11L4, Xario 200; Toshiba, Zoetermeer, The Netherlands; Genova Italy: DC-T6, Mindray Medica, Schenzen, China). Ultrasound gel was applied on each eyelid and recordings were performed in the axial and longitudinal planes. An electronic caliper was used to mark 3 mm perpendicularly behind the retina and the ONSD was measured at the depth marker at right angles to the optic nerve.

TABLE 1A | ONSD (mm) (median [IQR]) values in healthy volunteers and patients with traumatic brain injury (TBI) according to age groups and sex.

Population	Volunteers		TBI patients	
	4.2 (3.8–4.4)		4.5 (4.0–5.4)	
Age Group				
1	4.0 (3.7–4.2)		4.3 (3.9–5.3)	
2	4.2 (3.6–4.5)		4.8 (4.3–5.4)	
3	4.7 (4.2–4.8)		5 (3.8–5.4)	
Sex	**Males**	**Females**	**Males**	**Females**
	4.2 (3.9–4.6)	4.1 (3.6–4.2)	4.4 (3.9–5.0)	5.2 (4.3–6.2)
Age Group				
1	4.1 (3.8–4.4)	4.0 (3.6–4.2)	4.3 (3.9–5.1)	4.7 (4.2–5.6)
2	4.3 (4.2–4.8)	3.8 (3.6–4.2)	4.7 (4.3–5.0)	5.2 (4.2–6.7)
3	4.8 (4.5–4.9)	4.6 (4.2–4.27)	4.1 (3.8–5.0)	5.4 (5.4–5.5)

TABLE 1B | ABP (mm Hg) (median [IQR]) values in healthy volunteers and patients with traumatic brain injury (TBI) according to age groups and sex.

Population	Volunteers		TBI patients	
	84.8 (77.8–93.7)		86.7 (81.3–92.4)	
Age Group				
1	79.2 (72.8–87.8)		87.4 (82.0–92.4)	
2	87.7 (80.7–96.0)		86.1 (80.5–93.6)	
3	95 (89.3–104.0)		85.1 (80.2–89.3)	
Sex	**Males**	**Females**	**Males**	**Females**
	86.7 (78.2–94.7)	84.7 (76.3–92.8)	86.5 (80.4–92.1)	88.9 (82.8–93.5)
Age Group				
1	79.8 (75.7–88.2)	78.3 (70.8–85.0)	86.9 (81.8–91.7)	91.4 (84.1–95.5)
2	86.7 (80.3–97.0)	88.3 (81.7–94.0)	85.5 (80.0–93.6)	87.7 (82.4–92.6)
3	102.5 (92.5–109.6)	91.3 (86.5–99.8)	85.0 (77.6–89.2)	85.1 (82.8–89.4)

TABLE 1C | ICP (mm Hg) (median [IQR]) values in patients with traumatic brain injury (TBI) according to age groups and sex.

Population	TBI patients	
	10.69 (7.31–13.95)	
Age Group		
1	10.82 (8.04–13.53)	
2	10.51 (8.00–12.59)	
3	8.04 (6.50–12.15)	
Sex	**Males**	**Females**
	10.73 (7.09–13.42)	10.08 (8.04–13.26)
Age Group		
1	10.82 (7.86–13.48)	10.47 (9.36–13.99)
2	10.52 (7.09–12.47)	10.18 (9.11–12.59)
3	9.10 (6.43–11.60)	8.04 (7.04–13.08)

TABLE 1D | Age (years) (median [IQR]) values in healthy volunteers and patients with traumatic brain injury (TBI) according to age groups and sex.

Population	Volunteers		TBI patients	
	45.0 (32.2–57.2)		43.0 (28.0–61.0)	
Age Group				
1	31.0 (24.7–38.0)		29.5 (21.0–41.25)	
2	50.0 (46.0–55.0)		54.0 (51.7–61.0)	
3	72.0 (67.0–76.0)		72.0 (66.5–78.0)	
Sex	**Males**	**Females**	**Males**	**Females**
	44.5 (31.5–58.5)	45.0 (33.0–54.5)	43.0 (28.0–61.0)	48.0 (34.0–59.0)
Age Group				
1	31.0 (25.0–38.7)	31.0 (23.0–37.25)	29.5 (20.7–41.2)	31.0 (26.2–41.2)
2	52.0 (48.75–58.5)	48.0 (46.0–53.0)	54.0 (50.7–62.0)	54.0 (53.0–58.2)
3	71.0 (65.0–74.0)	72.0 (69.5–76.5)	73.0 (66.2–80.2)	68.0 (67.0–78.0)

The final ONSD measurement was calculated as the average of the transversal and sagittal diameters for both eyes.

Statistical Analysis

Statistical analyses were performed using RStudio software (version 3.6.0). Continuous variables were expressed as median [interquartile range (IQR)]. Data were checked for normality using the Shapiro-Wilk test. Pearson or non-parametric Spearman correlation coefficients were used to relate continuous variables. Welch Two Sample *t*-test or non-parametric Wilcoxon rank sum test were applied to evaluate the differences in ONSD concerning sex in healthy volunteers and TBI patients. One-way analyses of variance (parametric ANOVA and non-parametric Kruskal-Wallis test), followed by parametric (using *t*-test with pooled standard deviation) or non-parametric (using Wilcoxon rank sum test) *post-hoc* pairwise comparison tests with Bonferroni correction for multiplicity were applied to evaluate the differences in ONSD concerning age groups. A multivariable linear model was applied to verify whether age, sex and arterial blood pressure were independently related to ONSD in both healthy volunteers and TBI cohorts (following the linear model structure: $ONSD \sim age + sex + ABP$). In the TBI cohort, we also verified whether intracranial pressure alongside with age, sex and arterial blood pressure were independently related to ONSD (following the linear model structure: $ONSD \sim age + sex + ABP + ICP$). ABP and ICP were included as outcome measures to account for their modulating effect on global cerebral hemodynamics. The level of significance was set at 0.05.

RESULTS

The characteristics of the cohorts of healthy volunteers and TBI patients and the median (IQR) values of assessed variables are shown in **Tables 1A**–**E**. **Table 2** presents the summaries of the multivariable linear models.

Healthy Volunteers

A significant positive correlation was found between ONSD and age ($R = 0.50$, $p < 0.0001$) (**Figure 1A**) and ABP and age ($R =$

TABLE 1E | Sample size of cohorts in healthy volunteers and patients with traumatic brain injury (TBI) according to age groups and sex.

Population	Volunteers		TBI patients	
	122		95	
Age Group				
1	60		52	
2	41		28	
3	21		15	
Sex	**Males**	**Females**	**Males**	**Females**
	60	62	70	25
Age Group				
1	30	30	40	12
2	20	21	20	8
3	10	11	10	5

TABLE 2 | Summary of the multivariable linear models in healthy volunteers and patients with traumatic brain injury (TBI).

Dependent variables	Parameter	Estimate	Std. Error	*p*-value	95% Confidence Interval	
					Lower Bound	Upper Bound
	Healthy Volunteers					
ONSD	*Intercept*	3.29	0.35	**<0.0001**	2.59	4.00
	Age	0.02	0.003	**<0.0001**	0.01	0.02
$R^2 = 0.30$	*Sex*	−0.25	0.09	**0.005**	−0.43	−0.08
	ABP	0.002	0.005	0.55	−0.006	0.01
	TBI Patients					
ONSD	*Intercept*	0.95	1.55	0.54	−2.12	4.03
	Age	0.008	0.008	0.27	−0.007	0.02
$R^2 = 0.14$	*Sex*	0.41	0.31	0.20	−0.21	1.03
	ABP	0.03	0.02	0.06	−0.001	0.07
	ICP	0.04	0.02	0.07	−0.002	0.08

ONSD, optic nerve sheath diameter; ABP, mean arterial blood pressure, ICP, intracranial pressure.
Bold values indicate statistical significance (p < 0.05).

0.54, $p < 0.0001$) (**Figure 1B**). ONSD was significantly different between females and males [4.1 (3.6–4.2) mm vs. 4.2 (3.9–4.6) mm ($p = 0.01$), respectively] (**Figure 2A**). Considering the entire population (without sex stratification), ONSD showed a statistically significant difference between age groups 1 and 3 [4.0 (3.7–4.2) mm vs. 4.7 (4.2–4.8) mm, $p < 0.0001$] and groups 2 and 3 [4.2 (3.6–4.5) mm vs. 4.7 (4.8–4.2) mm, $p = 0.01$] (**Figure 2B**) (**Table 1A**). Considering only males, ONSD was significantly different between age groups 1 vs. 2 [4.1 (3.8–4.4) mm vs. 4.3 (4.2–4.8) mm, $p = 0.05$] and 1 vs. 3 [4.1 (3.8–4.4) mm vs. 4.8 (4.5–4.9) mm, $p = 0.004$] (**Figure 2C**) (**Table 1A**). Considering only the female population, ONSD was significantly different between age groups 1 vs. 3 [4.0 (3.6–4.2) mm vs. 4.6 (4.2–4.7) mm, $p < 0.001$] and 2 vs. 3 [3.8 (3.6–4.2) mm vs. 4.6 (4.2–4.7) mm, $p = 0.01$] (**Figure 2C**) (**Table 1A**). ABP was significantly different between age groups 1 vs. 2 ($p = 0.0002$) and 1 vs. 3 ($p < 0.0001$) [79.17 (72.83–87.83) mm Hg, 87.67 (80.67–96.00) mm Hg and 95.00 (89.33–104.00) mm Hg, respectively for groups 1, 2, and 3] (**Table 1B**). ABP did not differ between males and females ($p = 0.29$) (**Table 1B**). The multivariable linear model analysis revealed that age and sex were independently related to ONSD ($p < 0.0001$ and $p = 0.005$, respectively) (**Table 2**).

TBI Patients

We did not find a significant correlation between ONSD and age ($R = 0.13$, $p = 0.20$) (**Figure 1C**) or ABP and age ($R = -0.04$, $p = 0.68$) (**Figure 1D**). For illustrative purposes, the cases presenting ICP > 20 mm Hg are highlighted in blue in **Figures 1C,D**. No differences in ONSD were found among females and males of different age groups [5.2 (4.3–6.2) mm vs. 4.4 (3.9–5.0) mm ($p = 0.08$), respectively] (**Figure 2D**) (**Table 1A**). Moreover, ONSD was not significantly different among the age groups (**Figures 2E,F**) (**Table 1A**). ABP did not differ across the age spectrum or sexes (**Table 1B**). In this cohort, ICP was below the threshold for intracranial hypertension at patient admission (ICP > 20 mm Hg) (**Table 1C**), except for 5 cases (4 patients in the ICP range of 20–22 mm Hg and one with ICP > 70 mm Hg). The multivariable linear model analysis did not reveal any independently related variables to ONSD (**Table 2**). However, we observed borderline *p*-values for ABP and ICP ($p = 0.06$ and $p = 0.07$, respectively), which corroborates the positive and significant correlation between ONSD and these variables [$R = 0.25$ ($p = 0.01$) for ABP and $R = 0.42$ ($p < 0.0001$) for ICP; **Figure S1**].

Comparison Between Healthy Volunteers and TBI Patients

A statistically significant difference in ONSD was found between the population of healthy volunteers and TBI patients [4.2 (3.8–4.4) vs. 4.5 (4.0–5.4) mm ($p < 0.0001$), respectively], with no ABP difference between the two cohorts.

ONSD was significantly different within females [4.1 (3.6–4.2) mm vs. 5.2 (4.3–6.2) mm ($p < 0.0001$), respectively for volunteers and patients] but not within males [4.2 (3.9–4.6) mm vs. 4.4 (3.9–5.0) mm ($p = 0.12$), respectively for volunteers and patients] (**Figure 3A**) (**Table 1A**). Considering age differences, ONSD was significantly higher in TBI patients of groups 1 ($p < 0.0001$) and 2 ($p < 0.0001$) (**Figure 3B**) (**Table 1A**). Considering sex and age differences, ONSD was only larger in female TBI patients in comparison to female volunteers of age groups 1 and 2 ($p = 0.001$ and $p = 0.01$, respectively) (**Figure 3C**) (**Table 1A**).

DISCUSSION

In the present study, we found that: (1) in healthy volunteers, ONSD was larger in males compared to females and increased with age; (2) in TBI patients, sex and age did not affect ONSD. Our findings suggest that different ONSD cut-off values considering sex and age are not relevant for the non-invasive assessment of increased ICP in TBI patients.

Several studies have previously attempted to investigate the normal values of ONSD in healthy individuals. Generally, they

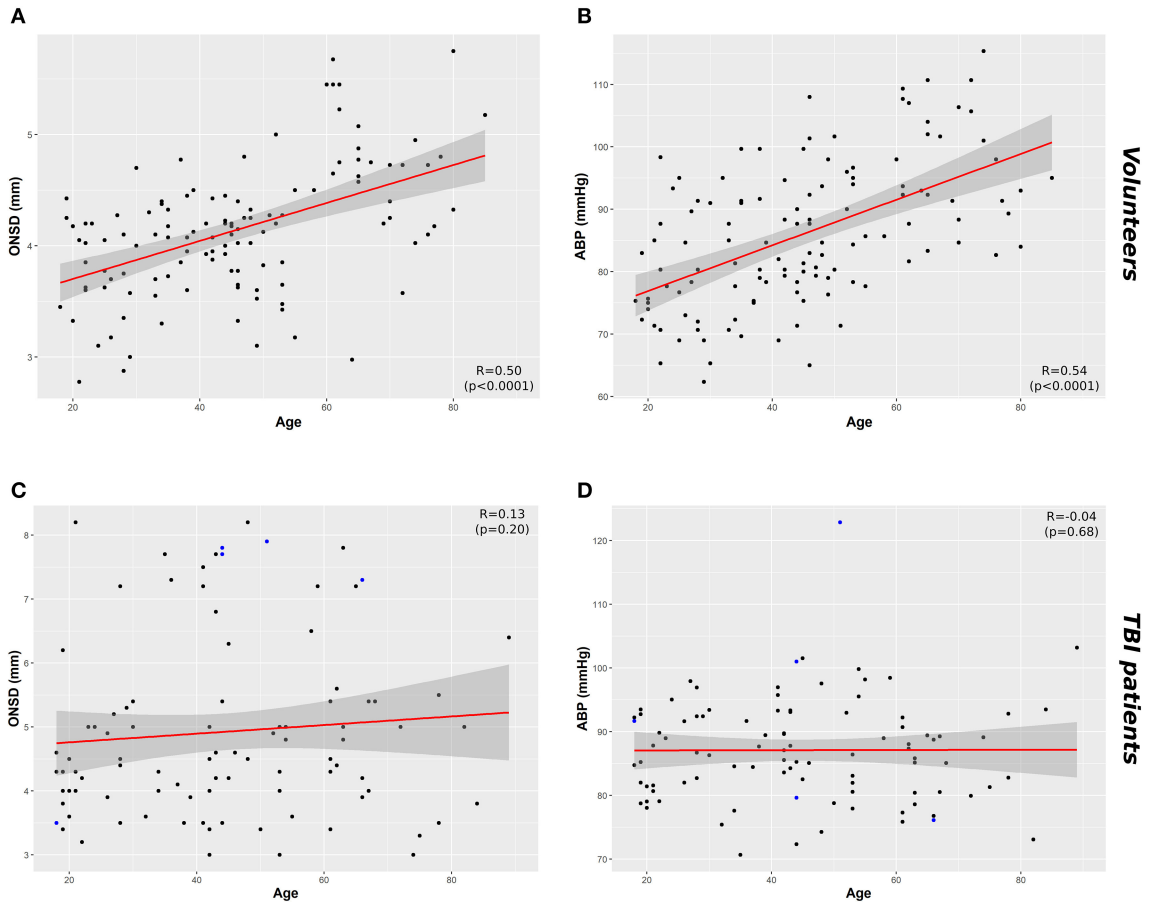

FIGURE 1 | Scatterplots of ONSD (mm) and ABP (mm Hg) in healthy volunteers and TBI patients. **(A)** Correlation between ONSD and age in healthy volunteers (R = 0.50, $p < 0.0001$) and **(C)** in TBI population (R = 0.13 $p = 0.20$). **(B)** Correlation between age and ABP in healthy population (R = 0.54, $p < 0.0001$) and **(D)** TBI population (R = 0.04, $p = 0.68$). Data points highlighted in blue in **(C)** and **(D)** indicate the cases in which ICP > 20 mm Hg. Dark gray shaded areas on the plots represent 95% confidence intervals for the linear regressions; ABP, arterial blood pressure; ICP, intracranial pressure; ONSD, optic nerve sheath diameter; TBI, traumatic brain injury.

have suggested that ONSD remains relatively constant during the adult life (12–17), however, our results indicate that ONSD increases with age. This finding could be related to age-related physiological changes in the cerebrospinal fluid circulation, such as increases in CSF stroke and forward flow volumes in elderly individuals (18), possibly leading to an increased CSF volume in the subarachnoid space surrounding the optic nerve which would then produce an enlarged ONSD.

Previously, Kim et al. (19) studied a cohort of 585 healthy adults, finding a significant correlation of ONSD with sex, height and eyeball transverse diameter (ETD) in a simple linear regression analyses, but multiple linear regression analysis revealed only ETD to be independently associated with ONSD. However, this study had the limitation of having recruited only young adults (18–30 years), therefore not considering age differences across the cohort. Goeres et al. (17) studied a population of 120 healthy adults, finding that mean ONSD did not vary with age, weight or height but varied with sex wherein males also presented significantly larger ONSD than females. On the other hand, a study in 400 Nigerian healthy adults (20) showed no significant correlation of ONSD with age, sex, height, weight and measurement side (right and left eyes). In regard to the effect of sex in healthy volunteers, few studies have explored the nature of this relationship and it appears to be associated with variations in optic nerve fiber density between sexes (21).

Other studies have suggested that the optimal ONSD cut-off relating to increased ICP should be tailored to different ethnic groups. For instance, Wang et al. (15) studied ONSD in 230 Chinese adults, finding that the upper ONSD limit was lower than those in previous studies in Caucasian and African populations. They also found that underweight women had the smallest ONSD values, underlining differences due to sex, body mass index and ethnicity. Maude et al. (13) found a relatively higher and narrower range of ONSD (4.24–4.83 mm) in a mixed cohort of healthy Bangladeshi adult and children in contrast to the ranges previously reported in western healthy volunteers [for instance, 2.5–4.1 mm in 50 UK adults (22) and 2.1–4.3 mm in 102 UK children (23)]. In this scenario, the potential issue of ethnic

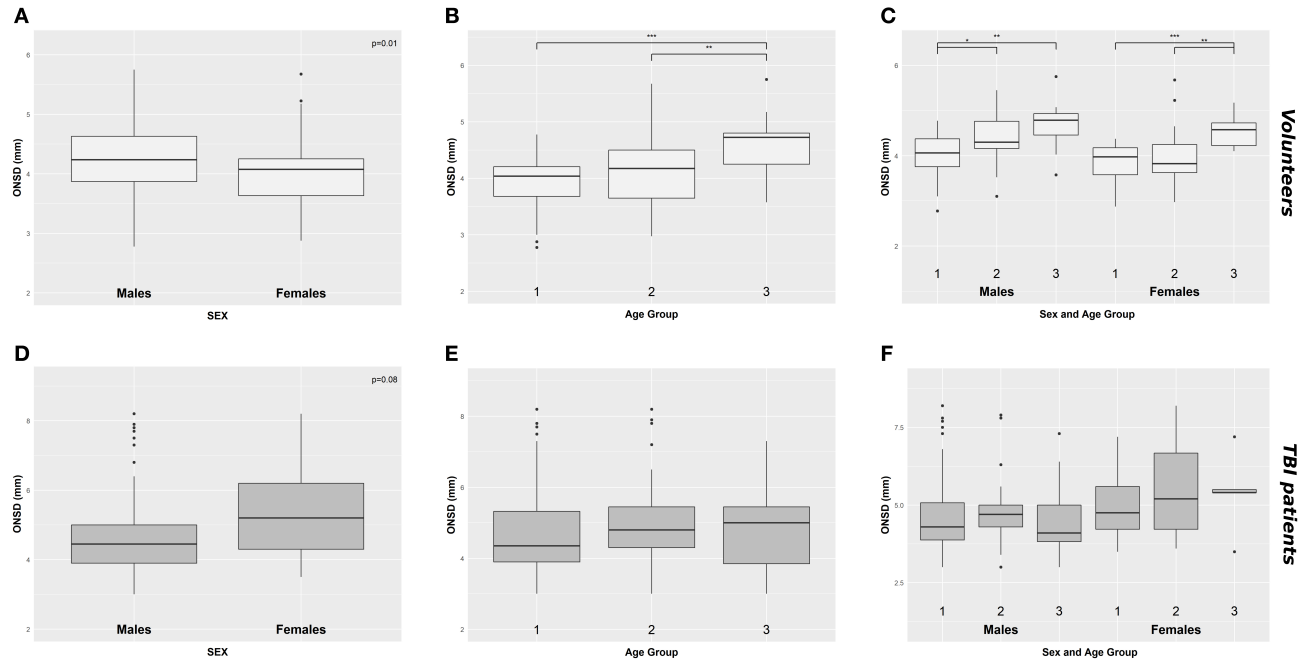

FIGURE 2 | Boxplot demonstrating the differences of ONSD in healthy **(A–C)** and TBI population **(D–F)** according to sex **(A,D)**, age groups **(B,E)**, and considering both sex and age **(C,F)**. ONSD, optic nerve sheath diameter; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; TBI, traumatic brain injury.

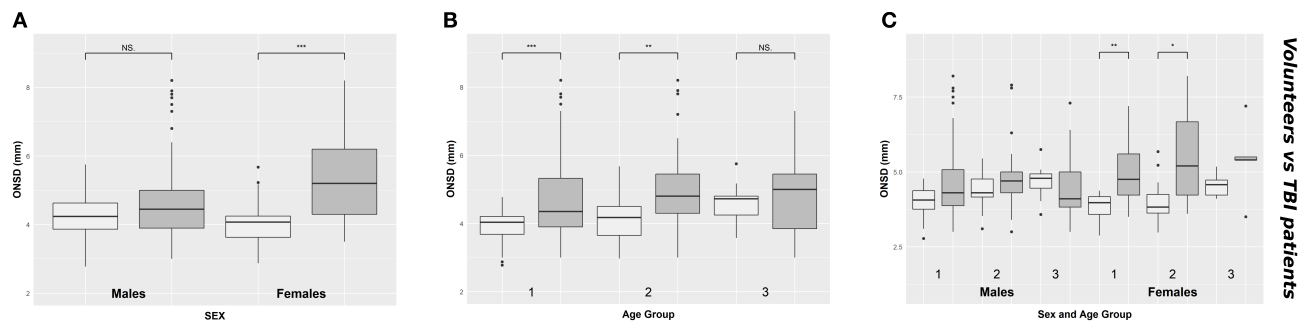

FIGURE 3 | Boxplot comparing healthy (light gray) and TBI patients (dark gray) values of ONSD, according to sex **(A)**, age groups **(B)**, and considering both sex and age groups **(C)**. ONSD, optic nerve sheath diameter; NS. indicates $p > 0.05$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; TBI, traumatic brain injury.

differences in ONSD should be pondered in the interpretation of our results.

A novelty of our study is the assessment of differences concerning sex and age in TBI patients. The importance of describing such differences in this group of patients relies on ONSD being extensively reported as a predictor of increased ICP. In addition, understanding whether an appropriate threshold should be considered to account for potential confounds of age and sex is fundamental to the application of this technique for the non-invasive assessment of ICP. However, there is an ongoing debate about the optimal thresholds of intracranial hypertension itself to be used in clinical practice and this uncertainty would further affect the cut-off for pathological ONSD values. Most studies have investigated ONSD values considering the threshold for intracranial hypertension as ICP > 20 mm Hg (8, 10, 24–26), whereas few others used a higher threshold (ICP > 25 mm Hg) (27, 28). Moreover, there is another element of heterogeneity attributable to some studies wherein the reference value was ICP > 20 cm H_2O or ICP > 25 cm H_2O instead of mm Hg (9, 29, 30), as these values are not equivalent (20 mm Hg corresponds to 27.19 cm H_2O, and 25 cm H_2O corresponds to 18.39 mm Hg). A recent meta-analysis that evaluated the diagnostic accuracy of ultrasound measurement of ONSD for the assessment of intracranial hypertension found that ONSD cut-off values varied from 4.80 to 6.30 mm (10). Therefore, given the intrinsic variability this parameter might present, ONSD should be considered more as a trend assessed over time rather than "a single number."

Furthermore, the conventionally accepted threshold for intracranial hypertension as ICP > 20 mm Hg (31) has been recently challenged due to discrepancies observed among different centers. For example, the DECRA trial randomized patients to decompressive craniectomy using an ICP threshold > 20 mm Hg even for a short duration (>15 min within 1 h-period) (32). In the RESCUE-ICP trial, patients underwent craniectomy when their ICP was sustained above 25 mm Hg for hours (1–12 h) (33). The latest American Brain Trauma Foundation guidelines for severe TBI proposed an ICP threshold of >22 mm Hg. This limit was derived from a single centre's (Cambridge, UK) retrospective study whose aim was not to determine a threshold for intracranial hypertension but to report an association between a single summary ICP value and 6 month outcomes after TBI (34). Moreover, Güiza et al. (35) showed that ICP is not only important as "a number" since the duration of intracranial hypertension has been associated with worse outcome, which supports the concept of "dose of ICP" (the magnitude and duration of ICP values above a pathologic threshold). In summary, there has not been a consensus about the optimal threshold for intracranial hypertension, and decisions regarding treatment and therapy escalation should be taken with a combination of ICP values, multimodal monitoring, clinical assessment and brain computed tomography findings (36).

In light of the above considerations, we demonstrated that different ONSD cut-off values considering age and sex do not appear to be relevant for the assessment of increased ICP in TBI patients. Similarly to the recommendations for determining a threshold for intracranial hypertension, ONSD should be assessed in combination with clinical findings as well as a trend over the course of patient management following the previously reported ONSD ranges associated with elevated ICP (10, 37).

Our study presents several limitations. Firstly, the data were collected by two operators in the two different centers. Although they were experienced and had equivalent level of training, we did not consider the interobserver variability as a potential confounder since the operators performed measurements in different individuals. Secondly, although reasonably expected in the TBI patient population given the heterogeneous incidence of this condition (38), the sample size of the TBI cohort was not homogeneous in terms of age and sex, and this could represent a source of bias. We also investigated whether age and sex alongside with ABP and ICP would be independently related to ONSD in a multivariable linear model analysis, based on the inference that TBI patients would present higher ONSD levels due to elevated ICP regardless of their age or sex. Nevertheless, none of these parameters were independently related to ONSD, which disregards ICP as a potential confounding factor. Moreover, in TBI patients, arterial blood pressure and intracranial pressure were actively controlled as part of the institutional management protocol, therefore the variability across individuals was small. In respect to age and sex not being independent predictors of ONSD in TBI patients, this could represent a type-I statistical error given the small sample size applied to a multivariable model adjusted for 4 variables (ICP, ABP, sex, and age). Finally, differences in ONSD values concerning ethnicity might be relevant in our comparison of healthy volunteers and TBI patients, and further studies with larger and more homogeneous recruitments are required to elucidate this potential confounding factor.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Research Ethics Boards of Genova, Italy (REC 031R8G2015) Research Ethics Boards at the University of Cambridge (REC 15/lo/1918). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

CR, DC, PH, and MC conceived the study design. DC and CR contributed to data acquisition, analysis, and/or interpretation. DC, CR, and KC drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the manuscript for submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2020.00764/full#supplementary-material

Figure S1 | Scatterplot of the relationship between ONSD and ICP in TBI patients. ICP, intracranial pressure; ONSD, optic nerve sheath diameter; TBI, traumatic brain injury; R indicates the Spearman correlation coefficient for this relationship.

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Deciding Under Uncertainty: The Case of Refractory Intracranial Hypertension

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A challenging clinical conundrum arises in severe traumatic brain injury patients who develop intractable intracranial hypertension. For these patients, high morbidity interventions such as surgical decompression and barbiturate coma have to be considered against a backdrop of uncertain outcomes including prolonged states of disordered consciousness and severe disability. The clinical evidence available to guide shared decision-making is mainly limited to one randomized controlled trial, the RESCUEicp. However, since the publication of this trial significant controversy has been ongoing over the interpretation of the results. Is the mortality benefit from surgery merely a trade off for unacceptable long-term disability? How should treatment options, possible outcomes, and results from the trial be communicated to surrogates? How do we incorporate patient values into forming plans of care? The aim of this article is to sketch an approach based on insights from *Decision Theory*, and specifically *deciding under uncertainty*. The mainstream normative decision theory, Expected Utility (EU) theory, essentially says that, *in situ*ations of uncertainty, one should prefer the option with greatest expected desirability or value. The steps required to compute expected utilities include listing the possible outcomes of available interventions, assigning each outcome a utility ranking representing an individual patient's preferences, and a conditional probability given each intervention. This is a conceptual framework meant to supplement, and enhance shared decision making by assuring that patient values are elicited and incorporated, the possible range and nature of outcomes is discussed, and finally by attempting to connect best available means to patient-individualized ends.

Keywords: traumatic brain injury, shared decision making, intracranial hypertension, intracranial pressure, decompressive craniectomy, expected utility

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Intracranial hypertension (IHT) has been associated with high mortality and poor outcomes after traumatic brain injury (TBI) (1, 2). Guidelines and experts advocate a "staircase" management approach wherein higher tiers involve therapies with higher propensity for adverse effects and a narrowing benefit to risk margin (3, 4). Clinical decision-making becomes particularly challenging for the 10–20% of patients refractory to first-line therapies (the requirement for stage-2 interventions increases the relative risk of death by 60%) (5). For these patients, rescue interventions include hypothermia, decompressive craniectomy (DC), and further metabolic suppression via barbiturate coma (BC) (6). The decision to offer a life-saving treatment for refractory IHT has to be balanced against great uncertainty in regards to functional outcomes

and quality of survival; it is to be made in conjunction with surrogate decision makers via shared decision making (SDM) for establishing patient-specific goals (7, 8). A recent international consensus convened to provide direction on the use of DC following TBI; participants almost unanimously recommended that before contemplating DC for refractory IHT, providers should conduct frank discussions with surrogates regarding the risks, benefits, and potential alternatives (9). However, no insights were offered on how these discussions should be structured, how the alternatives should be presented, and how the potential outcomes should be understood. Furthermore, no guidance was furnished on how patient values are to be weighed in on choosing among alternatives.

This article attempts to offer a conceptual framework to assist clinicians think through the available choices, and to incorporate patient preferences into shared decision-making deliberations in the setting of refractory IHT after TBI. The plan of the article is as follows: the first section reviews clinical evidence with a focus on the Randomized Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure (RESCUEicp), an international, multicenter, parallel-group, superiority randomized clinical trial (RCT), that compared last-tier secondary DC with continued medical management including barbiturate coma (10). The second section offers a deliberation scheme based on principles of *Decision Theory*. The third section applies insights from decision theory to the conundrum of choosing among alternatives, and advising surrogates in the case of refractory IHT after TBI. At the end, limitations are discussed.

EVIDENTIARY BASIS FOR ADDRESSING REFRACTORY IHT

RESCUEicp assessed the efficacy of DC after first- and second-tier therapies had failed to control refractory and sustained IHT in TBI patients. It is the only RCT that has aimed answering the clinical problem of *refractory* intracranial pressure (ICP) after TBI, and that allows a comparison of surgical decompression with most aggressive medical therapy including mild to moderate hypothermia and barbiturates [the preceding Decompressive Craniectomy -DECRA- trial is not analogous since it evaluated DC as an earlier measure to control ICP (11)]. RESCUEicp took over 10 years to complete, across 52 hospitals in 20 countries (although the majority of patients were enrolled in the UK). Such undertaking is unlikely to be repeated, and so this trial may serve as the only RCT-derived clinical guide (for the foreseeable future at least). The recruited cohort comprised TBI patients aged between 10 and 65 years, and ICP exceeding 25 mmHg for 1–12 h, despite first and second-tier measures for ICP control. The surgical treatment was a DC (either large unilateral frontotemporoparietal or bifrontal). The primary outcome measure was the Glasgow Outcome Scale-Extended (GOSE) at 6 months; 408 patients were recruited: 206 randomized to the surgical, and 202 to the medical group. At 6 months, the DC group had a significantly lower mortality rate compared to the medical group (26.9 vs. 49.9%). Surgery resulted into higher rates of vegetative state, lower severe and upper severe disability, but the rates of moderate disability and good recovery were comparable. Favorable outcome was pre-specified, and dichotomized at upper severe disability or better on the GOSE; 42.8% of surgical patients had a favorable outcome compared to 34.6% of medical patients ($p = 0.12$). At 12 months, 45.4% of surgical patients had a favorable outcome vs. 32.4% of medical patients ($p = 0.01$). It should also be noted that a large proportion (37%) of the medical treatment group did not achieve adequate ICP control and crossed-over to DC (the surgical crossover to BC was 9%).

Since the publication of the trial significant controversy has been ongoing over the interpretation of the results. Is this a positive trial for DC? Does the significant reduction in mortality merely translates to unacceptable long-term disability? How should these results be communicated to surrogates, and who should evaluate if an outcome is favorable or not? Critics of the trial objected that RESCUEicp did not follow the conventional definition of "favorable outcome" that is full independence at 6 months (12); under conventional dichotomization the proportion of patients with favorable outcomes would be similar for the two groups (27% at 6-months, and 32% surgical vs. 28.5% medical at 12-months). Others further argued that the point of comparison should be nothing less than disability-free survival, where there was no difference between the surgical and medical groups (9.8 vs. 8.4% at 12-months). According to such a criterion, surgery is not associated with any true long-term benefits; it only increases the number of patients in a vegetative state or suffering serious disability, and should therefore not be used (13). As a response, the investigators have in general defended DC under the premise that the unconventional dichotomization they chose was set a priori, and justified in view of these patients being in extremis. They have also argued that the final arbitrators of what is favorable or acceptable ought to be the patients, and their families (12, 14). The ensuing debate was highlighted early in the New England Journal of Medicine editorial for the trial (15). The authors of the editorial remarked that "quality of life is an individual determination, and it is important to engage surrogates in discussions that focus on patients' previously stated wishes and personal values". They called for *the development of more refined clinical decision-making tools*, although no such account has been offered.

PRINCIPLES OF DECISION THEORY: DECIDING UNDER UNCERTAINTY

Decision theory explores the reasoning underlying an agent's choices, whether this is a simple, trivial situation, or a far more involved, complex process as required in medical decision-making. A decision is said to be made *under ignorance* when no probabilistic information in terms of outcomes is available; the opposite prospect, where outcome probabilities are determined and known, refers to decision *under risk* (e.g., lotteries). In the real world, and in most medical decision-making, outcome probabilities are only partially determined, and with various degrees of confidence; this creates exemplary situations of *deciding under uncertainty* (16). Many lifesaving interventions

produce a variety of outcomes, and no one can predict precisely where a particular patient will end up. Concurrently, it is extremely hard to anticipate how patients (and their caretakers) will evaluate and adapt to outcomes that leave them with various degrees of disability. We should also remain skeptical of disability-free or neurotypical peoples' capacity to predict how patients will evaluate these outcomes; this relates to the *disability paradox*, a significant underestimation (among able-bodied people) of actual quality of life associated with a certain disability (17). Relevantly, the disability paradox has been documented in surveys showing a disparity between what is considered a favorable outcome among healthy adults and patients treated with surgical decompression (18, 19).

In neurocritical care, we need a model for rationally guiding decisions applicable to situations that combine high degrees of multi-dimensional uncertainty over life-altering high-stake outcomes (20). The mainstream normative decision theory, Expected Utility (EU) theory, essentially says that, *in situ*ations of uncertainty, one should prefer the option with greatest expected desirability or value (21, 22). This article employs EU as a normative theory—that is, a theory of how people should make decisions (this differs from the approach in classical economics, where EU is often used as a descriptive or predictive theory). Roughly, we say that an agent "prefers" one option over another just in case, for the agent in question, the former is more desirable or choice-worthy than the latter. As one investigates rational preferences over prospects, the measurement of preference orderings will become important. The measures in question are known as *utility functions*. As long as the set of prospects is finite, any order can be represented by an ordinal utility function. The term U(O) represents the utility of a certain outcome—roughly, how valuable it is. Formally, U is a function that assigns a real number to each of the outcomes (the units associated with U are typically called *utiles*). The greater the utility, the more valuable the outcome. Assigning utilities to these options forces us to compare them. To say that X has greater utility than Y (for an agent) is simply to say that the agent prefers X to Y [to demonstrate, say that u is a utility function, it follows $u(X) > u(Y)$]. This is a depiction of how the preference relation can be represented as maximizing utility, since it favors the option with highest utility. The expected utility of an act is a weighted average of the utilities of each of its possible outcomes, where the utility of an outcome measures the extent to which that outcome is preferred, or preferable, to the alternatives. The utility of each outcome is further weighted according to the probability that the act will lead to that outcome. EU provides a way of ranking the acts according to how *choiceworthy* they are: the higher the expected utility, the better it is to choose the act.

Based on this framework, we can now rigorously define expected utility of possible medical interventions. The expected utility of an intervention i (in our scenario DC or BC) depends on two features of the problem: the value (how desirable it would be) of each outcome for the patient, and the probability of each outcome conditional on each intervention. Given these features, the expected utility of an i, EU(i), for different outcomes (O) can be conceptualized as a function of the product of the probability of a certain outcome $P_i(O)$ and *utility* of the outcome U(O). Following this, one could derive EU(DC) and EU(BC) for the different Glasgow Outcome Scale outcomes [this would lead to directly comparable expected utilities as for e.g., $EU_{GOSEx}(DC)$ vs. $EU_{GOSEx}(BC)$]. For our purposes, will be employing intervention-contingent outcome probabilities as degrees of belief warranted by the evidence provided in RESCUEicp [see Table 3 in the original publication, reference (10)]. The *utility* of outcomes will be derived according to the values of the patient as elicited via SDM with surrogates. Even if it would be impossible to assign numeric values to these preferences, we can still use them as comparative modifiers in deriving expected utilities for the different interventions. The next section examines different patient-value preferences to exemplify how EU theory can rationalize SDM in the setting of refractory IHT.

DECISION THEORY AND DECOMPRESSIVE CRANIECTOMY

The definition of shared decision making, as endorsed by the American College of Critical Care Medicine, is "a collaborative process that allows patients, or their surrogates, and clinicians to make health care decisions together, taking into account the best scientific evidence available, as well as the patient's values, goals, and preferences" (7). There are multiple nuances to this process, and merely "sharing" decision-making may not fulfill the above definition. Importantly, clinicians should be aware of cognitive biases (affecting clinicians and surrogates) that may operate at an unconscious level yet may influence behavior and potentially the care provided (8, 23). Cognitive biases and heuristics can affect SDM by distorting the understanding of the nature of a certain choice or decision and the foreseeable consequences (24, 25). A decision-theoretical model could shield SDM against biases, and enhance it by providing a method to rank available choices according to patient-specific values. What follows is an application of EU-guided decision-making to two refractory IHT scenarios as informed by different patient/surrogate preferences. For both scenarios, further action (in the form of DC or BC) is to be understood as primarily life-preserving in the sense that without it there is very high likelihood that the patient will die. Surrogates ought to be also informed that although these interventions confer a significantly higher chance for survival, possible outcomes are highly uncertain and include the potential for prolonged, and severe, physical and neurocognitive disabilities. The first scenario is one where the patient would foremost opt for the intervention associated with the highest chances for preserving life. In the second scenario, the patient would foremost opt for the intervention associated with the highest chances for functional independence. Preferences focusing on saving life, or on functional independence are the most common considerations that come up in neurocritical care family conversations. In emergency situations involving life-threatening neurologic illness, people want to know what can be done to preserve life, and also if a certain intervention or treatment paradigm can restore as much as possible of premorbid function. A clinical

caveat to be recalled is that age (RESCUEicp had an age limit of 65) and comorbidities may affect eligibility, risk, and outcomes of anti-IHT treatments.

Preserve Life

Formally, in terms of EU theory, the utilities of different outcomes can be represented by $U_{GOSE2-8} > U_{GOSE1}$. Outcomes from RESCUEicp (understood as probability distributions contingent to each intervention) show that DC confers a 22% absolute risk reduction for mortality, and a number needed to treat of 5; it follows that $EU_{GOSE2-8}(DC) > EU_{GOSE2-8}(BC)$. For this preference ranking, decompressive craniectomy is the rational choice to make in line with the value to foremost preserve life.

Functional Independence

Here, the utilities of different outcomes is represented by $U_{GOSE5-8} > U_{GOSE1-4}$. By using the outcomes distribution, it appears that $EU_{GOSE5-8}$ (DC) $\approx EU_{GOSE5-8}$ (BC). The two interventions have similar chances leading to an outcome of functional independence. It would be important though to further understand if the patient would consider a life of functional dependence as a life not worth living. Such a stance would favor the intervention associated with higher mortality but less vegetative state and severe disability, meaning BC (DC increases the absolute risks for vegetative state by 6%, and severe disability by 15%). A difficult dilemma would remain in the case of refractory IHT despite BC (recall the 37% cross over). RESCUEicp results are based on intention-to-treat analysis; it would be very helpful to have specific empirical data on the outcomes of patients who crossed-over to surgery. The argument has been made that if a substantial portion of these patients went on to make favorable long-term recoveries that would be grounds to argue in favor of DC. Otherwise, support for surgery would be seriously called into question (26).

Accepting Upper Severe Disability

The verdict would again change for another patient who would minimally accept up*per se*vere disability (GOSE 4). This is somebody who would value their independent ability to spend time at home, even if this would entail total dependency on others for outside activities. This approach introduces a *maximin rule* ("maximize the minimum" regret or loss to well-being) where via SDM we would attempt eliciting the minimally acceptable vs. death outcome for a given patient. If this threshold is set at up*per se*vere disability, that would favor DC as the recommended strategy (**Figure 1** offers a depiction of the above process and conclusions; **Box 1** provides a case example to illustrate the process).

LIMITATIONS

The presented model purports to offer a "formula" for guiding decision-making based on ranking of outcomes according to patient values, together with probabilistic information of alternative interventions associated with these outcomes. An objection is that it leaves out potentially relevant considerations that should weigh in, such as social utility, allocation of scarce resources, and cost-benefit analyses (27, 28). These are indeed important variables, however the multidimensional uncertainty (empirical and ethical) that surrounds the care of acutely brain-injured patients complicates significantly any effort to incorporate such considerations early on. Nevertheless, there is little doubt that SDM would significantly benefit from data on identifying patient and injury phenotypes that would recommend them for one treatment approach over another, and reliable predictors of longer-term outcomes. Saliently, these outcomes should be evaluated from the perspectives of patients, their families and caretakers (29). RESCUEicp has provided 6 and 12-month outcomes; ongoing planned analysis is anticipated to provide 24-month outcomes. Natural history of recovery from brain injury can be significantly longer than what is usually recorded and reported. Contemporary series with extended follow-ups provide encouraging data in terms of recovery potential beyond the first year from injury, and show that GOSE categories as reported from trials are not necessarily static end-states (30, 31). In terms of DC, surrogates should be also informed about the need of additional future surgery such as cranioplasty, which carries both promise in terms of neurologic function improvement, and concern due to its own moribidity and complications (32). Finally, any use of outcome probabilities directly from RESCUEicp, as priors, should take into account the particularities of the trial, some mentioned earlier; in addition, one should consider the technical fact that most decompressions in the trial were bifrontal vs. unilateral.

CONCLUSION

A most challenging clinical conundrum arises in severe TBI patients who develop life-threatening intractable intracranial hypertension. For these patients, last tier, high morbidity interventions, such as surgical decompression or pharmacologic coma, have to be considered against a backdrop of uncertain outcomes including prolonged states of disordered consciousness and severe disability. The clinical evidence basis available to guide shared decision-making is limited. Concurrently, there are no decision aids that could assist in rationally navigating available options, describing the nature and range of outcomes to surrogates, and incorporating patients' values into goals of care. The aim of this article has been to sketch such an approach employing insights from Expected Utility theory. The steps required to compute expected utilities include listing the possible outcomes of available interventions, assigning each outcome a utility ranking representing an individual patient's preferences, and a conditional probability given each intervention. This is not an algorithmic procedure meant to substitute for involved and nuanced shared-decision making, nor it promises to solve difficult real-world clinical dilemmas by a simplistic calculus like process. It is meant to supplement, and enhance SDM by assuring that patient values are elicited and incorporated,

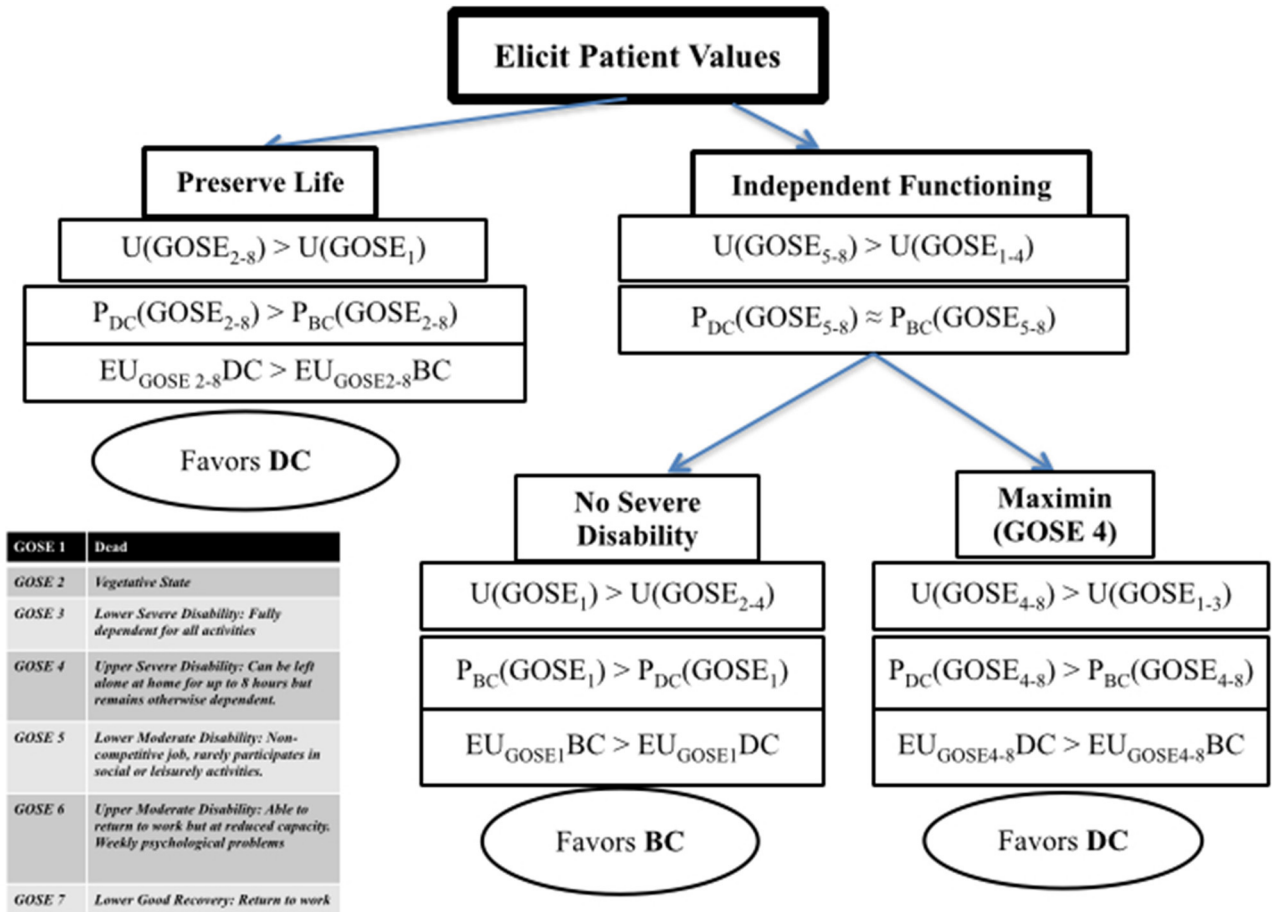

FIGURE 1 | Expected utility guided decision making for refractory intracranial hypertension. U, utility of an outcome; GOSE, Glasgow Outcome Scale-Extended; P, probability of an outcome; EU, expected utility (function of the product U and P); DC, decompressive craniectomy; BC, barbiturate coma.

BOX 1 | Case Example.

A 57-year-old man was admitted with severe diffuse TBI after a car accident, and developed refractory ICP despite first and second tier measures. An urgent family meeting was held. His surrogates described the patient as someone who lived alone mostly spending his time reading at home, who would also enjoy visits from friends and family, and who would also seek opportunities to travel. He had consistently said that he would prefer to be dead than vegetative, but no advance directive existed. As the next step in management, the medical team discussed the options of either a decompressive craniectomy or barbiturate coma for control of ICP; the family was informed about the results of a recent clinical trial showing that for every 100 patients treated with DC rather than barbiturates, there were 22 more survivors; of these, six were in a vegetative state, and the other 16 were dependent on daily support for combinations of cognitive and physical disabilities. Family members disagreed about the best course of action.

In applying the flowchart from **Figure 1** for this patient, one would have to follow the "independent functioning" path since this patient's previously expressed wishes were against preserving life at all costs as he considered survival in a vegetative state as worse than death. Here, the family was further asked what possible level of dependency the patient would potentially deem acceptable, if any. The more direct question to the family was if partial dependency with the ability to have unsupervised hours at home would be acceptable. The family was also informed that the patient could potentially achieve further functional improvement, however this was highly uncertain at the time being. Surrogates agreed that a functional state of home-independency, even if dependent for outside activities, would not be against the patient's wishes and interests. Such a stance would lead to the "Maximin" side of the chart, recommending a DC as the action maximizing expected utility in this scenario, for this patient (this is only an example illustrating how one could consult an EU-inspired approach to decision-making; it is meant to complement a further nuanced approach that would include patient-specific features such as neuroimaging and multimodality monitoring data, other organ-system function and co-morbidities, as well as family and social factors that could impact long term care).

the possible range and nature of outcomes is discussed, and finally by attempting to connect best available means to patient-individualized ends.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

CL conceived and drafted the manuscript.

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The Association Between Peri-Hemorrhagic Metabolites and Cerebral Hemodynamics in Comatose Patients With Spontaneous Intracerebral Hemorrhage: An International Multicenter Pilot Study Analysis

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Background and Objective: Cerebral microdialysis (CMD) enables monitoring brain tissue metabolism and risk factors for secondary brain injury such as an imbalance of consumption, altered utilization, and delivery of oxygen and glucose, frequently present following spontaneous intracerebral hemorrhage (SICH). The aim of this study was to evaluate the relationship between lactate/pyruvate ratio (LPR) with hemodynamic variables [mean arterial blood pressure (MABP), intracranial pressure (ICP), cerebral perfusion pressure (CPP), and cerebrovascular pressure reactivity (PRx)] and metabolic variables (glutamate, glucose, and glycerol), within the cerebral peri-hemorrhagic region, with the hypothesis that there may be an association between these variables, leading to a worsening of outcome in comatose SICH patients.

Methods: This is an international multicenter cohort study regarding a retrospective dataset analysis of non-consecutive comatose patients with supratentorial SICH undergoing invasive multimodality neuromonitoring admitted to neurocritical care units pertaining to three different centers. Patients with SICH were included if they had an indication for invasive ICP and CMD monitoring, were >18 years of age, and had a Glasgow Coma Scale (GCS) score of ≤8.

Results: Twenty-two patients were included in the analysis. A total monitoring time of 1,558 h was analyzed, with a mean (SD) monitoring time of 70.72 h (66.25) per patient. Moreover, 21 out of the 22 patients (95%) had disturbed cerebrovascular autoregulation during the observation period. When considering a dichotomized LPR for a threshold level

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of 25 or 40, there was a statistically significant difference in all the measured variables (PRx, glucose, glutamate), but not glycerol. When dichotomized PRx was considered as the dependent variable, only LPR was related to autoregulation. A lower PRx was associated with a higher survival [27.9% (23.1%) vs. 56.0% (31.3%), $p = 0.03$].

Conclusions: According to our results, disturbed autoregulation in comatose SICH patients is common. It is correlated to deranged metabolites within the peri-hemorrhagic region of the clot and is also associated with poor outcome.

Keywords: autoregulation cerebral compliance, intracerebal hemorrhage, metabolism, hemodynamics, microdialyis

INTRODUCTION

Spontaneous intracerebral hemorrhage (SICH) accounts for almost 15% of all strokes worldwide, with the incidence rates of primary SICH in low- and middle-income countries being twice the rates compared to high-income countries (22 vs. 10 per 100,000 persons/year) in 2000–2008, and with case fatality rates of 30–48% in low- to middle-income countries and 25–30% in high-income countries (1, 2). The outcome of these patients is multifactorial, and poor outcomes are related to both metabolic and hemodynamic derangements. In fact, following SICH-induced acute brain injury, an imbalance of consumption, utilization, and delivery of oxygen and glucose, along with intracranial hypertension and a reduced cerebral perfusion pressure (CPP) which accompanies hematoma expansion, are responsible for secondary injuries (3–6). Monitoring these parameters in order to properly direct treatment is possible with cerebral microdialysis (CMD).

CMD, first introduced in 1966, aids clinicians in better understanding brain tissue metabolism in intensive care settings (7, 8). In particular, variations in the lactate/pyruvate ratio (LPR) may correspond to a mismatch between oxygen delivery and utilization, also influenced by hemodynamic variables.

Control of hemodynamic variables after SICH is in fact paramount in avoiding secondary brain injury. There is consensus regarding the fact that the initial dimension and growth of the hematoma can cause both primary and secondary tissue damage. The latter may be the consequence of a series of complications such as ischemia, brain edema, development of apoptotic processes, and toxic effects due to the degraded components of hemoglobin and complement activation (8). Additionally, although the exact pathophysiological mechanisms remain undetermined, cerebrovascular autoregulation (CA) derangement could play an important role in promoting additional brain injury, especially in the peri-hemorrhagic penumbra region, thus affecting outcomes (9–11).

Abbreviations: CMD, cerebral microdialysis; SICH, spontaneous intracerebral hemorrhage; LPR, lactate/pyruvate ratio; MABP, mean arterial blood pressure; ICP, intracranial pressure; CPP, cerebral perfusion pressure; CA, cerebrovascular autoregulation; PRx, cerebrovascular pressure reactivity; GOS, Glasgow Outcome Scale.

Based on the above-mentioned hypothesis, this study sought to evaluate the association between LPR and the hemodynamic [mean arterial blood pressure (MABP), intracranial pressure (ICP), CPP, and CA expressed by cerebrovascular pressure reactivity (PRx)] and metabolic variables (glutamate, glucose, and glycerol) within the peri-hemorrhagic penumbra region of the blood clot in comatose patients with SICH. Moreover, it explored the association of metabolic and hemodynamic variables with outcome.

METHODS

This was a multicenter cohort study regarding a retrospective dataset analysis of non-consecutive comatose patients who underwent multimodal monitoring following SICH. The study took place between April 2014 and June 2017 within three neurocritical care units: Spedali Civili University Hospital of Brescia, Columbia University New York Presbyterian Hospital Medical Center of New York, and the CHUV-Lausanne University Hospital and University of Lausanne, Switzerland. Patients were included if they: (1) had a diagnosis of SICH; (2) had an indication for invasive ICP and CMD monitoring; (2) were comatose with a Glasgow Coma Scale (GCS) score of $\leq$8 at enrollment; and (3) were >18 years old.

Patients were excluded if there were any contraindications for invasive intracranial catheter placement (e.g., an INR >2 or a platelet count <100,000/mL), moribund patients, and age <18 years.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Brescia Ethics Committee. In Brescia, patients' informed consent was waived due to the fact that the Italian legislation lacks a clear definition of what is considered a legal representative of temporarily incapacitated adult patients (12). Informed consent was therefore obtained from the patients once, and if, they regained mental competency. Regarding the Lausanne center, waiver of consent was authorized since the study consists of a retrospective dataset analysis of standard-of-care procedures, and at the Columbia center, the University Institutional Review Board approved the collection and analysis of data and a data-sharing agreement was executed.

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed for reporting the results of this cohort study (13).

Patient Management

All patients were intubated and mechanically ventilated during the entire monitoring period, and arterial blood gas samples were obtained every 2 h in order to maintain a target range of end-tidal carbon dioxide [etCO2] between 35 and 45 mmHg. Intravenous midazolam or propofol and fentanyl were used for analgo-sedation, and, if required, a muscle relaxant was added. Therapy was aimed at maintaining systolic arterial blood pressure (SABP) between 140 and 160 mmHg and a mean MABP <130 mmHg according to current guidelines (14). When necessary, antihypertensive or catecholamine therapy was used to reach the arterial blood pressure (ABP) target range. ICP and CPP were maintained respectively at <20 mm Hg and between 50 and 70 mmHg, depending also on PRx-based optimal CPP values. The diagnostic and therapeutic strategies for the patients enrolled were not modified by this study.

Hemodynamic and Neuro-Monitoring

Systemic hemodynamic monitoring consisted of invasive ABP from the radial artery, continuous electrocardiography, and pulse oximetry (Edwards Life Sciences, Irvine, CA). For all three centers, the decision to apply the multimodality monitoring [invasive ICP and microdialysis (MD)] was made based on an individual case decision, according to the neurosurgeon, and on intensive discussion. Intracranial pressure monitoring was performed either by means of an intraparenchymal fiber-optic transducer (Camino Laboratories, Integra NeuroSciences, San Diego, CA) or through catheter insertion into the brain ventricles and connected to an external pressure transducer and drainage system (Codman, Johnson & Johnson Medical Ltd., Raynham, MA).

Microdialysis

The MD catheters (membrane length, 10 mm; CMA 70,71 CMA Microdialysis, Sweden) were implanted either through tunneling or following burr hole and bolt insertion and were positioned within the brain tissue surrounding the clot, corresponding to the metabolic/ischemic penumbra. To ensure correct placement of the probes within the peri-hematomal region, a brain CT scan was performed following CMD catheter placement. The catheters were perfused with artificial cerebrospinal fluid at a rate of 0.3 μL/min and the samples were collected in microvials for analysis at 1- to 2-h intervals immediately after collection. The samples were analyzed for glucose, pyruvate, lactate, glutamate, and glycerol using the ISCUS Clinical Microdialysis Analyzer (CMA Microdialysis, Sweden). The first sample obtained following catheter placement was discarded since the measurements may have been altered by tissue trauma induced by the catheter insertion itself.

Multimodal Monitoring

For multimodal data acquisition and calculation of the derived indices, we used the Intensive Care Monitoring software system (ICM+®, Cambridge Enterprise, UK) running on bedside laptop computers. Simultaneous recordings of analog signals from the ICP and ABP signals were digitalized with an analog-to-digital converter, sampled (sampling at 50 Hz) and averaged every 5 s. Artifacts were manually detected and removed. In the Brescia and New York centers, CA assessment was measured continuously through the calculation of the PRx every 60 s as a Pearson's correlation coefficient between 30 consecutive samples of the mean arterial pressure and ICP and was evaluated as a variable index, changing in time along with ICP, CPP, and arterial pressure, as described by Smielewski et al. (15). This coefficient represents an index of covariance ranging from −1 to 1; a PRx >0.2 is indicative of a defective CA (16). Regarding the Lausanne center, PRx was not available; therefore, the correlations between the mean arterial pressure and ICP were calculated *a posteriori* after the data were derived retrospectively from the patients' database. We adopted this same threshold to define defective CA because no specific threshold was available for SICH patients during the time this study was conducted. The data acquired from the patients' MD values in relation to CA were used for research purposes only and did not influence the clinician's therapeutic strategy.

Outcome

The primary outcome was to evaluate the correlation between LPR and metabolic and hemodynamic variables, measured in the peri-hemorrhagic area of the SICH. The secondary outcomes were the Glasgow Outcome Scale (GOS) score and mortality at 6 months, obtained retrospectively.

Statistical Analysis

The data derived from the CMD analyzer were visualized through the LAB Pilot software (Solna, Sweden). For each patient, the consecutive values of pyruvate, lactate, glycerol, glutamate, and glucose were gathered and the LPR was derived. The data obtained were transferred to an Excel spreadsheet containing the registration of MAP, ICP, CPP, and PRx every minute. The hourly mean hemodynamic variables (MAP, ICP, CPP, and PRx) were compared to the metabolic variables acquired every hour with CMD.

We expressed continuous variables as mean (standard deviation, SD) for the normally distributed variables or median (interquartile range, IQR) for the non-normally distributed variables. Qualitative variables were expressed as frequencies and percentages.

To compare the different collected covariates between centers, a linear mixed-effects model (package lme4 in R) has been used to compare continuous variables in order to take into account the repeated patient measurements nested in each center, whereas ordered logistic regression for repeated measures was used to compare the GOS scores.

Concerning the unadjusted analysis, LPR was firstly dichotomized into normal and abnormal values (cutoffs of 25 and 40), as well as PRx (normal value ≤0.2), and a generalized mixed-effects model with a single variable was used including both CMD and the hemodynamic covariates. Alternatively, the dichotomized LPR and PRx were considered as dependent variables and each CMD and hemodynamic covariate as independent variables, and patients were considered nested in the center as a random effect (package nlme).

TABLE 1 | Demographic, hemodynamic, microdialysis, and outcome data divided by centers.

Variables	Columbia ($n = 8$)	Italy ($n = 9$)	Lausanne ($n = 5$)	Total mean values	p-Value
Age, mean, SD (years)	74.75 (6.80)	73.11 (5.90)	53 (17.23)	67.88 (13.61)	0.0064
Admission GCS, median (IQR)	7 (5)	3 (1)	4 (2)	4 (4)	0.001
HEMODYNAMIC DATA					
PRx, mean (SD)	0.04 (0.23)	0.15 (0.24)	−0.016 (0.307)	0.036 (0.284)	0.130
MABP, mean (SD)	112.08 (18.22)	99.77 (15.28)	87.24 (7.89)	96.73 (16.80)	0.926
ICP, mean (SD)	14.01 (9.58)	12.61 (7.23)	10.88 (5.59)	12.06 (7.27)	0.195
MICRODIALYSIS DATA					
LPR	35.27 (18.14)	25.05 (14.15)	36.43 (17.22)	33.263	0.833
Lactate	4.83 (1.77)	3.393 (2.23)	6.14 (3.97)	5.021	0.855
Pyruvate	144.71 (56.00)	132.96 (23.19)	167.92 (62.30)	151.23	0.837
Glucose	0.82 (0.57)	2.05 (1.19)	1.38 (0.70)	1.346	0.833
Glutamate	40 (2.65)	34.62 (19.41)	63.61 (71.63)	50.06	0.728
Glycerol	63 (4.35)	110.20 (139.25)	244.97 (180.79)	193.27	0.051
OUTCOMES					
GOS at 6 months, median (IQR)	NA	3 (2)	3 (2)	3 (2)	0.212
Survivors, *n* (%)	2 (25%)	3 (33%)	2 (40%)	7 (32%)	0.918

GCS, Glasgow Coma Scale; PRx, cerebrovascular pressure reactivity; MABP, mean arterial blood pressure; ICP, intracranial pressure; LPR, lactate/pyruvate ratio; GOS, Glasgow Outcome Scale; NA, not available.

Lme4 R package was used to perform an adjusted analysis using a linear mixed-effects model of the relationship between LPR and MD and CA variables, adjusted for age and admission GCS (17). An empty model was first performed (using only the intercept for LPR), and then the fixed effect was then added followed by the random effects. As a fixed effect, PRx was entered first, followed by glucose, glutamate, glycerol, age, and GCS. As a random effect, the intercept for patients nested in the centers was added. ANOVA comparison between all the resulted models was performed in order to choose the final model, for which the p-values for fixed effect were obtained through Satterthwaite's method (lmerTest package).

For patients' outcomes (mortality and GOS), we first dichotomized GOS into unfavorable (GOS $\leq$ 3) and favorable (GOS $>$ 3). In order to see whether there were any differences in the hemodynamic or CMD covariates, we ran an unadjusted analysis using a linear mixed model. The dichotomized GOS or mortality was used as a fixed effect, each of the hemodynamic or CMD covariates as dependent variables, and patients nested in the center as random effects. Verification of the results was performed with ANOVA for repeated measures with the function aov in R.

RESULTS

The multimodal monitoring data were obtained from a total monitoring time of 1,558 h, with a mean (SD) monitoring time of 70.72 h (66.25 h) per patient. There were a total of 1,901 readings and an average of 79 readings per patient.

Patients' characteristics are represented in **Table 1**, divided by the participating centers. There was no statistically significant difference in the demographics, hemodynamic variables (PRx, MABP, and ICP), and the MD data between centers. Except for the admission GCS, there was a difference concerning the outcome variables between the two centers which provided GOS data (it was not possible to obtain GOS data from one of the three centers).

When considering a dichotomized LPR (25 or 40), except for glycerol, there was a statistically significant difference in all the measured variables PRx, glucose, and glutamate (**Table 2** and **Figure 1**). When dichotomizing PRx as the dependent variable, the unadjusted logistic mixed model shows LPR as the only CMD variable related to CA. Moreover, 21 out of the 22 patients (95%) had disturbed CA during the observation period (**Figure 2**). In the adjusted analysis using linear mixed-effects analysis, considering LPR as the dependent variable, the best model resulting from the ANOVA comparison was the one which included PRx, glucose, and glutamate (BIC = 3,585) as fixed effects and a random intercept for patients but not for centers (**Table 3**). Adding a slope random effect for patients and centers did not improve the model, and the ANOVA comparison between the null model with only random intercepts only and the final model yielded $\chi^2 = 517.51$, $p < 0.0001$. The correlation between PRx and LPR showed a significant variance in the intercepts across patients (SD = 8.66, 95% CI = 5.192–11.838), and visual inspection of the residual plots did not reveal any obvious deviation from homoscedasticity or normality. Worth noting is that, although the LPR difference between PRx <0.2 and >0.2 is statistically significant [33.33 (16.56) vs. 33.08 (19.74)], it is minimal and, therefore, may suggest that the PRx threshold chosen may not be the most clinically relevant in this population.

Regarding outcomes, surviving patients had a statistically significant lower PRx and spent on average less time with an abnormal PRx compared to patients who did not survive (27.9%

TABLE 2 | Unadjusted analyses for pathological and non-pathological LPR ratios with two different cutoffs and pathological and non-pathological PRx.

	≤25 (*n* = 383)	>25 (595)	*p*-Value	≤40 (518)	≥40 (460)	*p*-Value
Pathological and non-pathological LPR ratios						
PRx	0.008 (0.3)	0.076 (0.25)	0.0387	0.026	0.086	<0.0001
Glucose, mean (SD) (mmol/L)	1.85 (1.04)	1.00 (0.65)	<0.0001	1.57 (0.93)	0.68 (0.50)	<0.0001
Glutamate, mean (SD) (μmol/L)	21.22 (17.78)	90.80 (64.96)	0.001	25.15 (23.77)	126.56 (56.18)	<0.0001
Glycerol, mean (SD) (μmol/L)	115.00 (131.77)	267.75 (185.09)	0.218	175.08 (168.39)	253.17 (196.94)	0.6750
		≤0.2		**>0.2**		***p*-Value**
Pathological and non-pathological PRx						
LPR		33.33 (16.56)		33.08 (19.74)		0.039
Glucose, mean (SD) (mmol/L)		1.35 (0.96)		1.34 (0.86)		0.903
Glutamate, mean (SD) (μmol/L)		49.37 (58.16)		51.59 (50.14)		0.085
Glycerol, mean (SD) (μmol/L)		185.61 (182.75)		209.56 (167.99)		0.816

PRx, cerebrovascular pressure reactivity; LPR, lactate/pyruvate ratio.

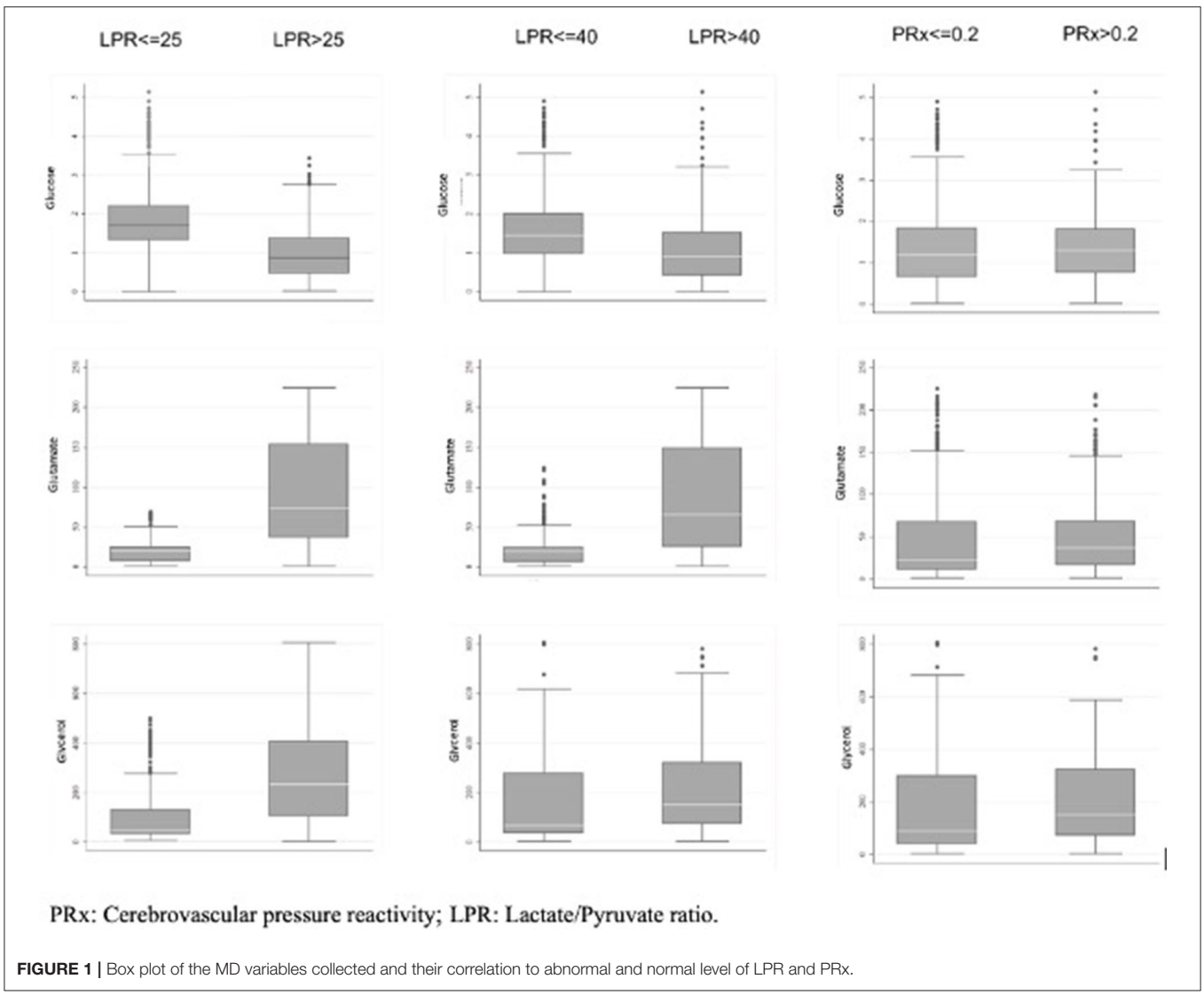

FIGURE 1 | Box plot of the MD variables collected and their correlation to abnormal and normal level of LPR and PRx.

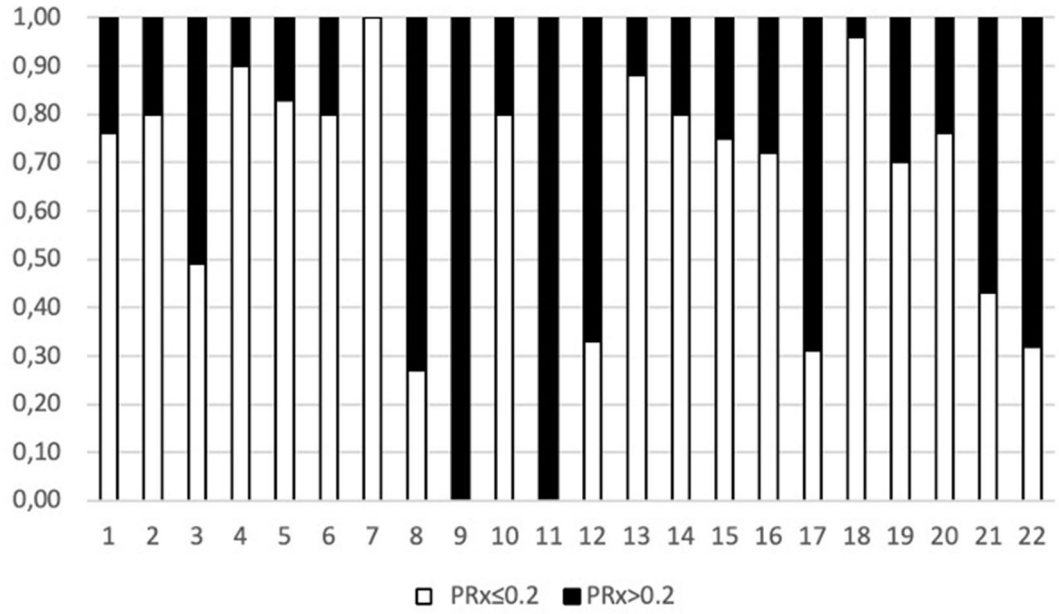

FIGURE 2 | Representation of percentage of time in which each patient had an abnormal PRx (>0.2).

TABLE 3 | Adjusted linear mixed-effects model for lactate/pyruvate ratio (LPR).

Variables	β	SE β	95% CI (β)	*p*-Value
Prx	1.65	1.05	−0.40 to 3.72	0.022
Glucose	−4.69	0.70	−5.70 to −3.69	<0.0001
Glutamate	0.15	0.015	0.12–0.19	<0.0001

The fixed effect coefficient for the final mixed model are represented along with the p-value.

of the total time vs. 56.0%, $p = 0.03$). Surviving patients had lower glycerol values, whereas the glucose level and the mean ABP (both higher in surviving patients) were at the limit of significance (**Table 4**).

DISCUSSION

In this multicenter retrospective observational cohort study performed in patients suffering from SICH, we confirmed the hypothesis that alterations in LPR may be correlated to the disturbance of CA (expressed as a PRx > 0.2) and to the glucose and glutamate levels. Patients who survived had a statistically significant lower PRx, spent less time with an altered PRx, and had lower glycerol and higher glucose values. Those who died had a higher LPR, higher ICP, and lower MABP values, although not statistically significant (**Table 4** and **Figure 1**).

For spontaneous intracerebral hemorrhage (ICH), there are only limited data available on dynamic autoregulation and CPP management, and so far, there are no data regarding autoregulation-based CPP management (18, 19). There was a statistically significant correlation between LPR and the measured variables (PRx, glucose, glutamate, and glycerol) present in both threshold levels of 25 and 40 (**Table 2**). Interestingly, the brain glucose concentrations were <1 mmol/L in the majority of patients with an LP ratio >25.

Multimodality monitoring in this study did not involve brain oxygenation (PbO_2), which possibly would have provided further insight toward the understanding of the various interactions between the metabolic and hemodynamic variables. The results from one study where the ICH patients were monitored with both PbO_2 and CMD suggest that this type of monitoring can demonstrate local derangements in the peri-hematoma cavity that are not reflected in global indices such as the PRx (20).

Recently, the existence of an ischemic penumbra in SICH patients has been challenged and a switch of concept from am ischemic to a metabolic penumbra was suggested, referring to the finding of an increased glucose metabolism in the peri-hemorrhagic region in the absence of ischemia (19, 21). The transient focal increases in glucose metabolism have been interpreted as signs of ongoing neuronal injury lasting for several days. Worthy of note is that the patients in our analysis with disturbed CA had the lowest glucose levels and those with a favorable outcome had higher values. The LPR was not independently correlated to the outcome.

The association between a low ABP and the outcome has been known for almost two decades (22, 23). Among the modifiable risk factors for SICH, arterial hypertension is the most frequent (24). Hypertension has been associated with early hematoma growth and poor outcomes in patients with spontaneous SICH (25). However, an excessively low ABP might cause cerebral hypoperfusion and ultimately lead to a poor outcome (24). Despite the important secondary outcomes found in recent trials, when attempting to establish the optimal ABP level following acute SICH, there was either a small

TABLE 4 | Unadjusted analysis of measured outcomes.

	Outcomes				*p*-Value	
	Death, *n* = 7 (mRS = 6, GOS = 1)	**Alive (*n* = 15)**	**Unfavorable GOS (*n* = 12)**	**Favorable GOS (*n* = 2)**	**Dead vs. alive**	**Favorable vs. unfavorable**
PRx, mean (SD)	0.12 (0.22)	0.03 (0.12)	0.085 (0.28)	−0.12 (0.17)	0.003	0.167
MABP, mean (SD) (mmHg)	82.77 (30.58)	97.80 (11.32)	95.31 (9.33)	88.80 (5.77)	0.071	0.878
ICP, mean (SD) (mmHg)	20.82 (26.17)	11.26 (4.92)	6.34 (4.74)	11.75 (4.590)	0.182	0.754
L/P ratio	30.44 (19.24)	34.52 (16.56)	32.73 (17.15)	18.28 (1.00)	0.092	0.437
Glucose, mean (SD) (mmol/L)	1.35 (0.57)	1.38 (1.10)	1.55 (0.82)	4.149 (0.23)	0.057	0.011
Glutamate, mean (SD) (μmol/L)	30.18 (27.09)	63.01 (64.72)	17.98 (1.49)	52.53 (57.20)	0.718	0.616
Glycerol, mean (SD) (μmol/L)	271.02 (191.96)	149 (97.9)	29.90 (1.23)	201.36 (178.65)	0.009	0.412

PRx, cerebrovascular pressure reactivity; MABP, mean arterial blood pressure; ICP, intracranial pressure; LPR, lactate/pyruvate ratio; GOS, Glasgow Outcome Scale (unfavorable, GOS ≤ 3).

benefit (INTERACT-2, Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial) or no benefit (ATACH-2, Antihypertensive Treatment of Acute Cerebral Hemorrhage II Study) when intensive systolic ABP reduction was compared with modest or standard BP reduction (24, 26). The more recent meta-analyses including studies investigating this issue yielded similar conclusions: aggressive ABP control in the acute phase of SICH is not beneficial. The 2018 European Society of Cardiology/European Society of Hypertension Guidelines for the management of arterial hypertension do not recommend treatment to immediately lower ABP in patients with acute SICH and a careful lowering of systolic blood pressure (SBP) to <80 mmHg *via* intravenous infusion may be considered only in patients with SBP ≥ 220 mmHg (14).

Disturbed CA in patients with SICH may worsen the effect of an excessively low ABP by increasing the lower threshold of CA below which cerebral hypoperfusion and ischemia ensue (25). Since substrate supply depends on cerebral blood flow, patients suffering from an impaired global autoregulation may be more vulnerable to secondary brain injury.

This study shows that SICH patients with disturbed CA and low blood pressure may be at risk of hypoperfusion and, therefore, of poor outcomes. Previous literature suggests that optimal CPP thresholds may be higher in SICH patients, adding further support that target directed CPP thresholds should be based on patient-specific monitoring parameters in order to individualize therapy (27).

Although the association of low MABP and high LPR with poor outcome, and *vice versa*, was reproduced in our study, whether low MABP and disturbed CA occurred simultaneously is not known.

Many factors may reduce the cerebrovascular autoregulatory reserve; however, studies showing CA as a consequence of cerebral metabolism dysfunction are lacking (28). There is literature questioning the presence of an ischemic penumbra, hypothesizing of the existence of important metabolic derangements in the tissue surrounding the clot. Although our results do not confirm the existence of a metabolic penumbra, the presence of disturbed glucose utilization may be the result of metabolic derangements near this region (21, 29, 30).

Limitations

The sample size was small, not predetermined, and the study included a highly selected population of SICH patients.

Some data comparing the different variables did not reach statistical significance. Therefore, these findings must be weighed critically, and only speculative conclusions can be drawn so far.

The study was an explorative retrospective analysis of non-consecutive patients pertaining to three different centers with data which were partially incomplete, for example the GOS, available in only two of the three centers. This study was not able to obtain sufficient data regarding the volume and size of the clot, which would have provided useful information regarding the neurological severity through grading scores such as the ICH score (31). Data regarding the APACHE or SAPS were also lacking from all three centers and therefore not included in the analysis.

The PRx threshold of 0.2, above which CA is considered to be altered, has been validated in traumatic brain injury (TBI) patients, but has not been extensively validated in patients with ICH (9).

Only the MABP was available for all three centers and not the SABP. However, MABP was fundamental in order to calculate PRx.

Finally, GOS was collected by chart review following telephone interview, therefore representing a retrospective collection of outcome.

Although accompanied by its limitations, this study helps set the base from which future large prospective trials may be designed, powered in order to confirm the results obtained. If so, multimodality monitoring which includes the measurement of metabolites and their correlation with CA would represent an important adjunct in avoiding secondary brain injury and help improve the outcomes in patients with SICH.

CONCLUSIONS

With its limitations, this study demonstrates that disturbed CA in comatose SICH patients is frequent and is associated with

deranged cerebral intraparenchymal metabolites. Moreover, a trend toward worse outcomes in patients with altered PRx was observed in our study.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Spedali Civili Comitato Etico. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

FR, NL, SPi, and SPa contributed to the study conception and design. FR, NL, SPi, SPa, IM, LG, MO, MM, DC, CR, and FT performed the data analysis and interpretation. FR, SPa IM, LG, and MO enrolled the patients for each corresponding study center. FR, NL, SPi, SPa, MO, MM, DC, CR, and FT revised the manuscript for important intellectual content. FR and NL gave final approval of the version to be published. All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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REVIEW
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Escalate and De-Escalate Therapies for Intracranial Pressure Control in Traumatic Brain Injury

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Severe traumatic brain injury (TBI) is frequently associated with an elevation of intracranial pressure (ICP), followed by cerebral perfusion pressure (CPP) reduction. Invasive monitoring of ICP is recommended to guide a step-by-step "staircase approach" which aims to normalize ICP values and reduce the risks of secondary damage. However, if such monitoring is not available clinical examination and radiological criteria should be used. A major concern is how to taper the therapies employed for ICP control. The aim of this manuscript is to review the criteria for escalating and withdrawing therapies in TBI patients. Each step of the staircase approach carries a risk of adverse effects related to the duration of treatment. Tapering of barbiturates should start once ICP control has been achieved for at least 24 h, although a period of 2–12 days is often required. Administration of hyperosmolar fluids should be avoided if ICP is normal. Sedation should be reduced after at least 24 h of controlled ICP to allow neurological examination. Removal of invasive ICP monitoring is suggested after 72 h of normal ICP. For patients who have undergone surgical decompression, cranioplasty represents the final step, and an earlier cranioplasty (15–90 days after decompression) seems to reduce the rate of infection, seizures, and hydrocephalus.

Keywords: trauma, intracranial hypertension (ICH), escalation, traumatic brain injury, staircase algorithm

INTRODUCTION

Traumatic brain injury (TBI) is a major public health problem, affecting ∼64–74 million people and causing 5 million deaths every year, although its true impact seems to be underestimated owing to incomplete data from developing countries (1). TBI carries high rates of hospitalization, morbidity, and mortality. Its pathophysiology is characterized by an elevation of intracranial pressure (ICP), followed by a reduction in cerebral perfusion pressure (CPP) with possible secondary brain damage (2, 3). Monitoring of ICP and surveillance of risk factors for secondary brain injury is recommended by international guidelines (2–4), despite a randomized multicenter international trial investigating monitored and non-monitored patients did not reveal substantial differences in term of

outcome (5). Besides, 23–89% of patients are managed without ICP monitoring both for limited resources and expertise, although this can occur also in high-resource countries (6, 7).

A step-by-step approach to treatment escalation, known as the "staircase approach" (3), aiming to obtain normal ICP values and adequate CPP as well as to reduce the risks of secondary damage is recommended for ICP management in patients who present an invasive ICP (inv-ICP) monitoring device (3, 4). Otherwise, in case of non-availability of ICP monitoring, the SIBICC Consensus Protocol for escalating treatments should be followed (6). Hence, two different approaches have been described to manage severe TBI patients, depending on the standard of care, resources-limit, and expertise: (1) pursuing the indications of inv-ICP monitoring, or (2) following brain imaging and clinical examination to escalate therapies. Even though inv-ICP monitoring is not easy to manage, it is recommended by most guidelines (3, 4, 6, 8, 9). Concerning inv-ICP placement, the Brain Trauma Foundation (BTF) and the 2019 SIBICC Consensus Conference leave the decision to the clinician, because previous recommendations were not as strong as needed—previous indications included patients with pathological findings on computed tomography (CT) and a Glasgow Coma Score (GCS) < 8, or impossibility to perform the neurological examination, and patients with normal CT-scan with unavailable neurological examination and two or more of the following risk factors: age > 40 years, hypotension, and abnormal flexion/extension in response to pain (4, 10). TBI is frequently complicated by HICP, which is defined as an increase in ICP over 20–22 mmHg (in inv-ICP monitored patients) (3, 4), while in non-invasively monitored patients who are managed according to imaging and clinical criteria, HICP can be suspected when one major or two minor criteria are met. Major criteria include compressed cisterns (CT classification of Marshall diffuse injury III), midline shift of more than 5 mm (CT classification of Marshall diffuse injury IV), and non-evacuated mass; minor criteria include GCS motor score ≤ 4, pupillary asymmetry, altered pupillary reactivity, midline shift 0–5 mm, and/or lesion of 25 or less cm^3 (CT classification of Marshall diffuse injury II). The risk of not monitoring ICP could be an overtreatment of patients with acceptable ICP and an undertreatment of patients with potentially harmful HICP (6, 11). Refractory HICP is defined as intracranial pressure that exceeds 22–25 mmHg for 30 min, or 30 mmHg for 15 min, or 40 mmHg for 1 min (12), and this is the recommended ICP threshold to pursue more aggressive therapies (3, 4). According to the most recent guidelines for the management of TBI, the treatment of HICP is divided into several steps, until the most aggressive including surgical decompression (4, 9, 10). A main concern in neurointensive care unit practice remains how to manage and de-escalate the employed therapies once ICP and CPP targets have been achieved. In fact, each step of treatment escalation carries potential side effects (e.g., hypotension, infection, pneumonia, brain ischemia, electrolyte, and fluid disturbances), frequently related to the duration of treatment (3). Although the management of intracranial hypertension has been widely explored in literature, little evidence is available for withdrawing these treatments and returning to baseline condition.

Therefore, the aim of our narrative review is to briefly describe current practice for the management of intracranial hypertension and to analyze how and when it is recommended to de-escalate HICP therapies in patients with severe TBI, with or without inv-ICP monitoring.

ICP PATHOPHYSIOLOGY

The normal ICP value in adults is around 15 mmHg, increasing physiologically during cough or sneeze. The skull is a closed and rigid container, whose volume consists of three components: cerebrospinal fluid, blood, and brain parenchyma. Cranial volumes and pressures are normally self-equilibrated and self-regulated, thereby keeping cerebral blood flow (CBF) constant in case of variation in any one of these compartments or additional volume. Under normal conditions, the compliance curve that describes the relationship between ICP and intracranial volume is exponential. In the first part of the curve, ICP increases slowly, then rises steeply when the compensatory systems are saturated (as in the case of CSF displacement through the foramen magnum, compression of the cerebral venous system, displacement of brain tissue, and herniation syndromes) (3, 8, 9). After TBI, these mechanisms occur in case of an ICP increase and progressive neurological deterioration. ICP values over 20 mmHg (2, 3, 13) or 22 mmHg (4) are considered pathological in adults, and should follow a conservative "staircase approach" or the surgical evacuation of any hematoma if present (3), with the goal of achieving CPP values between 60 and 70 mmHg (4). Any rise in ICP leads to CPP reduction; indeed, CPP is calculated as the mean arterial pressure minus ICP. CBF impairment may progress until the onset of inadequate oxygenation and ischemia (secondary brain injury), which can lead to cytotoxic edema, resulting in further increase in ICP (2–4, 9, 10). Brain trauma or metabolic impairment can cause tissue ischemia, leading to failure of the sodium-potassium pump with subsequent water influx into the cells, followed by brain swelling and lysis. Other compensatory mechanisms are activated after TBI, such as the sympathetic nervous system, which increases cardiac output and blood pressure and triggers systemic vasoconstriction (14). An overview of ICP pathophysiology is depicted in **Figure 1**.

INTRACRANIAL HYPERTENSION (HICP): HOW TO ESCALATE THERAPY

The standard management of intracranial hypertension after TBI includes an escalation of therapies, that consists of gradual steps of intervention, which could be skipped when

Abbreviations: AQP4, aquaporin-4; BBB, blood-brain barrier; BTF, Brain Trauma Foundation; CBF, cerebral blood flow; $CMRO_2$, cerebral metabolic rate of oxygen; CPP, cerebral perfusion pressure; CSF, cerebral spinal fluid; CT, computed tomography; DC, decompressive craniectomy; EEG, electroencephalographic; $ETCO_2$, end-tidal carbon dioxide; EVD, external ventricular drainage; FiO_2, fraction of inspired oxygen; GABA, gamma-aminobutyric acid; GCS, Glasgow coma scale; HTS, hypertonic saline; HICP, intracranial hypertension; ICP, intracranial pressure; Inv-ICP, invasive intracranial pressure; MAP, mean arterial pressure; MRI, magnetic resonance imaging; NWT, neurologic wake-up test; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; $PbtO_2$, brain tissue oxygen tension; SpO_2, peripheral saturation of oxygen; TBI, traumatic brain injury; THAM, tromethamine; VPS, ventriculoperitoneal shunt.

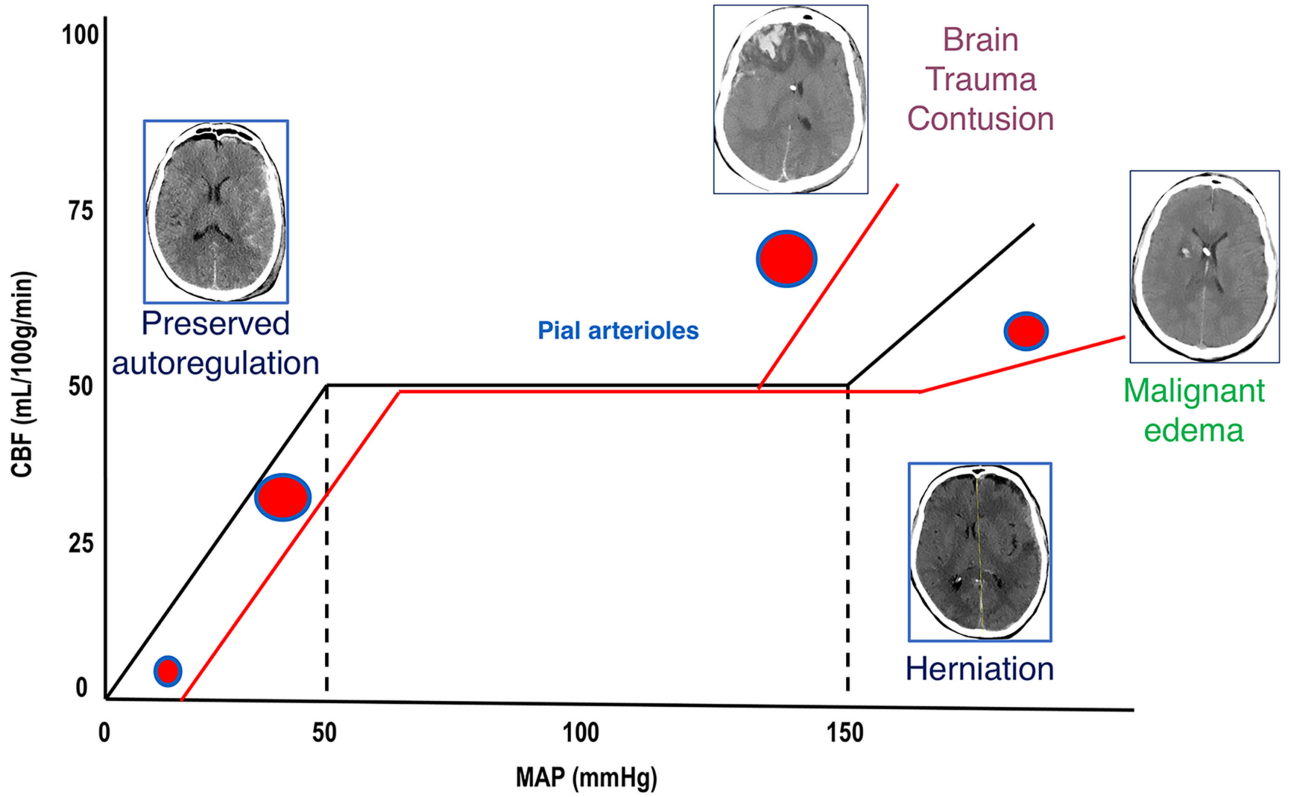

FIGURE 1 | Cerebral autoregulation. Cerebral autoregulation in healthy people is reached at a MAP of 50–150 mmHg and ICP below 20–22 mmHg. After TBI, autoregulation is initially preserved, and compensatory mechanisms act to control ICP and to perfuse the brain (CT scan on the left). When these mechanisms are saturated, cerebral autoregulation is lost, ICP increases, and CBF reduces; if left untreated, this culminates in the worst-case scenario of cerebral herniation (CT scan on the right side). When autoregulation is preserved, pial arterioles dilate in response to ICP increase in order to maintain adequate CBF. When autoregulation is lost, arterioles constrict or dilate causing further reduction of CBF (ischemia) or unnecessary increase of perfusion (hyperemia and contusion evolution or malignant edema). MAP, mean arterial pressure; ICP, intracranial pressure; TBI, traumatic brain injury; CT, computed tomography; CBF, cerebral blood flow, DAD, diffuse axonal damage.

felt indicated; hence, it is not always fundamental to ascend all the steps prior to advancing (i.e., early decompressive craniectomy in selected cases), except for hyperosmolar drugs. While the indication for initiating HICP treatment is clear in case of inv-ICP monitoring (ICP > 20–22 mmHg), the clinical examination and CT-based approach for non-invasively monitored patients is less straightforward. Based on clinical and radiological findings, escalation of therapy should be considered in case of neuroworsening, no improvement or impairment on CT scan, or no response to initial therapy (6). Neuroworsening is defined as a decrease in GCS motor score > 2, loss of pupillary reactivity, new pupillary asymmetry, and/or deterioration of neurological status (6).

The "staircase approach" usually starts from basic advisory (tier zero), till the need for the most aggressive treatments (tier one to three) (15). Stepping from a "baseline" to a higher tier is a potential indicator of increased severity. The higher the tier—the higher the risk, thus in case of non inv-ICP monitoring and neuroworsening, transferring the patient to a tertiary care hospital with more resources is highly recommended (6).

Tier Zero

Tier "zero" denotes those basic interventions that should be implemented irrespective of ICP elevation, and that can be pursued in all sub-populations of neurocritical care patients. Although no clear consensus has been reached as to which interventions compose this toolset, they include ICU admission, endotracheal intubation and mechanical ventilation, serial neurological evaluation, head-up position (15–30°), analgesia for pain management, sedation to prevent ventilator-patient asynchronies, normothermia, central line placement, end-tidal-CO_2 monitoring, a CPP threshold of 60 mmHg, hemoglobin > 7 g/dL, normal values of serum sodium, an arterial line for invasive continuous pressure monitoring, and a peripheral oxygen saturation (SpO_2) ≥ 94% (8, 9).

Tier One to Three

Tiers one to three comprise those interventions initiated only in case of HICP: (1) CPP maintenance (between 60 and 70 mmHg) (4), increasing analgesia and sedation, intermittent bolus administration of osmotic agents, cerebrospinal fluid (CSF) drainage if an external ventricular drainage (EVD) device has been placed, partial pressure of carbon dioxide ($PaCO_2$) between

35 and 38 mmHg, electroencephalography (EEG) monitoring, and prophylactic anticonvulsants if risk is deemed high; (2) mild hypocapnia (32–35 mmHg), neuromuscular paralysis, mean arterial pressure (MAP) challenge to assess autoregulation using inotropes/vasopressors, and use of inotropes/vasopressors when necessary if autoregulation is intact; (3) barbiturate coma, mild hypothermia (35–36°C), hyperventilation with a goal of 30–32 mmHg $PaCO_2$, and secondary decompressive craniectomy (4, 8, 9). These treatments may be implemented with (1) further increase of fraction of inspired oxygen (FiO_2) up to 60%, (2) ventilator management to reach a partial pressure of oxygen (PaO_2) up to 150 mmHg, CPP above 70 mmHg, and (3) transfusion of red blood cells if hemoglobin < 9 g/dL to increase the oxygen delivery in case of HICP with hypoxic brain (if brain tissue oxygen tension ($PbtO_2$) measurement is available), taking care to avoid moderate-severe hyperventilation in these specific cases (4, 8, 9), **Figure 2**.

Non-Barbiturate Sedatives and Analgesics

Analgesics and sedatives carry the risk of hypotension, which might reduce CPP and increase the risk of brain ischemia. After TBI, it is essential that cerebral oxygen delivery be increased, and cerebral metabolic demand be attenuated to achieve an adequate energy balance and oxygen availability. Sedatives and analgesics are used to suppress metabolism, reduce oxygen consumption and CBF, and improve ICP control (metabolic coupling) (16). Since the main problem of HICP is the decrease in CBF and tissue perfusion, the metabolic effect of sedatives on oxygen consumption becomes marginal (15). The metabolic suppression of cerebral metabolic rate of oxygen ($CMRO_2$) induced by sedatives is dose dependent. In particular, CBF reduction should be considered as an adaptive mechanism to reduce brain metabolism, which is dose-dependently suppressed by all intravenous sedative agents (17). Sedatives can exert hemodynamic side effects such as myocardial depression, MAP decrease, and peripheral vasodilatation. These effects should be carefully monitored in patients with impaired cerebral autoregulation, in order to avoid a critical reduction in CPP and oxygen delivery to the brain with possible secondary brain ischemia (18). Otherwise, in patients with preserved autoregulation, the use of sedatives with MAP reduction and compensatory vasodilatation may increase ICP (17). Thus, the use of sedatives and analgesics is essential to protect the brain in the acute phase (within 48 h of injury), and to control HICP.

How to Use Sedatives and Analgesics

Suggested sedatives and analgesics for protecting the brain within the first 48 h after TBI (in case of no ICP elevation) include propofol, followed by midazolam, and fentanyl, followed by morphine (17). The use of deeper sedation in mechanically ventilated general ICU patients has been associated with worse outcomes, while in the neuro ICU, it reduces the ability to assess a neurological response (15). The ideal sedative in TBI patients would be able to reduce the $CMRO_2$, while maintaining $CBF/CMRO_2$ coupling, CPP, cerebral autoregulation, and not raising ICP. Sedatives with antiepileptic and short-term activity should be preferred (19). Moreover, sedation and analgesia should reduce pain and agitation, improve tolerance of the endotracheal tube, and prevent high intrathoracic pressures (e.g., cough) in order to maintain normal ICP values (17).

In presence of HICP, propofol, fentanyl, and rocuronium are used in more than 80% of cases, while midazolam and ketamine are less frequently used (20). Propofol and midazolam seem effective for ICP control (21), although propofol shows greater effects on brain metabolism. These effects are dose-dependent: at <4 mg/kg/h, propofol ensures $CBF/CMRO_2$ coupling, adequate brain oxygenation, and cerebrovascular reactivity, while at higher doses (> 5 mg/kg/h) it can cause burst suppression (17). Propofol doses can be increased if the EEG monitoring does not suggest metabolism suppression and ICP control is not achieved (16).

Midazolam is supplied as a high-lipid formulation that may cause tissue accumulation irrespective of its short half-life, thus prolonging the weaning phase. Although controversial, midazolam can be suggested over propofol in case of hemodynamic instability (22, 23), but the need for higher doses for ICP control could lead to accumulation, leading to prolonged coma, mechanical ventilation, and ICU length of stay (21).

Ketamine has been avoided for many years to control ICP; however, when compared with opioids, it does not increase ICP and provides an optimal hemodynamic stability, reducing the need for vasopressors (20). Nevertheless, given the limited evidence and persistent doubts concerning its effect on ICP, ketamine is not included among the first-line sedatives for ICP control (24). Ketamine alone is not suggested for ICP management, but it may be administrated (dosage 1–5 mg/kg/h) together with other sedatives to reduce their doses (20).

In summary, a classical protocol for analgesia-sedation in patients with HICP may include propofol 4–6 mg/kg/h and fentanyl 1–4 μg/kg/h, plus vasopressors as needed for the maintenance of CPP at acceptable levels (15). Maintenance of the intravascular volume is mandatory to avoid hypotension during deep sedation (3, 4, 8, 13).

Hyperosmolar Therapy

Bolus administration of hyperosmolar therapy represents a fundamental step of the "staircase approach," which acts by inducing a gradient between the vascular circuit and the brain, determining free passage of water across the blood-brain barrier (BBB) with ICP reduction. Continuous infusion of hyperosmolar drugs is not recommended (25). Three main paths for evacuation of excess fluid from acute cerebral edema have been identified in animal models: (1) via the glia limitans externa to the subarachnoid space, (2) via the glia limitans interna and ependyma to the ventricles/central canal, and (3) via the BBB into the lumen of blood vessels (26). Fluid is also lost into the site of injury, which is converted into a "cavity of injury" (27). Recent research has confirmed that excess edema fluid leaves the brain through an integrated system of astrocytes which overexpress acquaporin-4 (AQP4) (28–30). After infusion of hyperosmolar therapies, plasma volume expansion, higher viscosity, and reduction in CBV are observed. These effects may last for hours, until the normal osmolar gradient is restored. Two medications are currently recommended as first-tier therapies

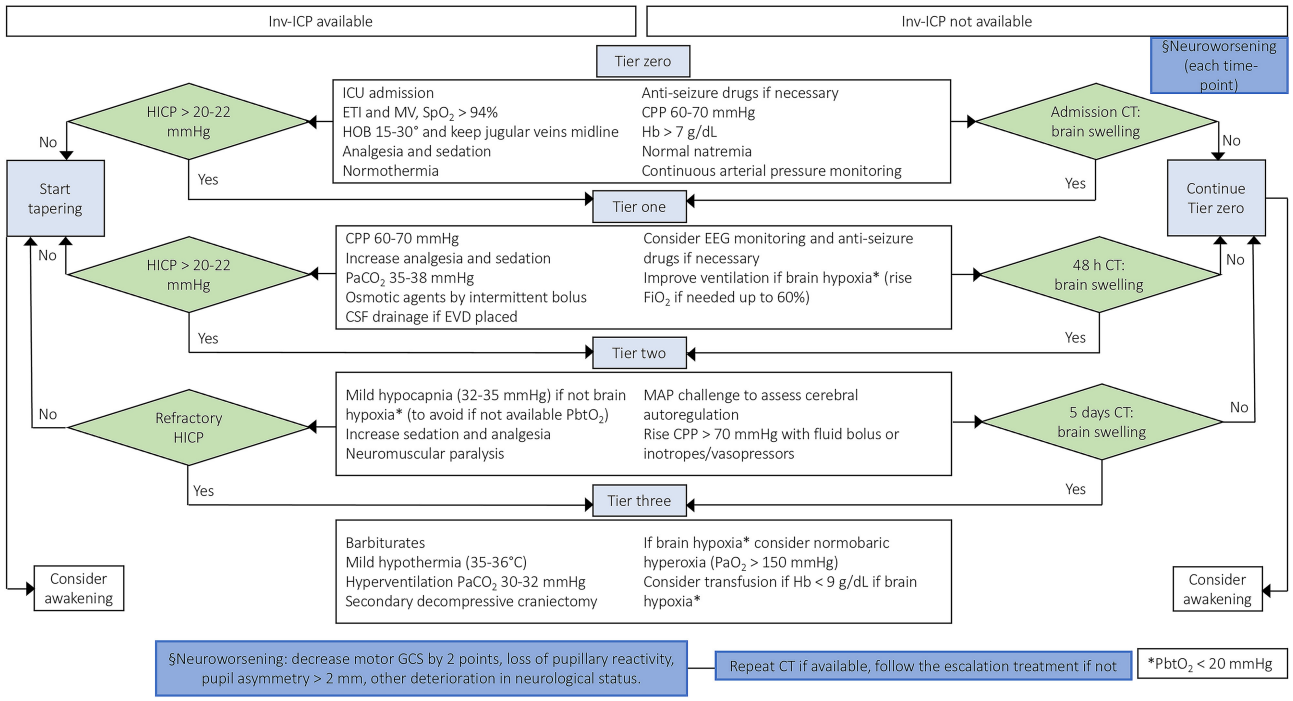

FIGURE 2 | Escalation management for controlling ICP in TBI patients with or without inv-ICP monitoring. Escalation of care in patients with HICP or neuroworsening/radiological impairment [Modified from Hawryluk et al. (9) and Carney et al. (4)]. inv-ICP, invasive intracranial pressure; ETI, endotracheal intubation; MV, mechanical ventilation; CPP, cerebral perfusion pressure; Hb, hemoglobin; $PaCO_2$, partial pressure of carbon dioxide; CSF, cerebral spinal fluid; SpO_2, peripheral saturation of oxygen; HOB, head of the bed; CT, computed tomography; HICP, intracranial hypertension; $PbtO_2$, brain tissue oxygen tension; EVD, external ventricular drainage; EEG, electroencephalography; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, partial pressure of oxygen; GCS, Glasgow coma scale.

for lowering ICP via osmotic mechanisms: hypertonic saline and mannitol (17).

Mannitol is a mannose sugar alcohol. In addition to moving free water from brain tissue to the interstitial space and vascular compartment, it modifies the osmolarity of glomerular filtrate because it is not reabsorbed by the renal tubules, thereby inhibiting sodium and chloride reabsorption and increasing diuresis (31, 32). However, mannitol has been implicated in the occurrence of renal tubular epithelial damage and acute renal failure, especially in patients with hypo- or normonatremic hyperosmolality. For this reason, both mannitol and hypertonic saline should only be used in patients with normal/low plasma osmolarity, with a target of 300–320 mOsm/Kg. Other negative effects of mannitol include prolonged QTc interval, arrhythmias, and myocardial ischemia. Therefore, many clinicians prefer hypertonic saline over mannitol (9). Hypertonic saline can be used at different concentrations of sodium chloride, each yielding distinct responses (**Table 1**). Experimental studies have found that hypertonic saline also reduce proinflammatory cytokine levels in activated microglia (66).

How to Use Osmotic Agents

There is still no consensus as to which osmotic agent is superior for controlling ICP without major side effects. Mannitol is commonly administered at the dose of 0.25–1 g/kg every 4–6 h, while the concentration of hypertonic saline can vary from 3 to 7% and even 23.4% (**Table 1**). Their effects continue for 4–6 h until the normal osmolar gradient is restored. They also lead to hemodilution, as well as increased cardiac output and blood pressure (15). Possible adverse effects of mannitol include dehydration, hypovolemia, and renal damage, whereas hypertonic saline may lead to dangerous hypernatremia (3, 25). In fact, if severe hypernatremia develops rapidly, it could causes shrinking of the brain with vascular damage and subsequent hemorrhage. Acute hypernatremia could also lead to central nervous system demyelination, while chronic hypernatremia may lead to encephalopathy (67). Although current guidelines for the management of severe TBI suggest the use of mannitol (0.25–1 g/kg body weight) over hypertonic saline for HICP control, the debate between these two approaches is still open (3, 4, 25, 68). **Table 1** summarizes all studies available in literature from 1995 to 2020 concerning osmotic therapies for the treatment of HICP. In this line, recent studies confirmed that mannitol is not superior to hypertonic saline in terms of long-term efficacy and safety after TBI (68–70). A useful strategy is to test both agents with an equimolar bolus, in order to evaluate which therapy has the greatest efficacy for each patient (15).

Limited, retrospective data on continuous infusion of hypertonic saline suggest that patients with low serum sodium require more hypertonic fluid than those with normal serum sodium, while those with serum sodium >155 mEq/L can develop hypernatremia and renal dysfunction. Moreover,

TABLE 1 | State of the literature concerning mannitol and hypertonic saline for intracranial hypertension.

Year	Study design	HTS or M concentration	HTS or M dose	Effects
Jagannatha et al. (33)	Randomized controlled trial	HTS 3% M 20%	2.5 mL/kg 2.5 mL/kg	At equimolar doses, HTS and M are equally effective in reducing HICP, but HTS acts faster
Mangat et al. (34)	Retrospective	HTS 3–23.4% and M 20%	NR	HTS reduces HICP more than M, and is less expensive for prolonged ICU stays
Major et al. (35)	Prospective observational	HTS 30%	10 mL	Highly concentrated HTS does not affect laboratory values
Colton et al. (36)	Retrospective	HTS 3%	250–500 mL	When HTS reduces ICP for more than 2 h, it is associated with decreased mortality and long-term disability
Dias et al. (37)	Prospective observational	HTS 20%	0.5 mL/kg	HTS reduces ICP, improves CBF and CPP, and does not affect cerebral oxygenation
Ichai et al. (38)	Randomized controlled trial	Sodium Lactate Isotonic Saline	0.5 mL/kg/h 0.5 mL/kg/h	Hyperosmolar lactate is effective in reducing HICP without modifying plasma osmolarity
Roquilly et al. (39)	Randomized controlled trial	Balanced isotonic Isotonic saline	30 mL/kg/day 30 mL/kg/day	No effects on HICP
Eskandari et al. (40)	Prospective observational	HTS 14.6%	40 mL	HTS administrated as repeated boluses reduces ICP, even in refractory HICP
Diringer et al. (41)	Prospective observational	HTS 20%	1 mg/kg	Mannitol reduces HICP, but does not reduce CBV
Wells et al. (42)	Retrospective	HTS 3 or 7%	150 mL bolus, continuous infusion	Patients with low serum Na+ require more HTS than those with normal serum Na+
Scalfani et al. (43)	Prospective observational	HTS 23.4% M 20%	0.686 mL/kg 1 g/kg	HTS and M reduce HICP, increase CPP, and increase CBF
Paredes-Andrade et al. (44)	Retrospective	HTS 23.4%	30 mL	Boluses of HTS can reduce HICP without modifying serum or CSF osmolarity
Sakellaridis et al. (45)	Randomized controlled trial	HTS 15% M 20%	0.42 mL/kg 2 mL/kg	HTS and M are equally effective in reducing HICP
Roquilly et al. (39)	Retrospective	HTS 20%	Continuous infusion	HTS continuous infusion does not cause HICP rebound when stopped
Bourdeaux et al. (46)	Randomized controlled trial	HTS 5% Na^+HCO3^- 8.4%	100 mL 85 mL	HTS and Na^+HCO3^- are equally effective in reducing HICP
Rhind et al. (47)	Randomized controlled trial	HTS 7.5% IS 0.9%	250 mL 250 mL	HTS reduces neuroinflammation and hypercoagulation
Oddo et al. (48)	Prospective observational	HTS 7.5% M 25%	250 mL 0.75 g/kg	HTS is an effective treatment for refractory HICP to M, also improving CPP
Kerwin et al. (49)	Retrospective	HTS 23.4% M	30 mL	HTS and M are equally effective in reducing HICP
Ichai et al. (50)	Randomized controlled trial	Sodium Lactate M 20%	1.5 mL/kg 1.5 mL/kg	Hyperosmolar lactate is effective in reducing HICP and the effect is maintained longer than M
Froelich et al. (51)	Retrospective analysis of prospective data	HTS 3%	1.5 mL/kg bolus, continuous infusion	HTS can cause hypernatremia and induce renal dysfunction (especially when serum Na+ >155 mEq/L)
Rockswold et al. (52)	Retrospective	HTS 23.4%	30 mL	HTS reduces HICP and increases CPP
Francony et al. (53)	Randomized controlled trial	HTS 7.45% M 20%	100 mL 231 mL	M and HTS are equally effective in reducing HICP. HTS is preferred in hypovolemic and hyponatremic patients; M is preferred in hypoperfused patients
Sorani et al. (54)	Retrospective	M 20%	50–100 g	Each 0.1 g/kg increase in M decreases ICP by 1 mmHg, only in case of HICP
Sakowitz et al. (55)	Prospective observational	M 20%	0.5 g/kg	M reduces HICP by tissue dehydration
Soustiel et al. (56)	Prospective observational	M 20%	0.5 g/kg	M reduces HICP and increases CPP as hyperventilation does. CBF improves with M in respect to hyperventilation
Ware et al. (57)	Retrospective	HTS 23.4% M 75 g or 0.86 g/kg	continuous infusion bolus	HTS and M are equally effective in reducing HICP. HTS acts longer than M
Gasco et al. (58)	Prospective observational	M 20%	100 mL	M reduces HICP and improves cerebral oxygenation

(Continued)

TABLE 1 | Continued

Year	Study design	HTS or M concentration	HTS or M dose	Effects
Munar et al. (59)	Prospective observational	HTS 7.2%	1.5 mL/kg	HTS reduces HICP without affecting hemodynamics for at least 2 h
Horn et al. (60)	Prospective observational	HTS 7.5%	2 mL/kg	HTS can reduce HICP even in cases refractory to mannitol
Suarez et al. (61)	Retrospective	HTS 23.4%	30 mL	HTS reduces HICP and increases CPP
Hartl et al. (62)	Prospective observational	M 20%	125 mL	M reduces HICP, increases CPP, and does not alter cerebral oxygenation
Hartl et al. (63)	Prospective observational	HTS 7.5%	Continuous infusion	HTS reduces HICP, increases CPP, and does not affect hemodynamics
Unterberg et al. (64)	Prospective observational	M 20%	125 mL	M reduces HICP. If CPP>60 mmHg, M does not improve brain tissue oxygenation
Fortune et al. (65)	Prospective observational	M	25 g	M reduces HICP, but increases CBV

M, mannitol; HTS, hypertonic saline; ICP, intracranial pressure; HICP, intracranial hypertension; CPP, cerebral perfusion pressure; CBF, cerebral blood flow; CBV, cerebral blood volume.

continuous infusion of hypertonic saline does not cause rebound HICP when stopped and has demonstrated equal efficacy in reducing HICP than mannitol, increasing CPP without affecting hemodynamics (**Table 1**). Therefore, the potential efficacy of a continuous infusion over bolus may be related to the patient's osmolarity, but further studies are needed to corroborate this hypothesis. In the absence of more conclusive evidence, hyperosmolar therapies (whether hypertonic saline or mannitol) should be administered by bolus; continuous infusion is not recommended (25).

Cerebral Spinal Fluid (CSF) Drainage

In case of inv-ICP monitoring with an external ventricular drainage (EVD) system, CSF drainage represent an effective technique to reduce ICP, but there is no strong evidence of ICP long-term reduction (3, 4). Intraventricular ICP monitoring device consists of a catheter with a transducer (fiberoptic strain gauge or pneumatic sensor) placed into the cerebral ventricle system, which is connected to an external pressure monitoring system capable of ICP detection (71). It is an EVD, which allows CSF subtraction in case of HICP. Intraventricular ICP is the first and oldest system of inv-ICP monitoring described (72, 73), and still represents the more reliable device capable to detect ICP and to assess intracranial compliance (71, 74, 75). The device is usually placed in the frontal horn of the ventricle through the Kocher point, 2 cm anteriorly to the coronal suture and 2.5–3 cm laterally from the midline, directed toward the intersection point between the sagittal plane on the medial canthus of the ipsilateral eye and the coronal plane on the external auditory meatus (approximately the location of the foramen of Monro) (76, 77). The most correct calibration point (zero-point) should be at the foramen of Monro (at level of the external auditory canal). Complications associated to the placement of intraventricular inv-ICP device may include technical problems misplacement, dislocation, kinks, obstruction from debris, and blood (74, 78–80), which ranges from 4.5 to 25% (81–83), hemorrhage [reported in 0.7 and 0.61% two meta-analysis considering only the symptomatic bleeding (80, 84) and in 2.5% (considering all hemorrhages) (81), and infection [which ranges from 1 to 27%, and is correlated with the duration of device maintenance and number of tapping (85)]. In short, intraventricular inv-ICP represents the best device for intracranial compliance evaluation, but it needs a careful management due to possible complications. Furthermore, intraventricular device is often difficult to position in young patients because of the smaller ventricle volume, and in TBI patients with HICP in whom the ventricular system is collapsed as a compensatory mechanism (75). Although ventricular inv-ICP monitoring is usually considered the "gold standard," variable impacts on long-term outcome have been shown in studies comparing intraventricular and intraparenchymal systems (7, 86–88). We therefore recommend either placement of an inv-ICP device when indicated, or monitoring of the ICP by non-invasive means (i.e., transcranial doppler, optic nerve sheath diameter) (89).

Partial Pressure of Carbon Dioxide Management

Cerebral physiology is deeply modified by $PaCO_2$ changes. $PaCO_2$ can modulate vasomotor tone, leading to cerebral vasoconstriction in case of hypocapnia, or cerebral vasodilatation in case of hypercapnia (90, 91). A systematic review demonstrated that both hypocapnia and hypercapnia are associated with poor outcomes after TBI (92). Hypocapnia can reduce CBF and cerebral blood volume (CBV) and is usually achieved through hyperventilation. Hyperventilation decreases ICP and induces brain relaxation. Despite the well-established efficacy of hyperventilation for ICP control, the effect of this practice on long-term outcome is unclear. Hypocapnia may increase cerebral metabolic activity by raising oxygen and glucose consumption, producing excitatory amino acids, and triggering the switch to anaerobic metabolism, thereby increasing the risk of seizures and hyperexcitability. Patients with TBI show less CBF reduction than those with uninjured brains, due to the fact that hyperventilation redistributes blood flow to injured tissue. Finally, hyperventilation followed by hypocapnia may lead to

alkalosis by shifting the oxygen-hemoglobin dissociation curve (Bohr effect) (91, 93).

Induction of Hypocapnia

Hyperventilation can be performed by increasing tidal volume or respiratory rate in mechanically ventilated patients (4, 94). In general neurocritical care as part of the "tier zero," $PaCO_2$ should be maintained between 35 and 38 mmHg, while prophylactic moderate hyperventilation in case of HICP should be weighted on risk/benefit to patients, considering that it may be harmful for GCS < 4–5 (62), because $PaCO_2$ levels between 20 and 25 mmHg correspond to a 40–50% decrease in CBF (90). Particularly, literature on pre-hospital TBI cares suggests to avoid hyperventilation within the first 24 h following TBI, except in clear case of refractory HICP or cerebral herniation (4). Besides, in case of elevated ICP mild hypocapnia (32–35 mmHg) could be considered. On the other side, a brief period (15–30 min) of hyperventilation in case of refractory HICP, targeting $PaCO_2$ of 30–32/30–35 mmHg (for the SIBICC/BTF guidelines, respectively), may be appropriate. However, prolonged hypocapnia should be prevented (4, 8, 9). Hyperventilation is not devoid of complications. In fact, brain ischemia may represent a potential harmful side effect of this treatment. In a randomized controlled trial in which patients were randomized to receive normal ventilation ($PaCO_2$ 35 mmHg), moderate hyperventilation ($PaCO_2$ 25 mmHg), or tromethamine (THAM) plus hyperventilation, hyperventilation for 5 days resulted in worse outcomes at 3–6 months. Better 12-month outcomes were found in the THAM plus hyperventilation group (95). This was also confirmed by Brandi et al. (96), who showed that 50 min of hyperventilation do not change glucose, lactate, or pyruvate concentrations, but can modify brain tissue oxygenation tension. Hence, considering patients with HICP and brain hypoxic damage, the SIBICC consensus does not suggest hyperventilation (8, 9). As early as 1997, a Cochrane review found that data were inadequate to conclude whether hyperventilation could be considered detrimental or beneficial for the treatment of acute TBI; in 2008, an updated review reached the same deduction (97). Notwithstanding these conclusions, hyperventilation, is effective for HICP therapy in non-hypoxic brain. However, since the $PbtO_2$ monitoring is occasionally available and the hypoxic brain ($PbtO_2$ < 20 mmHg) difficult to detect without such specific monitoring, hyperventilation should be used as a last resort.

Metabolic Suppression Management (Barbiturates)

Barbiturates are gamma-aminobutyric acid (GABA) receptor agonists which suppress cerebral electrical activity, leading to a reduction in CBF, CPP, and CBV. The reduction in CBF is proportional to the $CMRO_2$ and lowers ICP. Barbiturate therapy was widely employed for decades in the management of TBI patients refractory to "second-tier" interventions (94), given the ability of these agents to suppress brainstem reflexes, cerebral activity and metabolic demand, until potentially reaching the deepest state known as burst suppression (98). The aim of barbiturates administration is to control ICP, and their effects on cerebral metabolism should be observed through EEG monitoring. A state of burst suppression is not the goal of barbiturates, and if it appears, no further dose increases are indicated (9, 94, 99). Barbiturates also induce vasoconstriction and decrease cardiac output, thus modulating cerebral metabolic demand, with no effects on mortality or disability. Barbiturates are indicated only for the treatment of refractory HICP and refractory seizures, and should be titrated to the lowest effective dose (17). EEG should be used to guide titration of therapy, as it is now known that burst suppression is not the aim of barbiturate administration and must not be pursued if ICP control has been obtained. Likewise, increasing barbiturate doses in case of refractory HICP should be avoided if burst suppression is already present, as it is unlikely to lead to further reduction of ICP (9, 94, 99). One-fourth of patients treated with barbiturates can develop hypotension, which mirrors the substantial effects of CPP on ICP (100). Other complications include respiratory depression, infections, immunosuppression, hepatic, and renal dysfunction (101).

Induction of Metabolic Suppression

Initial therapy with barbiturates consists of a bolus followed by continuous intravenous infusion for maintenance (14). Thiopental and pentobarbital are the most used barbiturates. Thiopental is metabolized into five metabolites, one of which is pentobarbital (102); this may explain the higher efficacy of thiopental when compared to pentobarbital. When compared to thiopental, pentobarbital is less effective in reducing ICP as first-line therapy (102). The classic dose of pentobarbital should be 5–7 to 10 mg/kg, while thiopental should be used with a median loading dose of 15 mg/kg followed by continuous infusion of 100 mg/kg/day (99). Depressive effects on the central nervous system occur within 15 min, but this varies from patient to patient.

Decompressive Craniectomy (DC)

Decompressive craniectomy (DC) consists in the removal of a portion of skull in order to treat refractory HICP and represents the most aggressive step of the "staircase approach" (103). When the bone flap is not replaced after surgery for the evacuation of an intracranial mass lesion, DC is named "primary," while it is considered "secondary" when DC is performed later after other treatments have failed (104). DC can be performed as a large frontal-temporal-parietal flap (at least 12 × 15 cm diameter) (104) or as a bifrontal flap; both techniques have shown an efficacy close to 100% for ICP control (1–4, 9, 13, 99, 105). However, the optimal indications, technical aspects, and timing for DC are still debated. Two major multicenter randomized controlled trials (RCTs) comparing decompressive craniectomy with medical management tried to provide guidance to clarify timing and indications of DC: Decompressive Craniectomy in Patients with Severe Traumatic brain Injury (DECRA) and Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension (RESCUEicp) (2, 13). The DECRA trial showed a similar rate of mortality between medical and surgical cohorts, with a higher rate of unfavorable neurologic outcomes in the surgical group. On the other hand, the RESCUEicp study observed lower mortality for DC, but higher rates of vegetative state, as well as lower and upper severe disability at 6 months, in

comparison to medical therapy (2). A key difference between the two studies was that DECRA investigated the effects of DC for *early* HICP, while the effects of DC for *late* HICP were analyzed by RESCUEicp (104). In fact, DECRA included patients with HICP (> 20 mmHg) for 15 min over a 1-h period although the tier 1 therapies within the first 72 h after trauma, while RESCUEicp included patients with HICP (> 25 mmHg) for 1 to 12 h despite the tiers 1 and 2 therapies within the first 10 days after TBI (2, 13). Therefore, the interpretations and recommendations extrapolated from these studies should refer to *early* and *late* refractory HICP. A recent update on DC by the Brain Trauma Foundation (104), based on the RESCUEicp and DECRA findings, developed Level IIA recommendations, suggesting that secondary DC for *early* refractory HICP is not recommended to improve mortality and outcome, while is suggested in case of *late* refractory HICP. Otherwise, DC performed both in *early* and *late* refractory HICP is recommended to reduce ICP and ICU length-of-stay. Moreover, Authors observed that bifrontal DC (the technique used in the DECRA trial) is effective to reduce ICP and ICU-stay, but it is not recommended to improve outcome and mortality if performed in accordance with the DECRA inclusion criteria. Besides, the 2020 update of the BTF guidelines (104) concluded that a frontal-temporal-parietal DC (12 × 15 cm) is recommended over a small flap for mortality and outcome improvement after severe TBI (106, 107). Many other studies analyzed the use of DC in severe TBI and its implications for long-term neurological outcome, confirming its efficacy for ICP control and reduction of mortality, but increasing long-term disability (108–115). The socioeconomic context, patients' priorities, and the recognition of clinical and radiological prognostic factors (for which further validation studies are needed) should be considered before indicating DC.

TAPERING THERAPIES AFTER THE CONTROL OF INTRACRANIAL HYPERTENSION

Once HICP is controlled, the aggressive therapies applied following the "staircase approach" should be carefully tapered in order to avoid secondary brain damage induced by excessive brain metabolism suppression, reduced oxygen delivery, and impaired systemic hemodynamics with dangerous consequences to the brain. Based on the aforementioned, the choice to taper therapies should be weighted on the stability of ICP, but it is extremely hard to define in patients who do not present an inv-ICP monitoring. **Figure 3** depicts a possible step-by-step approach for the tapering of care after HICP control.

Timing for Cranioplasty After Decompressive Craniectomy

By definition, decompressive craniectomy creates a skull defect of varying size and complexity. Cranioplasty has the goal of restoring brain protection, CSF dynamics, and aesthesis after DC (116). Although cranioplasty itself is a routine procedure, it still carries a significant complication rate (100, 117), affecting 23.8–26% of patients (118, 119) (range 7–47%) (116). Risk factors for developing complications after cranioplasty include previous surgery, *in-situ* ventriculoperitoneal shunt (VPS), and systemic and cardiovascular comorbidities (118). Wound complications (e.g., dehiscence, ulcers, necrosis) are reported in 1.6% of cases (118), and may be caused by poor preoperative conditions, underlying infection, or inadvertent sacrifice of the skin flap vascular supply during DC (116). Infection is described in 3–12% of cases (116, 118, 120, 121). Hydrocephalus is reported in 10–45% of cases after DC, but resolution of ventriculomegaly after cranioplasty is well-documented; it appears to persist only in 1–5% of cases (118, 121). Epidural or subdural hemorrhage is described in 3–7% of cases, and is more frequent in case of VPS placement, whereas new-onset seizures are reported in 3–8% of cases (118, 119, 121). The optimal timing for cranioplasty after DC is a matter of debate, considering its hypothetical influence on postoperative infection (116, 119). A recent review (116) described that it is usually performed from 4 to 12 weeks after DC, in accordance with the possible scenarios that could influence the timing of cranioplasty: in the first scenario, the brain is depressed with respect to the skull defect because of post-traumatic brain atrophy or VPS *in situ* (high risk of post-cranioplasty blood collection); in the second scenario, the brain is in physiological position at the level of the inner table of the skull; while, in the third and worst scenario, the brain is over the level of the skull defect, because of edema or hydrocephalus (116). This review showed that the infection rate is higher within the first 14 days after DC (116), probably because a recent healing wound represents a weak point in which normal immune-cell recruitment is altered (118). Iaccarino et al. observed a higher incidence of hydrocephalus within the first 90 days, while seizures were more common after 90 days (116). Thus, an early cranioplasty (15–30 days after DC) may reduce the risk of infection and seizure. Archavlis et al. (122) retrospectively observed a better neurological outcome for patients who underwent cranioplasty within 7 weeks and between 7 and 12 weeks when compared to patients whose cranioplasty was performed at > 12 weeks. However, a higher rate of infection in those with comorbidities (such as diabetes, colonization with multidrug-resistant pathogens, and thromboembolism) was found in the early cranioplasty group. Thus, the authors concluded that the indication for early cranioplasty should take into account both the clinical and neurological patients' status, to better define the optimal timing of surgery and minimize the risk of complications (122). Many other studies reported similar conclusions (116): some authors described a lower rate of complications in *early* cranioplasty, while others observed no impact on complication rate. Few studies found that cranioplasty timing can influence the persistence of hydrocephalus and long-term neurological outcome. However, the most recent meta-analysis by Malcolm et al. (123) reported improved neurological function for patients who underwent an earlier cranioplasty (< 90 days after DC). In summary, as observed by the most recent studies (116, 123), there is a growing trend to perform earlier cranioplasties (15–90 days after DC), although there is only low-grade evidence (Class IIb, Level C) to support this. The timing of cranioplasty should be based on the neurological, clinical, and infective status of each patient; surgery should be performed as

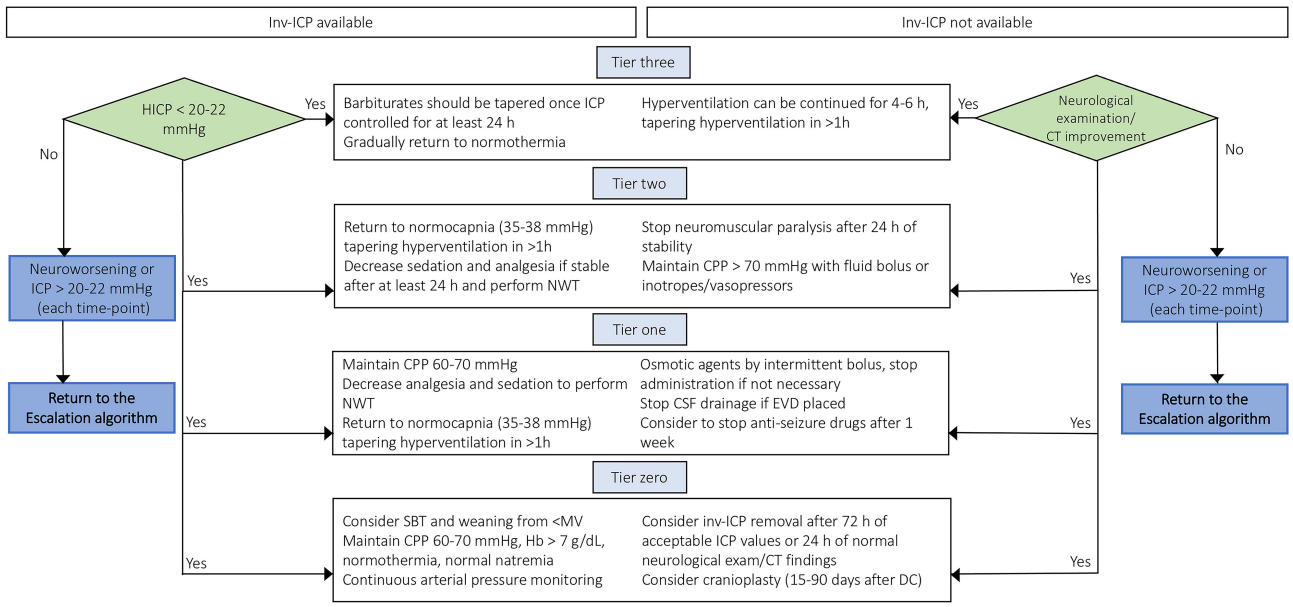

FIGURE 3 | De-escalation management after controlling intracranial hypertension in TBI patients with or without inv-ICP monitoring. De-escalation management for controlling intracranial hypertension basing on available current evidences [Modified from Stocchetti et al. (3), Hawryluk et al. (9) and Carney et al. (4)]. inv-ICP, invasive intracranial pressure; CPP, cerebral perfusion pressure; Hb, hemoglobin; $PaCO_2$, partial pressure of carbon dioxide; CSF, cerebral spinal fluid; CT, computed tomography; HICP, intracranial hypertension; EVD, external ventricular drainage; NWT, neurological wake-up test.

soon as brain swelling, and clinical condition allow intervention with a lower risk for the patient. A randomized controlled trial on the best timing for cranioplasty after DC, sponsored by NIHR Global Health Research Group, is ongoing, and may clarify the optimal management (116).

Weaning From Metabolic Suppression

Once a normal ICP value is reached, or clinical examination and imaging (in patients without inv-ICP) are improved, discontinuation of barbiturates can be initiated if the medical staff deems appropriate. The infusion should be tapered, not discontinued abruptly (14). When compared to decompressive craniectomy, thiopental (15 mg/kg followed by 100 mg/kg/day) was equally effective for the treatment of refractory HICP (105). The effects of thiopental can take 4 days to be observed (124). To date, there is no consensus on the duration of barbiturate therapy for refractory HICP (94), although some weaning protocols have been proposed (14). In a study performed on 153 TBI patients with HICP, barbiturates were used for a median time of 4 days, with a range of 2–12 days (99). Withdrawal from barbiturate therapy may result in serious issues, including possible rebound HICP and seizure activity. During discontinuation of therapy, both the long half-life of these drugs and their possible interactions must be taken into consideration; constant monitoring of drug levels has been suggested (14). In summary, we suggest tapering the barbiturate dose once ICP has been controlled for at least 24 h and discontinuing administration only if there is no rebound effect on ICP with progressively lower doses.

Return to Normocapnia

The BTF guidelines and the SIBICC consensus suggest proceeding with a brief period (15–30 min) of hyperventilation, targeting $PaCO_2$ levels to 30–35/32–35 mmHg or lower (30–32 mmHg) if more aggressive treatments are needed (4, 8, 9). Mild hyperventilation cannot be continued for long time; after 4–6 h, physiological buffer systems normalize the pH of the perivascular space, limiting the beneficial effects of hypocapnia, increasing CBF, and causing hyperemia with possible rebound of HICP (90). Moreover, hypocapnia may induce deleterious systemic effects, including decreased blood perfusion of the kidneys, gastrointestinal system, skin and skeletal muscles; platelet adhesion and hyper aggregation; bronchoconstriction, reduced hypoxic pulmonary vasoconstriction, surfactant production, and increased permeability of the alveolar-capillary membrane; respiratory alkalosis with potassium, calcium, and phosphate imbalance; and possible increase in coronary metabolic demand, with coronary spasm, myocardial ischemia, and arrhythmic complications (90).

In short, mild to moderate hyperventilation should be considered only in case of uncontrolled HICP at risk for cerebral herniation syndrome, life-threatening HICP elevation, HICP caused by hyperemia, and aggressive "second-tier therapy" for the control of refractory HICP, should be performed for 15–30 min only and should be avoided if there is risk of brain hypoxia. $PaCO_2$ and arterial partial pressure of oxygen (PaO_2) should be strictly monitored by using end-tidal carbon dioxide or serial arterial blood gases. When hyperventilation is initiated, it must not be stopped abruptly due to the risk of rebound HICP; instead, it should be tapered progressively by reducing

respiratory rate over 1 h until normal $PaCO_2$ values (35–38 mmHg) are achieved (57).

When to Stop Osmotic Agents

As noted above, the current evidence indicates that both mannitol and hypertonic saline should be administered as on-demand boluses, and strictly guided by ICP values. Once ICP control has been obtained (ICP < 20–22 mmHg), further boluses should be withheld (3, 8, 9, 15).

A retrospective study by Schomer et al. (125) evaluated the role of dexmedetomidine for refractory intracranial hypertension and for de-escalation from hyperosmolar therapies. The authors observed a reduction in the number of hyperosmolar boluses after initiation of dexmedetomidine. The difference was significant for mannitol ($p = 0.03$), but not for hypertonic saline ($p = 0.20$). There were no differences in episodes of hypertension, bradycardia, or CPP reduction. The authors concluded that dexmedetomidine could be a useful adjunct in the management of refractory HICP, reducing the need for hyperosmolar fluid without compromising hemodynamics (125). However, since this approach is extremely new and not confirmed by larger studies, the conventional use of hyperosmolar therapy alone is strongly recommended.

How to Wean From Sedatives and Analgesics

De-escalation of sedatives should not be encouraged during the first phases of ICP management; it is universally accepted that patients who suffer from HICP need sedation for at least 24 h, and sedation should not be discontinued as long as ICP values remain high (15). The decision to discontinue sedation and analgesia once ICP control is achieved is based on clinical neurological examination, optimization of patient status (e.g., maintenance of euvolemia, fluid balance, monitoring of respiratory, and hemodynamic parameters), appropriate levels of CPP (60–70 mmHg, according to the autoregulatory status and using vasopressors if needed), and appropriate mechanical ventilation to maintain normoxia and normocapnia (SpO_2 > 94% and $PaCO_2$ around 35 mmHg) (15). The neurologic wake-up test (NWT), which consists in reducing sedation and analgesia as part of the daily clinical examination, is not mentioned in TBI guidelines, although it is the only available test that could reliably detect neurological deterioration or improvement and focal neurological deficits (126), thus facilitating clinical decision-making. When performing NWT, the patient should be carefully monitored for ICP and CPP and placed in the supine position. Those few studies that have investigated the role of NWT in TBI concluded that it increases ICP and MAP, although there was no evidence of either brain injury exacerbation or benefit of the test (126).

In patients requiring sedation for longer than 7 days, propofol should be discontinued due to the risk of "propofol infusion syndrome" at doses > 4 mg/kg/h (15, 16, 20). This syndrome is characterized by rhabdomyolysis, green urine, elevated hepatic enzymes, and elevated triglycerides (127). In summary, a combined regimen of propofol (3 mg/kg/h), to reduce oxygen consumption and ensure suppression of seizures, and fentanyl (1–2 μg/kg/h), to facilitate patient-ventilator synchrony, could be recommended. At this dosage, propofol infusion can be withdrawn to allow a neurological examination (16). Propofol and fentanyl should be progressively reduced after at least 24 h of ICP control, except for patients who are still in the acute phase after TBI. In these cases, analgesia and sedation should be continued for 24–48 additional hours to protect the injured brain (17). Before weaning from sedatives and analgesics, endotracheal tube intolerance, and patient-ventilator asynchronies should be excluded as a matter of course (17). Once weaning has begun, the patient's pain and agitation should be carefully evaluated in order to avoid rebound HICP. Dexmedetomidine is a rapidly metabolized alpha-2 agonist that can provide adequate agitation control to allow neurological examination after withdrawal of sedation, but few data are available on its long-term effects in TBI. **Figure 4** depicts a proposed algorithm for sedative escalation and de-escalation in case of HICP and thereafter.

Inv-ICP Monitoring Removal

There is no universal consensus on inv-ICP monitoring in patients who are not neurologically evaluable. The timing of inv-ICP removal remains a matter of debate; the useful information that can potentially be gleaned from its maintenance even after ICP control has been achieved should be balanced with the complications associated with prolonged invasive monitoring (82, 124, 128, 129). Thus, removal of inv-ICP monitoring in these patients should be based on assessment of the risk/benefit ratio, given the potential for complications both as a result of insertion of the inv-ICP probe and of its prolonged maintenance *in situ* (e.g., infection and technical problems) (81, 82, 124, 128–134). The infection rate of inv-ICP monitoring ranges from 1 to 27% (3), and is usually related to the insertion procedure and the duration of monitoring (135). Winfield et al. did not observe a higher occurrence of infections in patients with longer inv-ICP monitoring, and they suggested that weaning from inv-ICP monitoring should be evaluated on a case-by-case basis, considering the true utility of continued monitoring after many days of controlled ICP (132). The SIBICC recommended removal of inv-ICP monitoring after 72 h of acceptable ICP values, and as soon as 24 h for those cases with normal CT-scan findings and who are neurologically evaluable (8).

RESEARCH AGENDA

A Former Point-of-View for Novel Pathophysiological Approaches

The degree of damage of the BBB is nowadays not considered as individualized therapy after TBI according to the individual pathophysiology. The occurrence of raised ICP in most of the cases is due to cerebral edema. Brain edema can be vasogenic when extravasation of fluid into the extracellular space occurs, followed by BBB damage; while cytotoxic edema appears as a consequence of the passage of extracellular water into the intracellular compartment, mainly due to the ionic gradient

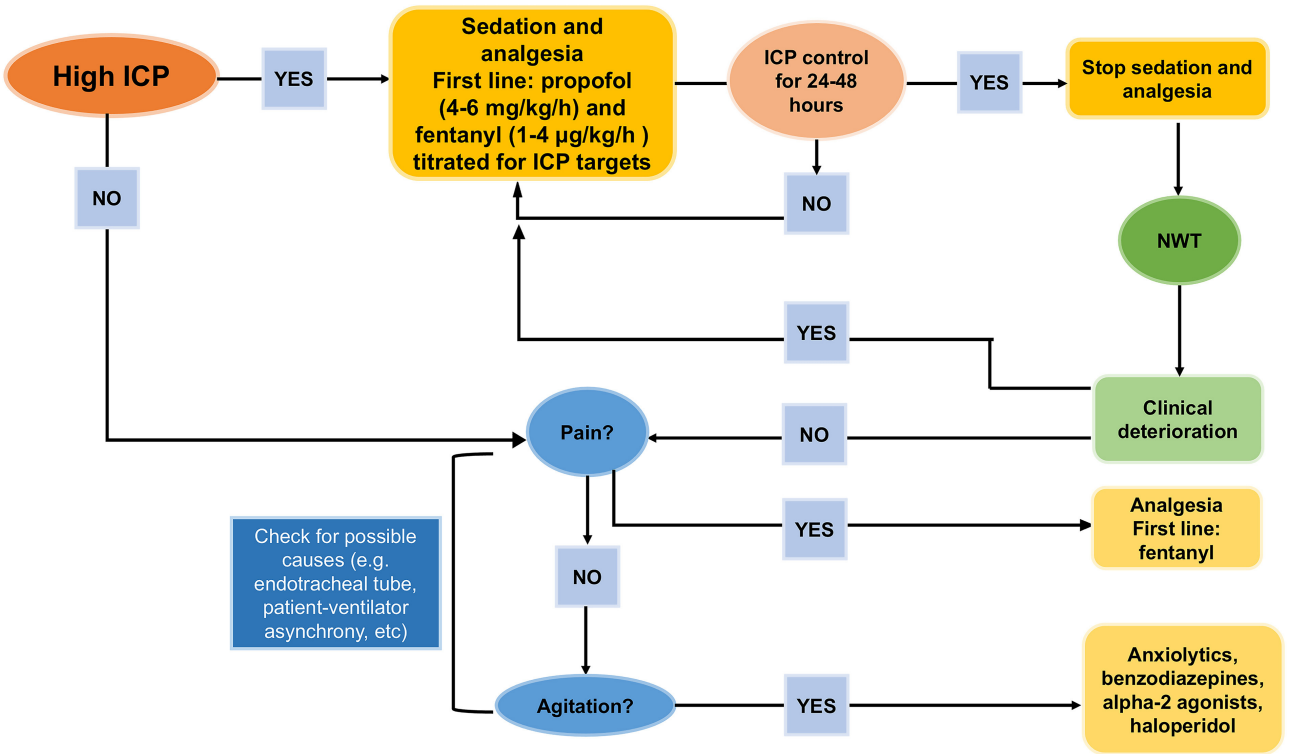

FIGURE 4 | How to de-escalate from sedatives and analgesics. Proposal for de-escalating sedatives and analgesics after intracranial hypertension control [Modified from Oddo et al. (17)].

(136, 137). The initial hypothesis of BBB damage after TBI includes an acute initial opening of the BBB, followed by the leak of plasma and cells increasing the brain specific gravity with diffuse and homogeneous distribution in the white and gray matters. This mechanism is of short duration and occurs in about 1/4 of the patients with severe TBI, independently of lesions at magnetic resonance images (MRI), thus remaining sequelae for about 2 weeks. It can also worsen the prognosis (138) through cerebral herniation (139, 140) MRI with apparent diffusion coefficient is used to distinguish between vasogenic and cytotoxic edema in TBI patients. While freely diffusible water at MRI is marker of vasogenic edema, restrict water movement represents cytotoxic edema (139). This is associated with a rapid disruption of the BBB within the first hours after the trauma, followed by a biphasic edema formation, starting from the vasogenic, and thus continuing with the cytotoxic until the minimum level after 1 week (141). However, this technique is not easily applied in the first phase of TBI when the patient could be unstable. Unfortunately, CT-scan still not allow the same information as RMI but is considered the first line diagnostic tool in the acute phase of TBI. Besides, volume, weight, and specific gravity can be analyzed. Data from CT images suggested a heavier brain tissue after trauma (136). In this line, a complete destruction of the BBB is associated with leakage of water, proteins and electrolytes with higher density than the brain; while a partial BBB destruction is associated with an added volume characterized by lower density in respect to the brain. In the acute phase of TBI, patients with increased density received more osmotherapy, had more frequently an external ventricular drainage positioned with possible CSF drainage, and received second-tier therapies more often. This suggested that in case of contusion interesting <2% of the brain, the BBB is predominantly intact, the osmolarity is the main driving force for edema formation, and the autoregulation is efficient (increasing pressure decreases cerebral blood volume) (142). In this setting, the first-line treatment of increased ICP could be CSF drainage, increase of CPP, and increase of osmolarity (by using hypertonic saline 40 mL/30 min) (143). The 2020 guidelines for the treatment of cerebral edema recommends *pros* the use of osmotic agents in the hospital setting, but *cons* in the pre-hospital setting (137). Otherwise, if the brain is contused in more than 2% of its tissue, the BBB can be disrupted in a large percentage. The increase of pressure and osmolarity worsens the edema, while the vasogenic edema should be prevented in the contusion area (144). In this setting, the first-line treatment of increased ICP could be the CSF drainage, reinforce of sedation, implement of hypothermia, and corticosteroids (143). This old but also innovative point of view should be further discussed and corroborated, since some of these therapies have been abandoned without trying to distinguish between patients who can benefit and those who cannot. This concept is proposed in **Figure 5**.

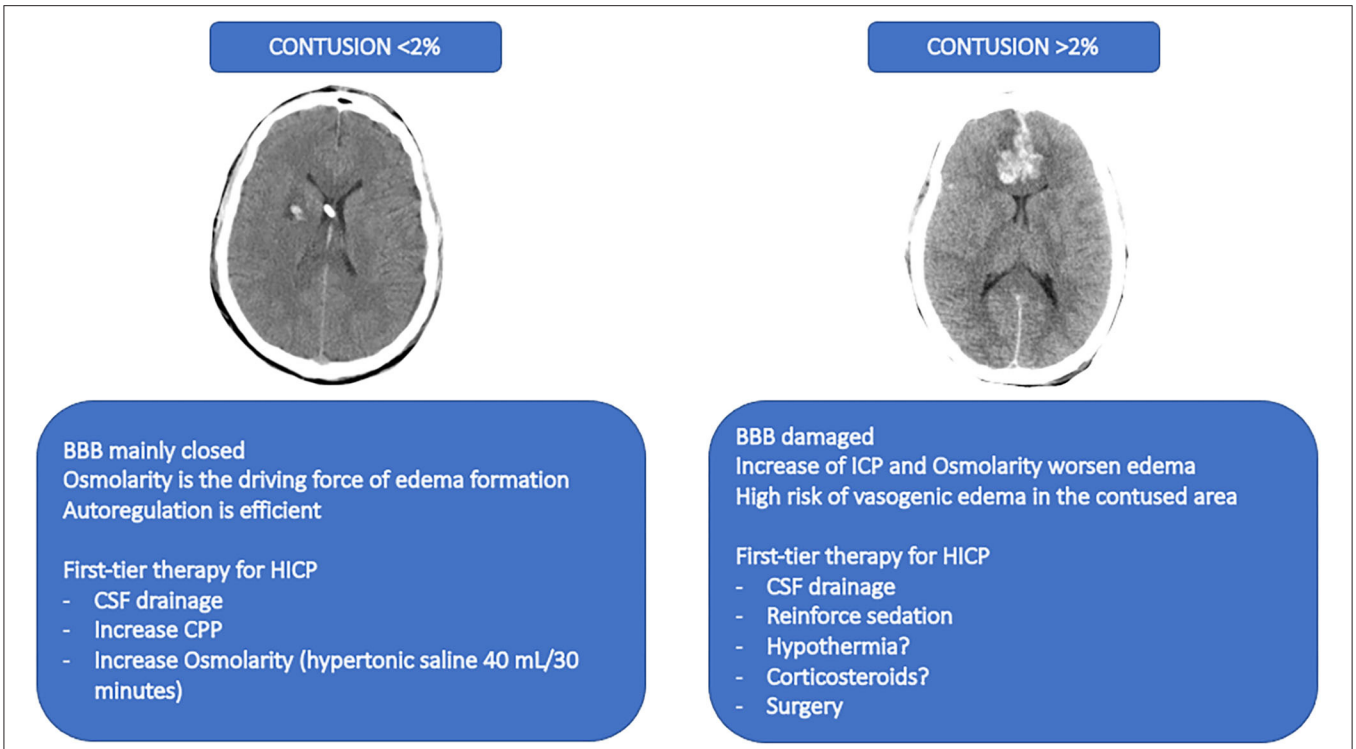

FIGURE 5 | A former point-of-view for novel therapeutic approaches. The figure depicts a proposed therapeutic approach based on a former point-of-view no longer investigated and that should be reinterpreted in light of the progresses in TBI research. The image on the left represents a CT-scan with a contusion <2%. The suggested therapies for this condition are described below. The image on the right represents a CT-scan of a contusion of more than 2%. The suggested therapies are described below. BBB, blood brain barrier; HICP, intracranial hypertension; CSF, cerebral spinal fluid; CPP, cerebral perfusion pressure.

CONCLUSIONS

The stepwise approach to escalate and de-escalate therapies, combined with continuous control of their efficacy, is still debated. This strategy should follow the individual pathophysiology of traumatic brain injury according to the brain-blood barrier injury. While the management of treatment escalation in TBI by several consensus conferences and guidelines is almost warranted, the tapering of therapies is still under debate and remains challenging. Further studies are necessary to define the best de-escalation management and to refine the current staircase approach; novel pathophysiological considerations may yet provide the ultimate answer.

AUTHOR CONTRIBUTIONS

DB and PA wrote the manuscript. DB, PA, PR, IB, AP, GZ, PP, and PF made substantial contributions to the revision, conception, and design of the manuscript. All authors read and approved the final version of the manuscript.

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The Association of Early Electrocardiographic Abnormalities With Brain Injury Severity and Outcome in Severe Traumatic Brain Injury

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The aim of this study was to evaluate the frequency of electrocardiographic (ECG) abnormalities in the acute phase of severe traumatic brain injury (TBI) and the association with brain injury severity and outcome. In contrast to neurovascular diseases, sparse information is available on this issue. Data of adult patients with severe TBI admitted to the Intensive Care Unit (ICU) for intracranial pressure monitoring of a level-1 trauma center from 2002 till 2018 were analyzed. Patients with a cardiac history were excluded. An ECG recording was obtained within 24 h after ICU admission. Admission brain computerized tomography (CT)-scans were categorized by Marshall-criteria (diffuse vs. mass lesions) and for location of traumatic lesions. CT-characteristics and maximum Therapy Intensity Level (TILmax) were used as indicators for brain injury severity. We analyzed data of 198 patients, mean (SD) age of 40 ± 19 years, median GCS score 3 [interquartile range (IQR) 3–6], and 105 patients (53%) had thoracic injury. In-hospital mortality was 30%, with sudden death by cardiac arrest in four patients. The incidence of ECG abnormalities was 88% comprising ventricular repolarization disorders (57%) mostly with ST-segment abnormalities, conduction disorders (45%) mostly with QTc-prolongation, and arrhythmias (38%) mostly of supraventricular origin. More cardiac arrhythmias were observed with increased grading of diffuse brain injury ($p = 0.042$) or in patients treated with hyperosmolar therapy (TILmax) (65%, $p = 0.022$). No association was found between ECG abnormalities and location of brain lesions nor with thoracic injury. Multivariate analysis with baseline outcome predictors showed that cardiac arrhythmias were not independently associated with in-hospital mortality ($p = 0.097$). Only hypotension ($p = 0.029$) and diffuse brain injury ($p = 0.017$) were associated with in-hospital mortality. In conclusion, a high incidence of ECG abnormalities was observed in patients with severe TBI in the acute phase after injury. No association between ECG abnormalities and location of brain lesions or presence of thoracic injury was present. Cardiac arrhythmias were indicative for brain injury severity but not independently associated with in-hospital mortality. Therefore, our findings likely suggest that ECG

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abnormalities should be considered as cardiac mimicry representing the secondary effect of traumatic brain injury allowing for a more rationale use of neuroprotective measures.

Keywords: severe traumatic brain injury, cardiac dysfunction, electrocardiography (ECG), computerized tomography (CT), therapy intensity level (TIL), mortality outcome

INTRODUCTION

Traumatic brain injury (TBI) is an important cause of mortality and morbidity in adults (1). Patients with severe TBI are initially stabilized at the Emergency Department (ED) and admitted to the Intensive Care Unit (ICU) for treatment based on intracranial pressure (ICP)-monitoring to prevent secondary deterioration of brain injury and optimize conditions for brain recovery (2–4). Vital functions are well-known predictors of outcome (5) and are monitored with several tools, including electrocardiography (ECG).

In various neurological and neurosurgical conditions ECG abnormalities are described caused by an elevated sympathetic tone with excessive catecholamine release which can lead to ECG changes that suggest primary myocardial dysfunction and ischemia (6). These cardiac mimicry have been reported in patients with subarachnoid hemorrhage as transient ST-segment changes (7, 8) based on left ventricular wall motion disturbances (9). In patients with ischemic or hemorrhagic stroke, ECG abnormalities with arrhythmias are frequently observed and associated with 3-month mortality (10), especially when lesions are located in the right-sided insular cortex (11).

Despite the growing literature on the peripheral interactions of TBI (12), only small case series or single cohort studies of patients with isolated TBI have highlighted the link between TBI and cardiac dysfunction, without data on early ECG abnormalities and outcome. The frequency of ECG abnormalities is related to Glasgow Coma Scale (GCS) on admission (13), but not to brain severity indices like computerized tomography (CT)-characteristics or ICP-treatment (14, 15) ECG abnormalities in patients with TBI can be regarded as a secondary effect of brain injury or an expression of primary cardiac dysfunction, due to thoracic injury (16, 17) and for that reason more difficult to interpret than in neurovascular diseases.

Therefore, we aimed in this current study to evaluate the incidence and clinical significance of ECG abnormalities in patients with severe TBI with and without thoracic injury and their association with brain injury severity and outcome. First, we determined the incidence of ECG abnormalities among patients with severe TBI admitted to the ICU by evaluating early ECG recordings obtained within 24 h after ICU admission. This time window was chosen because existing literature suggests that cardiac dysfunction occurs early after brain injury (18). Second, we evaluated the relationship of ECG abnormalities with brain injury severity defined by CT-characteristics and Therapy Intensity Level (TIL). Lastly we assessed the predictive value of these ECG abnormalities on in-hospital mortality.

MATERIALS AND METHODS

In this retrospective study data of patients aged ≥16 years with severe TBI (GCS score <8 after initial stabilization) with ICP-monitoring admitted to the ICU of the University Medical Center Groningen (UMCG) from 2002 till 2018 were analyzed. Data were collected from medical records and ambulance forms. Patients with ECG recordings obtained within 24 h after ICU admission were included. Patients with pre-existing cardiac disease like myocardial infarction, (paroxysmal) arrhythmias, congenital heart disease (cardiomyopathy), or the presence of a pacemaker or implantable cardioverter defibrillator were excluded for analyses. GCS score and pupillary reactivity were documented on admission including hypoxia (oxygen saturation <90%), hypotension (systolic blood pressure <90 mm Hg or requiring vasopressors) within the first 24 h that are known as predictors of outcome (5). Trauma severity was defined according to the Injury Severity Score (ISS) (19) derived from the Abbreviated Injury Scale (AIS) (20). Thoracic injury was defined as an AIS-Thorax score of ≥1, such as the presence of at least one rib fracture or a contusion of the sternum. Laboratory measurements of potassium [hypokalemia (<3.5 mmol/l) and hyperkalemia (>5.0 mmol/l)] were frequently determined on a Radiometer ABL 700/800 series analyzer and with standard ICU equipment. A waiver for this study was obtained by the Medical Ethical committee of the UMCG (M11.096947).

Computerized Tomography

All patients underwent a brain CT-scan directly after stabilization at the ED or during ICU admission in case of secondary deterioration. CT-scans were evaluated by a board-certified radiologist and brain injury severity was categorized according to the Marshall-criteria based on the absence or presence of diffuse injury (grade 1–4) or evacuated or non-evacuated mass lesion >25 cc (grade 5–6) (21). The highest Marshall-score obtained within 24 h of ICU admission was used for analysis. Location of traumatic lesions (subarachnoid hemorrhage, contusion, extra- or intradural hematoma, petechial hemorrhages) were recorded separately for both hemispheres per region (frontal, temporal, parietal, occipital, brainstem).

Intracranial Pressure Treatment

Patients with severe TBI were treated in accordance with international guideline-based management with ICP-monitoring (RAUMEDIC® NPS-2). The treatment protocol aims to maintain ICP ≤ 20–25 mm Hg and cerebral perfusion pressure (CPP) between 60–70 mm Hg with stepwise escalation of therapy according to Therapy Intensity Level (TIL) including sedation, cerebrospinal fluid (CSF) drainage, hyperosmolar

therapy [mannitol and/or hypertonic saline (HTS)], and second-tier therapy (surgical evacuation and/or barbiturates) (2, 3). Every hour ICP, CPP and TIL score were noted. For the current study the maximum TIL (TILmax) within 24 h of ICU admission was used for analysis.

Electrocardiographic Recording

The first abnormal ECG obtained at the ED or within 24 h of ICU admission was used for analysis. A 12-lead ECG was obtained and recorded with CardioPerfect equipment (Cardio Control) and digitally stored in MUSE^{TM} (General Electric Company) or manually in the patient record. Digitally stored ECGs were automatically examined for rate (abnormal: <60 or >100 beats/min) and intervals [abnormal: *PR*: <120 ms, >210 ms, *QRS*: >120 ms, *QTc* (22): >450 ms in men and >460 ms in women]. The presence of ventricular repolarization disorders (ST-segment, T-wave, presence of pathological Q-wave or U-wave), conduction defects, and cardiac arrhythmias (supra-/ventricular) were independently scored by two cardiologist-intensivists (IH and LK-K) according to standardized criteria (23). We considered an ECG as abnormal with presence of the following characteristics: A. ventricular repolarization disorder and/or B. conduction disorder and/or C. cardiac arrhythmia.

Statistical Analysis

Analysis is performed with IBM SPSS 23.0 and software package R. All normally distributed variables are presented as means, standard deviations and 95% confidence intervals and mean values between groups are analyzed with independent-samples *t*-tests. Non-normally continuous data are presented as medians and ranges and comparison between groups with the Mann-Whitney test. All nominal or categorical variables are described as frequencies and percentages. Comparison between groups was performed using Fisher's exact test. A *p*-value of <0.05 was considered to be statistically significant.

With logistic regression analysis we determined the predictive value of several established factors for outcome on presence of ECG abnormalities. As second step the predictive value of ECG abnormalities for in-hospital mortality was determined. First, univariate analysis was done with the following factors: baseline predictors derived from the literature (5) [age, hypoxia, hypotension, ISS, and brain injury severity (GCS, pupillary reactivity presence of diffuse injury)] combined with location of isolated traumatic brain lesions, increase of TIL, and electrolyte disorders (potassium). Second, variables with a *p*-value of <0.10 in univariate regression were used in multivariate logistic regression. Associations between independent- and depend variables were displayed as odds ratios (OR) and the discriminatory power as Nagelkerke's R^2.

RESULTS

From a total of 298 consecutive patients with severe TBI who received ICP-monitoring, 16 patients were excluded due to history of cardiac disease and 84 patients due to absence of ECG within 24 h after ICU admission. Clinical data of 198 patients with ECG recordings were available for analysis (**Table 1**), with similar patient characteristics in comparison to excluded patients. Patients had a mean (SD) age of 40 ± 19 years and median (IQR) admission GCS score of 3 (3–6), 78% were male. Two third of injuries were road traffic accidents (67%). Median ISS (IQR) was 29 (23–34) with concomitant thoracic injury (AIS-Thorax) in 105 patients (53%). Mean potassium levels were abnormal in 20% of the patients with respectively 16.5% hypokalemia and 3.5% hyperkalemia. Hypoxia was present in 12% and hypotension in 16% of patients until 24 h after ICU admission.

Incidence of Electrocardiographic Abnormalities

Patients showed in 88% abnormalities consisting of A. ventricular repolarization disorders (57%), B. conduction disorders (45%), and C. cardiac arrhythmias (38%).

Specific ECG characteristics were observed as follows:

A. Ventricular repolarization disorders: most common were ST-segment abnormalities (36%). An abnormal T-wave occurred in 28%. Presence of pathological Q-wave or U-wave was seldom, both in 1% of patients.

B. Conduction disorders: QTc-prolongation (36%) was the most common conduction disorder and significantly more present in men ($p = 0.023$) (40 vs. 22%). An abnormal QRS-interval was present in 11% and an abnormal PR-interval in 5% of patients.

C. Cardiac arrhythmias: were mostly supraventricular origin (95%) with respectively 66% sinoatrial node (sinus tachycardia 35% and sinus bradycardia 31%) and 29% atrial or atrioventricular (AV) junctional dysfunction. Ventricular arrhythmias were present in 5% of patients.

No further differences between men and women were observed for other ECG characteristics.

Computerized Tomography Characteristics

According to the Marshall-criteria, diffuse brain injury (grade 1–4) was present in 69% and an mass lesion (grade 5–6) was present in 31% of patients. Frequency of ventricular repolarization disorders was not significantly different between patients with diffuse injury or mass lesion (54 vs. 65%, $p = 0.166$). Conduction disorders were significantly more present in patients with diffuse injury compared to patients with mass lesions (respectively 50 vs. 34%, $p = 0.045$). Although the incidence of cardiac arrhythmias was comparable in patients with diffuse injury or mass lesion, namely 38 and 37% (**Table 2**), the increase in grading of diffuse brain injury was associated with more arrhythmias ($p = 0.042$). If traumatic lesions were present, ECG abnormalities were observed in 87–93% of patients, depending on the type of traumatic lesion. Subarachnoid hemorrhage (64%) and hemorrhagic contusion (63%) were most common, with ventricular repolarization disorder in 57–56%, conduction disorders in 39–44% and cardiac arrhythmias in 39–34% of patients (respectively **Table 3**).

Therapy Intensity Level

Increase of TIL within the first day of ICU admission occurred in 39% of patients, with the following TILmax levels:

TABLE 1 | Patient characteristics divided by in-hospital mortality.

Patient characteristics	Study cohort *n* = 198	Survivors *n* = 139 (70%)	Non-survivors *n* = 59 (30%)	*P*-value
Mean age at injury (SD)	40 years (19)	37 years (18)	46 years (19)	0.004
Male	154 (78%)	78%	76%	0.852
Place of accident				0.340
Road traffic	132 (67%)	68%	63%	
Home	32 (16%)	14%	22%	
Public space	16 (8%)	8%	8%	
Work	12 (6%)	6%	7%	
Sports	6 (3%)	4%	0%	
Mechanism of injury				0.483
Collision	110 (56%)	58%	49%	
Fall	71 (36%)	35%	39%	
Other	17 (9%)	7%	12%	
Hypoxia	24 (12%)	8%	22%	0.008
Hypotension	31 (16%)	12%	25%	0.019
ISS	29 (24–35)	27 (22–35)	29 (25–38)	0.067
AIS-Head	5 (4–5)	4 (4–5)	5 (5–5)	<0.001
AIS-Thorax	105 (53%) 3 (2–4)	79 (57%) 3 (2–4)	26 (44%) 3 (2–4)	0.031
GCS*	192 (97%) 3 (3–6)	3 (3–6)	3 (3–6)	0.330
Pupil reactivity*	180 (91%)			0.021
Bilateral	131 (73%)	77%	64%	
Unilateral	21 (12%)	13%	9%	
Absent	28 (16%)	10%	27%	
CT-scan (Marshall-criteria)				<0.001
Diffuse injury II	77 (39%)	50%	14%	
Diffuse injury III	46 (23%)	22%	25%	
Diffuse injury IV	13 (7%)	4%	12%	
Mass lesion V	11 (5%)	7%	3%	
Mass lesion VI	51 (26%)	17%	46%	

*Values are represented as medians (interquartile range) or numbers (%), unless indicated differently. *on admission. AIS, abbreviated injury scale; CT, computerized tomography; GCS, glasgow coma scale; ISS, injury severity score; SD, standard deviation; TBI, traumatic brain injury.*

CSF drainage (15%), hyperosmolar therapy (13%; 65% both mannitol and HTS, 22% only mannitol, 13% only HTS), surgical evacuation (11%) and barbiturate therapy (1%). ECG abnormalities varied from 79–92% without significant differences between TIL levels ($p = 0.280$). Ventricular repolarization disorders were present in 50–66% of patients, without differences between TIL levels ($p = 0.658$). Conduction disorders were observed in 38–50% of patients without significant differences between TIL levels ($p = 0.914$). Only in patients treated with hyperosmolar therapies, cardiac arrhythmias were significantly more frequent (65%, $p = 0.022$) compared to other TIL levels (sedation 35%, CSF-drainage 35%, surgical evacuation 24%). Hypotension until the first day of ICU admission was observed in 23% of patients ($n = 6/26$) treated with hyperosmolar therapies without an association with cardiac arrhythmias ($p = 0.628$).

Prediction of ECG Abnormalities and In-hospital Mortality

In-hospital mortality was 30%, with brain injury in 92% as primary cause of death and in 8% accompanied by systemic complications of which four patients died by cardiac arrest.

Univariate regression analysis showed no association between ECG abnormalities with left- or right isolated located traumatic lesions, thoracic injury, electrolyte disorders, or outcome predictors. Regarding specific EGC characteristics, multivariate analysis showed that only hypoxia (odds ratio (OR) = 3.88; confidence interval (CI) 1.20–12.54; $p = 0.024$; $R^2 = 0.151$) was independently associated with presence of conduction disorders. Cardiac arrhythmias were associated with a higher ISS ($p = 0.045$).

Non-survivors had a significantly higher age ($p = 0.005$), more hypoxia ($p = 0.007$) or hypotension ($p = 0.016$), more

TABLE 2 | Incidence of electrocardiographic abnormalities divided by Marshall-criteria.

Marshall-criteria		Study cohort $n = 198$			Abnormal ECG $n = 175$ (88%)	Ventricular repolarization disorder $n = 113$ (57%)	Conduction disorder $n = 89$ (45%)	Cardiac arrhythmia $n = 75$ (38%)
		n	%	ns%	%	%	%	%
Diffuse injury	II	77	39	10	88	51	46	30
	III	46	23	33	91	61	54	46
	IV	13	7	54	85	46	62	62
Mass lesion	V	11	5	18	73	64	18	36
	VI	51	26	53	90	65	37	37

Values are represented as numbers or percentages. ECG, electrocardiography; ns, non-survivors.

TABLE 3 | Incidence of electrocardiographic abnormalities divided by type and location of traumatic lesions.

Traumatic lesions	Study cohort $n = 198$		Abnormal ECG $n = 175$ (88%)	Ventricular repolarization disorder $n = 113$ (57%)	Conduction disorder $n = 89$ (45%)	Cardiac arrhythmia $n = 75$ (38%)
	n	%	%	%	%	%
Subarachnoid hemorrhage	127	64	87	57	39	39
Basal	9	7	78	11	67	56
Cortical	88	69	85	59	39	35
Multiple	30	24	97	63	33	47
Hemorrhagic contusion	124	63	88	56	44	34
L temporal (+)	37	24	89	51	41	35
L temporal (-)	14	8	86	50	43	21
R temporal (+)	36	23	78	61	22	28
R temporal (-)	16	10	69	50	13	31
Subdural hematoma	89	45	90	55	44	45
L (-)	33	37	91	55	46	42
R (-)	31	35	87	52	42	39
Petechial hemorrhage	41	21	93	49	54	29
Brainstem	15	37	93	53	47	40
Thalamus/IC	16	39	94	50	50	31
Corpus callosum	10	24	100	60	60	60
Epidural hematoma	32	16	88	59	47	34
L (-)	14	44	78	71	36	21
R (-)	15	47	93	47	47	47

Values are represented as numbers or percentages. ECG, electrocardiography; IC, Internal capsule; L, left-sided; R, right-sided.
For the concerning type of traumatic lesion: (-) isolated, (+) non-isolated.

arrhythmias ($p = 0.015$), more presence of diffuse brain injury ($p = 0.001$), and more frequently an increase of TIL ($p < 0.001$) (**Table 4**). In multivariate regression analysis in-hospital mortality was independently associated with hypotension (OR = 4.13; CI 1.16–14.78; $p = 0.029$; $R^2 = 0.271$) and presence of diffuse brain injury (OR = 0.33; CI 0.14–0.82; $p = 0.017$; $R^2 = 0.271$) (adjusted for age, hypoxia, cardiac arrhythmias, ISS, pupil reactivity, and increase of TIL).

DISCUSSION

Within a large sample of patients we observed that early ECG abnormalities are common in patients with severe TBI and are associated with brain injury severity but not to in-hospital mortality. Increased grading of diffuse brain injury and Therapy Intensity Level as indicators of brain injury severity were associated with more cardiac arrhythmias. ECG abnormalities were not associated with location of traumatic brain lesions nor with the presence of thoracic injury. These findings lend further support to the assumption that ECG abnormalities might be regarded as secondary effect of brain injury severity in the early phase after injury and may allow a more rational approach regarding neuroprotective measures.

In our cohort of patients with severe TBI, ECG abnormalities were very often observed in the acute phase after injury, in 88% of patients. Ventricular repolarization disorders were

TABLE 4 | Univariate- and multivariate linear regression analysis.

Predictor	Univariate OR (95% CI)	*P*-value	Multivariate OR (95% CI)	*P*-value
ECG abnormalities				
Age	1.01 (0.98–1.03)	0.486	..	..
Hypoxia	1.51 (0.33–6.89)	0.595	..	..
Hypotension	1.27 (0.35–4.56)	0.714	..	..
Thoracic injury	0.48 (0.19–1.20)	0.114	..	..
ISS	1.05 (0.10–1.10)	0.075	..	..
GCS	0.84 (0.67–1.05)	0.127	..	..
Bilateral pupil reactivity	0.82 (0.28–2.40)	0.709	..	..
Diffuse brain injury	1.20 (0.48–2.99)	0.703	..	..
Isolated left sided lesion	0.77 (0.28–2.12)	0.610	..	..
Isolated right sided lesion	0.71 (0.24–2.09)	0.534	..	..
Increase of TIL	0.56 (0.23–1.33)	0.186	..	..
Potassium abnormalities	1.33 (0.37–4.88)	0.664	..	..
In-hospital mortality				
Age	1.02 (1.01–1.04)	0.005	1.02 (1.0–1.04)	0.106
Hypoxia	3.29 (1.38–7.86)	0.007	2.05 (0.58–7.32)	0.267
Hypotension	2.62 (1.20–5.74)	0.016	4.13 (1.16–14.78)	0.029
ECG abnormalities	2.18 (0.71–6.70)	0.175	..	..
A. Ventr. rep. dis.	1.39 (0.75–2.60)	0.297	..	..
B. Conduction dis.	0.95 (0.52–1.76)	0.871	..	..
C. Cardiac arrhythmias	2.16 (1.16–4.03)	0.015	1.96 (0.88–4.34)	0.097
ISS	1.03 (1.00–1.06)	0.072	1.00 (0.96–1.04)	0.934
GCS	0.92 (0.77–1.01)	0.328	..	..
Bilateral pupil reactivity	0.53 (0.27–1.05)	0.070	1.01 (0.40–2.58)	0.980
Diffuse brain injury	0.32 (0.17–0.61)	0.001	0.33 (0.14–0.82)	0.017
Increase of TIL	3.62 (1.91–6.83)	<0.001	2.09 (0.93–4.73)	0.076

CI, confidence interval; CSF, cerebrospinal fluid; CT, computerized tomography; ECG, electrocardiography; GCS, glasgow coma scale; OR, odds ratio; ISS, injury severity score; TIL, therapy intensity level.

present in more than half of the patients, mostly comprising ST-abnormalities. Conduction disorders occurred in 45%, including mostly QTc-prolongation and arrhythmias, mostly of supraventricular origin, were present in 38% of patients. We observed more ECG abnormalities in comparison to findings of earlier studies, which might be related to their restricted age inclusion criteria (up to 50 years) and the presence of isolated TBI (24) or less severe head injured patients (13). These frequencies are also much higher compared to baseline ECG characteristics of the healthy adult patients from the LifeLines Cohort from our hospital with only 7.4% cardiac arrhythmias and 1.5% QTc-prolongation, with the latter being more prevalent in men in line with findings from our study (25). This cohort could be considered as a reliable base line comparison to our patients, and therefore suggests a secondary effect of the injury itself.

However, despite this high frequency of ECG abnormalities after injury, it is unclear whether these have to be interpreted as a secondary effect of brain injury or as primary cardiac dysfunction. First, it has to be determined if these ECG abnormalities are related to direct injury to a specific location within the brain or reflect the extent of diffuse injury of the traumatic cerebral insult (18). Cardiac mimicry are described in both neurological and neurosurgical patients (6). In patients with stroke, involvement of the insular cortex has been associated with QTc-prolongation (26) and ECG abnormalities occurred more frequently when lesions were located in the right-sided insular cortex (11). It has been demonstrated that stimulation of the left insular cortex causes parasympathetic cardiac responses with the right insular cortex showing sympathetic responses (27). Subsequently, arrhythmias and fatal cardiac outcome have been related to intracerebral infarct location, and a role of the insula in the occurrence of arrhythmia has been confirmed in later studies in ischemic stroke (28–31). However, in our cohort of patients with severe TBI, we did not find an association between isolated left- or right located temporal traumatic lesions and ECG abnormalities. An explanation for this absent relation of ECG abnormalities with a specific region in patients with severe TBI, could be that in stroke more circumscribed areas of injured brain are present while in TBI the more global effects of blunt head injury might obscure the relationship between the insular region and arrhythmias. This assumption is confirmed by our observation that arrhythmias were more frequent with increasing grading of diffuse brain injury. This finding is in line with the postulation that more severely injured patients have a higher sympathetic activation as a result of the stress response to the trauma itself (32). Diffuse brain injury is likely a surrogate for

a greater degree and extent of diffuse energy transition during the accident.

The maximum TIL was used as another indicator for brain injury severity since this is regarded a reliable determinant of ICP management in patients with TBI (3). In our patients with severe TBI, ECG abnormalities with ventricular repolarization disorders and conduction defects were often observed and not associated with different maximum TIL levels. However, only arrhythmias were significantly more frequently observed in patients who required ICP escalation hyperosmolar therapies, without an association with well-known adverse events like electrolyte disorders and acute hypotension in the acute phase of injury (33). These results are in line with observations of raised ICP with reversible cardiac arrhythmias in animal studies (34) and in a small human case series of patients with varying intracranial conditions (35). Arrhythmias were present in one out of three patients and associated with in-hospital mortality. These findings are in line with cardiac dysfunction in patients with (isolated) TBI (13, 24) and even higher than frequently observed ECG abnormalities in patients with ischemic (60%) or hemorrhagic stroke (50%) during admission, in which arrhythmias are associated with 3-month mortality (10).

However, after adjusting for baseline outcome predictors our study showed that only hypotension and the presence of diffuse injury were independently predictive for in-hospital mortality. These data suggest that cardiac arrhythmias by itself are of less importance for survival in the acute phase after injury.

Another issue is whether these ECG abnormalities might be caused by primary cardiac dysfunction instead of reflecting a secondary effect of brain injury. After trauma, ECG abnormalities can reflect cardiac dysfunction, caused by thoracic injury, with potentially life-threatening complications that require intensive cardiac monitoring and treatment with vasoactive agents (16, 17). Since half of our patients had concomitant thoracic injury and we did not observe an association with specific ECG characteristics in patients with thoracic injury, cardiac injury as cause of ECG abnormalities was considered less likely. Besides, systemic effects could also influence the ECG pattern. Electrolyte disorders including abnormal potassium levels, which are associated with specific ECG abnormalities (36), were only present in one in five patients and were not associated with ECG abnormalities. This finding may be related to our policy of aggressive correction of potassium disturbances directly after admission. In ICU patients, supraventricular arrhythmias are well-recognized and have been reported as a results of increased catecholamine release (37). In trauma patients admitted to the ICU, atrial arrhythmias were reported in 7% (38), which is in accordance with our association of cardiac arrhythmias and a higher ISS. Conduction disorders were independently associated with presence of hypoxia, which is in line with prolongation of QTc-interval in healthy subjects during acute exposure to hypoxia (39). Since arrhythmias were more common in secondary deteriorated patients, combined with the absent relation with thoracic injury, our data suggest that ECG abnormalities more likely reflect the secondary effect of brain injury (i.e., cardiac mimicry) rather than primary cardiac dysfunction.

Despite the interesting findings of our study, several limitations have to be mentioned. First, our study has a retrospective design and therefore we did not obtain data on all ECGs of patients as assessment was driven by clinical care and not by study design. However, since no differences were present regarding patient characteristics between patients with and without available ECGs along with a considerable number of patients, we deem it likely to conclude that ECG abnormalities occur often in patients with severe TBI. Second, our findings are derived from patients with severe TBI who received ICP-monitoring in a single level-1 trauma center, so our results might not be comparable for all patients with severe TBI and for other centers, although our treatment is in accordance with international guideline-based management. Another limitation is hat in the current study primary cardiac injury as cause of ECG abnormalities was not determined systematically by echocardiography. So far two small prospective case-control studies reported no early major systemic myocardial depression to be present in patients with isolated severe TBI (15, 40). An objective of future studies could be to monitor systematically whether ECG abnormalities are related to primary cardiac ischemia by echocardiography and high-sensitive cardiac troponin T and compare these findings to non-head injured trauma patients.

In summary, in this study we aimed to evaluate the incidence and clinical significance of ECG abnormalities in the acute phase of severe traumatic brain injury. We observed a high incidence of ECG abnormalities without an attribution of location of traumatic lesions on CT-scan to ECG characteristics. Cardiac arrhythmias were associated with brain injury severity but were not an independent predictor for in-hospital mortality after traumatic brain injury. Therefore, our findings likely suggest that ECG abnormalities should be considered as cardiac mimicry representing the secondary effect of traumatic brain injury allowing for a more rationale use of neuroprotective measures.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Medical Ethical committee of the University Medical Center Groningen (M11.096947). The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

JN, IH, and MN put together the study design and conceived the idea for the study. J-JL, JN, IH, MN, LK-K, BJ, SB drafted and

revised the manuscript. J-JL, JN, IH, LK-K, MN acquired and interpreted the collected data. J-JL, JN and SB did the statistical analyses. All authors contributed to the article and approved the submitted version.

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REVIEW
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Hyperventilation in Adult TBI Patients: How to Approach It?

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Hyperventilation is a commonly used therapy to treat intracranial hypertension (ICTH) in traumatic brain injury patients (TBI). Hyperventilation promotes hypocapnia, which causes vasoconstriction in the cerebral arterioles and thus reduces cerebral blood flow and, to a lesser extent, cerebral blood volume effectively, decreasing temporarily intracranial pressure. However, hyperventilation can have serious systemic and cerebral deleterious effects, such as ventilator-induced lung injury or cerebral ischemia. The routine use of this therapy is therefore not recommended. Conversely, in specific conditions, such as refractory ICHT and imminent brain herniation, it can be an effective life-saving rescue therapy. The aim of this review is to describe the impact of hyperventilation on extra-cerebral organs and cerebral hemodynamics or metabolism, as well as to discuss the side effects and how to implement it to manage TBI patients.

Keywords: traumatic brain injury, hyperventilation, hypocapnia, intracranial hypertension, cerebral ischemia

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INTRODUCTION

Intracranial hypertension (ICHT) is the most critical and potentially devastating complication in traumatic brain injury (TBI) patients (1). Since the skull is a rigid compartment, the total volume of the intracranial contents, i.e., brain tissue, blood, and cerebral spinal fluid, will remain constant over time. An increase in the volume of one of these components is initially compensated by shifting parts of the others (i.e., compression of the cerebral venous system can decrease global cerebral blood volume; increased CSF reabsorption and CSF displacement toward the basal cisterns and spinal compartment can decrease the CSF volume); when these mechanisms can no longer compensate for further volume changes intracranial pressure (ICP) will rapidly rise (2). Both the duration of ICHT and the absolute maximum value of ICP have an impact on patients' outcome (3); therefore, therapies aimed at controlling ICP and minimizing the ICHT burden are the cornerstone of TBI management (4).

Although different therapeutic interventions are available, none of them has shown a significant impact on patients' outcome and some potential side effects may limit their use. Modulation of arterial carbon dioxide pressure ($PaCO_2$) has been used since decades in neuro-anesthesia and in neuro-intensive care, because lowering $PaCO_2$ (i.e., hypocapnia) through increased minute volume ventilation (i.e., hyperventilation) can rapidly contribute to reduce the volume of the swollen brain and help control ICP (5); these effects are mediated by cerebral vasoconstriction and reduction in cerebral blood flow (CBF) and cerebral blood volume (CBV) (1, 2).

Although commonly used, hyperventilation has not been extensively supported by robust evidence, its effects might be transient and may not improve the probability of neurological recovery (3). Moreover, by decreasing CBF, hyperventilation may trigger or enhance brain ischemia (4, 5). In addition, hyperventilation has some extra-cerebral effects that may negatively impact

patients' outcome (6). As such, if hyperventilation is frequently employed in TBI patients (7), the potential risks associated with this therapy require an optimal understanding on how to manage $PaCO_2$ in TBI patients.

The aim of this review is to describe the effects of hyperventilation on brain physiology and to discuss its use in the management of TBI patients. Only studies focusing on controlled hyperventilation (i.e., modification of minute ventilation in TBI patients treated with mechanical ventilation and controlled modes) have been evaluated, while pre-hospital hyperventilation or spontaneous hyperventilation will not be discussed.

HYPERVENTILATION, HYPOCAPNIA AND SYSTEMIC EFFECTS

Hyperventilation is characterized by elevated minute alveolar ventilation, which can be secondary to an increase of tidal volume and/or respiratory rate, if the dead space remains constant. This condition is typically observed as a physiological response to hypoxemia, systemic inflammation, chest trauma, or pain; however, in the setting of TBI management, "controlled hyperventilation" is a modification of minute ventilation to obtain hypocapnia (i.e., $PaCO_2$ <38 mmHg) in order to manipulate cerebral hemodynamics and compliance (8). In this setting, acceptable ranges of $PaCO_2$ in clinical practice are considered between 35 and 45 mmHg at sea level (8); when hyperventilation is applied, it can classified into moderate ($PaCO_2$ 31–35 mmHg), forced ($PaCO_2$ 26–30 mmHg), or intensified forced ($PaCO_2$ <26 mmHg), according to $PaCO_2$ levels (9).

There are several non-cerebral effects related to this therapeutic strategy (**Table 1**); as TBI patients often have lung injury (7, 10, 11) due to micro-aspiration, pneumonia or lung contusions (12), promoting hyperventilation by increasing tidal volume can induce ventilator-induced lung injury (VILI) (13) and potentially delay pulmonary healing or worsen outcome (14–16). Moreover, hyperventilation may increase intra-thoracic pressure, which would favor right ventricular dysfunction or, in hypovolemic patients, cause an impairment of the venous return and decrease cardiac output (17). Moreover, hypocapnia compromises coronary blood flow and is associated with an increased risk of myocardial ischemia (18) and the development of arrhythmias (19). Prolonged hyperventilation is associated with respiratory alkalosis (20); alkalemia would shift the oxygen dissociation curve of hemoglobin toward the left, increasing the hemoglobin affinity for oxygen and compromising tissue oxygen delivery (18). Hypocapnia and respiratory alkalosis also lead to pulmonary vasodilation (19) and bronchoconstriction (21), which result in ventilation to perfusion (V/Q) mismatch and secondary hypoxemia in TBI patients with pre-existing lung injury. In animal studies, hypocapnia also decreased surfactant production (22) and increases the permeability of the alveolo-capillary barrier (23), although this has not well-demonstrated in humans. Hyperventilation may also increase intra-abdominal pressure, which can secondarily increase ICP (24); hypocapnia decreases blood flow to the kidneys, skin and muscles tissues and increases platelet adhesion and aggregation (12). Finally, hyperventilation is often associated with electrolytes disturbances, such as hypokalemia, hypocalcemia, and hypophosphatemia (12). Taken all together, these findings suggest that controlled hyperventilation and hypocapnia should be applied with extreme caution to all critically ill patients, because of several negative effects on targets organs.

TABLE 1 | Potential side effects associated with hyperventilation in the human setting.

Systemic	Cerebral
Ventilation-induced lung injury	Cerebral vasoconstriction
Right ventricular dysfunction	Reduced CBF
Reduced cardiac output	Reduced CBV
Myocardial ischemia	Brain hypoxia
Cardiac arrhythmias	Increased neuronal excitability
Tissue hypoxia	Reduced epileptic threshold
Lung V/Q mismatch	Increased release of excitatory amino-acids
Increased intrabdominal pressure	Increased dopamine levels
Reduced renal flow	Altered membrane cell synthesis
Reduced skin flow	
Reduced muscular flow	
Increased platelet adhesion	
Increased platelet aggregation	
Hypokalemia, hypocalcemia, and hypophosphatemia	

V/Q, ventilation to perfusion ratio; CBF, cerebral blood flow; CBV, cerebral blood volume.

EFFECTS OF HYPERVENTILATION AND HYPOCAPNIA ON BRAIN PHYSIOLOGY AND METABOLISM

The brain has a high energy requirement, being responsible for 20% of total body oxygen consumption (25). Since the brain is incapable of storing energy, rapid adjustments of CBF are essential to maintain an adequate supply of oxygen and nutrients to brain tissue (26). Several mechanisms, collectively called "cerebral autoregulation," are effective to keep CBF within the necessary values to meet the cerebral energetical demand (26). As such, CBF is heterogenous and varies according to the metabolic activity of each cerebral region (27); resistance arterioles contract and dilate to regulate CBF in response to different stimuli, such as blood pressure, blood viscosity, transmural pressure, metabolic demand, tissue pH, and electrolytes or $PaCO_2$ (28).

In particular, these resistance arterioles respond to variations in $PaCO_2$ between 20 and 60 mmHg by contracting (i.e., hypocapnia) or dilating (i.e., hypercapnia) (2), a phenomenon called "cerebro-vascular CO_2 reactivity." This response to $PaCO_2$ variations is probably pH-mediated (18) (i.e., low pH or high H^+ concentrations will promote vasodilation, while high pH and low

H^+ vasoconstriction), and is proportionally more relevant with hypercapnia than with hypocapnia (29). Around 70% of the CBV is located within the venous system and is not affected by changes in $PaCO_2$; therefore, changes in CBV following hyperventilation are restricted to the arterial component and are associated with a decrease in CBF (18). In particular, for each mmHg-decrease in $PaCO_2$, there is an approximate decrease of 3% in CBF (2), although the impact of hypocapnia on ICP is less pronounced (5).

Hyperventilation can also result in brain hypoxia (**Table 1**). The main mechanism suggested is the reduction of oxygen supply due global and/or regional hypoperfusion caused by the reduction in CBF (30, 31). Moreover, due to the above-mentioned systemic effects, hypocapnia can lead to additional VILI, with impaired gas exchanges and hypoxemia, and can alter the oxygen hemoglobin dissociation curve, with reduced oxygen delivery (18).

Finally, alkalemia and hypocapnia increase neuronal excitability (32), reduce the epileptic threshold and/or prolong convulsive activities (33). In animal studies, hypocapnia led to an increased cerebral consumption and depletion of local glucose (34, 35). Hypocapnia has also been associated with neurotoxicity (12), by inducing the release of cytotoxic excitatory amino-acid (36), increasing dopamine levels in the basal ganglia (37) and by promoting the inappropriate incorporation of choline into the phospholipids of cell membranes (38).

CONTROLLED HYPERVENTILATION IN TBI PATIENTS

Hyperventilation has been reported to effectively control ICHT in TBI patients (39, 40); in **Table 2**, a summary of most relevant studies reporting data on hypocapnia, ICP and outcome in this patients' population has been provided.

Obrist et al. showed that hyperventilation could rapidly reduce ICP in half of TBI patients, although this was associated to a reduction in CBF in almost all of them (4). The relationship between $PaCO_2$ and ICP is not linear and the most important effects are observed between $PaCO_2$ values of 30 and 50 mmHg (52). Moreover, prolonged hyperventilation (53) will be associated with a progressive reduction of its vasoconstrictive effects, because of the perivascular normalization of pH due to local buffering. As reduced CBF (i.e., oligemia) is frequently observed in the early phase after TBI (54), prolonged hyperventilation should not be initiated in these patients without CBF monitoring. Cerebral blood flow can be measured directly, using Xenon computed tomography (CT) scan, CT perfusion (CTP) scan, or positron emission tomography (PET) scan, but these techniques involve injection of radioactive tracers or contrast media and require patients' transportation, which is not always feasible in severe TBI cases with ICHT (55). Indirect CBF velocities assessment using transcranial Doppler (TCD) ultrasonography does not directly correspond to absolute CBF values (56), although elevated pulsatility index (PI >1.2), low diastolic velocities in the middle cerebral artery (<20 cm/s) and estimated ICP using validated formulas might be helpful to identify TBI patients at risk of hypoperfusion. Different studies have shown a reduction in CBF levels during hyperventilation (5, 57–59); also, the most relevant reduction in CBF was observed in the peri-contusional areas, which are more vulnerable to secondary injuries (59).

If the reduction in CBF is quite consistent, controlled hyperventilation (i.e., mean $PaCO_2$ from 37 to 30 mmHg) could improve indices of cerebral autoregulation function in TBI patients with disturbed pressure-reactivity at baseline, whereas those with intact pressure-reactivity at baseline would have no effect of such intervention (60). Another large cohort study also showed that mild hyperventilation was associated with lower pressure reactivity index (i.e., better autoregulatory function), in particular on day 2 after injury (61). One hypothesis is that hypocapnia and related vasoconstriction could reestablish endothelial reactivity in cerebral vessels, which were previously dilated in order to compensate for reduced cerebral oxygen delivery in the presence of ICHT.

Nevertheless, if a reduction in CBF is observed during hyperventilation, it remains unclear whether this phenomenon is associated with signs of cellular hypoxic injury and anaerobic metabolism. In severe TBI patients, Diringer et al. (62) observed that short and moderate hyperventilation significantly decreased CBF but did not impair global cerebral metabolism and oxygen extraction. As such, the use of neuromonitoring, in particular of cerebral oxygenation and/or metabolism, could provide important findings about the brain tolerance to controlled hyperventilation. Forced hyperventilation has been associated with reduced cerebral oxygenation, which was measured by the jugular bulb oximetry (SjO_2, i.e., the threshold for cerebral hypoxia being <55%), although these results were not consistent in all studies (63–65). However, SjO_2 reflect hemispheric global oxygenation and tissue hypoxia may occur even within normal SjO_2 values (66). Brain tissue oxygen tension ($PbtO_2$) is a regional technique, is well-correlated with local CBF and can directly monitor the areas at higher-risk of secondary ischemia (67). The effects of hyperventilation on $PbtO_2$ are variable, with some studies reported a significant reduction in brain oxygenation (68–71) while others showing no major changes (72, 73) and some reporting an increase in $PbtO_2$, in particular due to the large reduction in ICP with previous cerebral vasodilation (i.e., hyperemia) (45, 74). Recent studies reported unchanged $PbtO_2$ values in adult severe TBI patients undergoing moderate hyperventilation and with a median $PbtO_2$ value at baseline within normal values (i.e., >30 mmHg) (39, 40).

Cerebral metabolic function can be assessed at bedside using the microdialysis technique, or performing PET and magnetic resonance imaging (MRI) spectroscopy studies. In one study, early hyperventilation (i.e., 24–36 h after injury) was associated with a significant increase in tissue lactate and lactate/pyruvate ratio, suggesting anaerobic metabolism and tissue hypoxia (46); these metabolic effects were less pronounced at a late phase (i.e., 3–4 days after TBI). However, two recent studies showed no effect of moderate hyperventilation on cerebral metabolites in adult

TABLE 2 | List of most relevant clinical studies dealing with controlled hyperventilation in traumatic brain injury (TBI) patients.

References	Aim of the study	Study design Study patients	Study population	Main results	Safety issues
Cold	Association between hyperventilation and decreases of CBF below the ischemic threshold	Retrospective Single center 27	Comatose patients with TBI	Hyperventilation increased the number of areas with severe oligoemia Oligoemia was correlated to a poor outcome	Unsafe
Muizelaar et al. (41)	Effects of normo- and hyperventilation on the outcome	Prospective randomized interventional Single study 113	Patients >3 years old severe TBI	Hyperventilation was associated with poor outcome in 3 and 6 months	Unsafe
Carmona -Suazo et al. (42)	Effect of mild to moderate hyperventilation on cerebral oxygenation	Prospective observational Single center 90	Severe non-penetrating TBI	Increased hyperventilation caused a significant reduction in $PbrO_2$	Probably unsafe
Coles et al. (2002) (43)	Effect of hyperventilation on CBF	Prospective interventional Single center 47	Non-penetrating TBI	Reduction of ICP and CBF Increase in HypoBV Normal global oxygenation parameters	NR
Diringer et al. (44)	Association between hyperventilation and CBF reduction and energy failure	Prospective interventional Single center 13	Adults severe TBI	Reduction on CBF No energy failure	Safe
Imberti et al. (45)	Effects of moderate hyperventilation on ICP, jugular venous oxygen saturation and $PbtO_2$	Prospective interventional Single center 36	Patients>15 years severe non-penetrating TBI	Reductions of cerebral oxygenation (low $PbtO_2$)	Unsafe
Marion et al. (46)	Potential adverse effects of brief periods of hyperventilation	Prospective interventional Single center 20	Severe TBI patients with surgical intracranial mass lesions	Increase in of cerebral glutamate, lactate, and lactate/pyruvate ratio in areas next to injured brain Reduction of CBF in some patients	Probably unsafe
Soustiel et al. (31)	Effects of moderate hyperventilation and mannitol on CBF and cerebral metabolic rates of oxygen, glucose and lactate	Prospective Single center 36	Adult severe TBI and ICP monitoring	Reduction of CBF and $CMRO_2$ after hyperventilation Increase in anaerobic hyperglycolysis and lactate production	Unsafe
Mauritz et al. (47)	ICU management of TBI in Austria	Retrospective multicentric 145	Severe TBI	Aggressive hyperventilation were associated with poor ICU and 90-day outcomes Moderate hyperventilation was associated with better outcomes	Probably safe
Dumont et al. (48)	Inadequate ventilation and mortality in TBI	Retrospective Single center 77	Severe adult TBI patients	Hyper and hypoventilation were associated with increased in-hospital mortality	Unsafe
Rangel-Castilla et al. (49)	Effects of hyperventilation on cerebral hemodynamic	Prospective interventional Single center 186	Severe TBI patients	Reduction ICP, mean arterial pressure, jugular venous oxygen saturation, brain tissue oxygenation, and flow velocity	NR
Brandi et al.	Cerebral effects of moderate short-term hyperventilation	Prospective interventional Single center 11	Non-penetrating severe TBI adult patients Monitoring with ICP, $PbtO_2$, and cMD	Decreased ICP Reduced $PbtO_2$ but within normal ranges Cerebral glucose, lactate, and pyruvate unchanged	Safe
Tanaka et al. (50)	Association of ICP control management with neurological outcome	Retrospective Observational multicentric 195	Adult mild TBI patients	Hyperventilation was associated with poor outcome in 3 months	Unsafe
Svedung Wettervik et al. (51)	Cerebral effects of moderate short-term hyperventilation Outcome effects of moderate short-term hyperventilation	Retrospective observational Single center 120	Adult severe TBI patients Monitored with ICP and cMD	No effects on cerebral metabolism Hyperventilation was associated with better cerebral autoregulation indices	Safe
Zeiler et al.	Association between TIL for ICHT and cerebrovascular reactivity	Prospective Multicentric 249	Monitoring with ICP	Hyperventilation was associated with a modest improvement in cerebral autoregulation indices	NR

CBF, cerebral blood flow; TBI, traumatic brain injury; $PbrO_2$, regional brain oxygen pressure; ICP, intracranial pressure; HypoBV, hypoperfusion brain volume; $PbtO_2$, brain tissue oxygenation; CMRO, cerebral metabolic rates of oxygen; cMD, continuous microdialysis; TIL, therapeutic intensity level; ICHT, intracranial hypertension; NR, not reported.

TBI patients (39, 40). Using PET scan, one study ($n = 9$) showed that moderate and intense hyperventilation resulted in reduced CBF and increased oxygen extraction, but a constant oxygen metabolism (i.e., no energy failure) (44). In two larger studies (43, 75), hyperventilation (i.e., $PaCO_2$ <30 mmHg) increased the volume of hypoperfused cerebral areas within the injured brain, which, in the absence of increased oxygen extraction, would result in tissue hypoxia.

With all these potential side effects, which is the effect of controlled hyperventilation on the outcome of TBI patients? In one large retrospective study ($n = 251$), Gordon et al. (76) reported a lower mortality in TBI patients undergoing hyperventilation (i.e., $PaCO_2$ between 25 and 30 mmHg for 6 to 41 days); however, more severe neurological sequelae were observed among survivors in the hyperventilation group when compared to the other. Only one prospective randomized clinical trial has investigated the effects of hyperventilation in this setting; Muizelaar et al. (41) compared the 3- and 6-month neurological outcome of patients who were kept at a median $PaCO_2$ of 25 mm Hg to those kept at a median of 35 mmHg for 5 days: forced hyperventilation was associated with a higher proportion of patients with poor outcome. Interestingly, among patients being treated with controlled hyperventilation and tromethamine (THAM, i.e., a buffer that prevents pH changes within the extracellular cerebral fluid and excessive vasoconstriction), there was a higher proportion of patients with long-term favorable neurological outcome when compared to the others.

DISCUSSION: A PRACTICAL APPROACH

The initial $PaCO_2$ targets in TBI patients with normal ICP values undergoing mechanical ventilation should be within normal values (i.e., 38–42 mmHg—**Figure 1**); although Brain Trauma Foundation guidelines could not identify an optimal threshold for $PaCO_2$ values in the initial phase of TBI management [(66), international consensus recommended for these "physiological" values as oligemia is frequent in the first 24–48 h after injury and could be aggravated by hypocapnia (49, 50). Prophylactic (i.e., in the absence of ICHT) and prolonged hyperventilation is not recommended and should not be used, (61) as it would provide no benefits and could result in tissue hypoxia and cerebral metabolic disturbances. In order to detect cerebral oligemia in these patients, an initial CTP scan could be helpful to identify very low CBF values, which would result in secondary ischemia in case $PaCO_2$ would decrease below physiological values. In the

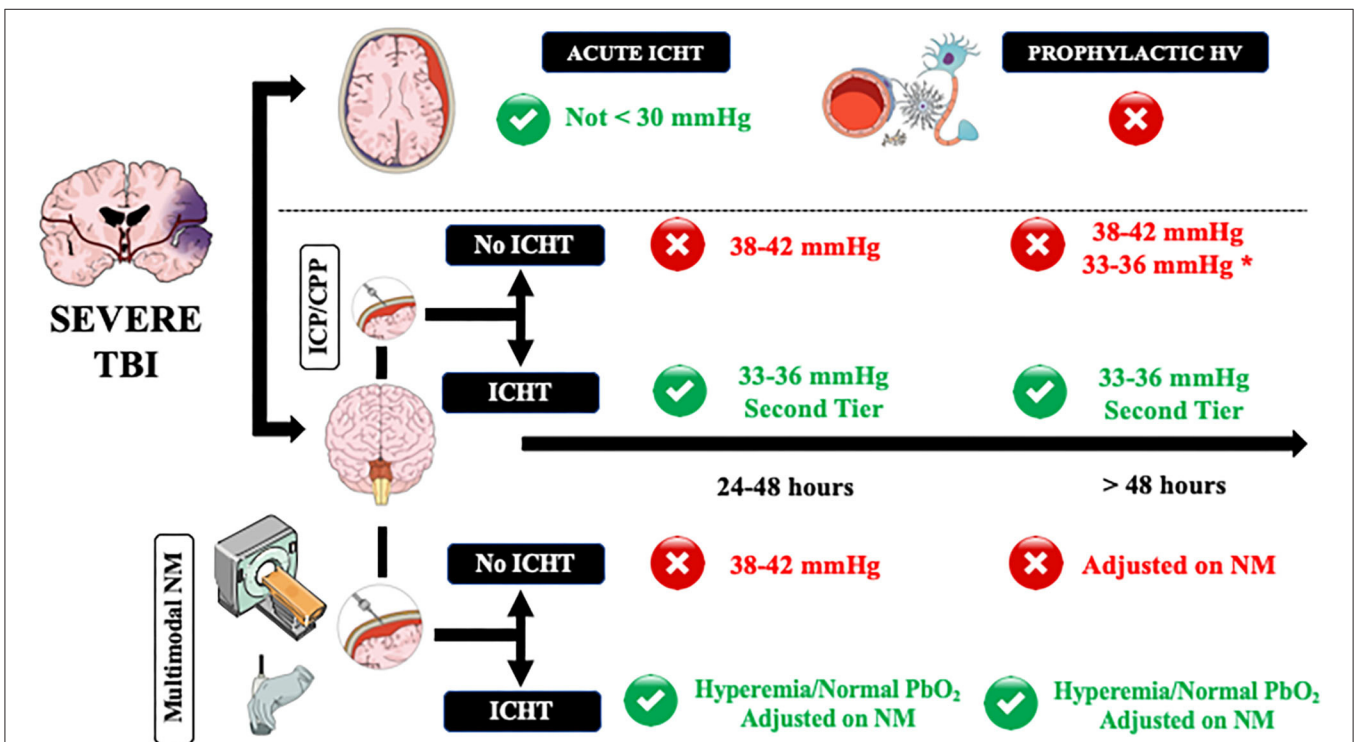

FIGURE 1 | A practical approach on how to manage controlled hyperventilation and hypocapnia in traumatic brain injury (TBI) patients. Acute intracranial hypertension (ICHT) = life-threatening elevation in ICP, in particular when signs of herniation (i.e., anisocoria, apnea, hypertension, bradycardia) are present. ICHT, intracranial pressure close to the critical threshold for therapy without signs of herniation; HV, controlled hyperventilation and hypocapnia. Green and red circles refers to the potential use (green) or contraindication (red) to the use of HV. NM, neuromonitoring. *In case of diffuse brain injury but with high potential risk of tissue hypoxia. **Adjusted on neuromonitoring.

absence of CTP, cerebral ultrasound, using a combination of PI, estimated ICP and diastolic CBF velocity, could identify patients at risk of cerebral hypoperfusion. A close attention on gas analyses monitoring, requiring repeated sampling and end-tidal CO_2 ($etCO_2$) monitoring, is necessary in this phase, as hyperventilation in the absence of elevated ICP is frequently observed in adult TBI patients (61). Importantly, $etCO_2$ might have some limitations in case of concomitant severe chest trauma and hemodynamic instability (i.e., low cardiac output) (77). Whether targeting normal $PaCO_2$ or pH values would be the most appropriate approach remains unknown in these patients. However, as cerebral perivascular pH could be influenced by other factors than $PaCO_2$ and systemic pH (i.e., local metabolism, K^+, isolated cerebral hypoxia) and therefore be less accurately predicted, using $PaCO_2$ levels and quantifying changes in cerebral hemodynamics and physiology to $PaCO_2$ changes at bedside is more feasible for physicians. If ICP remains within acceptable values after 48 h from the injury (i.e., <15 mmHg), lower $PaCO_2$ values (i.e., 33–36 mmHg) could result in improved cerebral autoregulation (66), however it is hard to recommend this approach routinely in all severe TBI patients. TBI patients at the highest risk of impaired cerebral autoregulation are those with diffuse brain injury (51); as such, if TCD assessment shows normal CBF velocities in these patients, lower $PaCO_2$ values (i.e., 33–36 mmHg) could be tolerated, although a more comprehensive neuromonitoring would be the only effective solution to detect the potential occurrence of tissue hypoxia.

As hyperventilation combined with hypocapnia is the most rapidly available method to reduce ICP, moderate and brief hyperventilation should be used to treat life-threatening elevation in ICP, in particular when signs of herniation (i.e., anisocoria, apnea, hypertension, bradycardia) are present (61) and could be used as a bridge toward additional interventions (i.e., repeated CT-scan; osmotic therapy; surgery). In this setting, hyperventilation should be of short duration and, if possible, should never decrease below $PaCO_2$ values of 30 mmHg because: (a) the most important effects of $PaCO_2$ on ICP are observed between 30 and 50 mmHg and (b) most of the relevant cerebral side effects were reported for forced hyperventilation. If possible, the use of hyperventilation should be minimized for these patients during the first 24 h after injury, when CBF often is the most reduced (61), unless CBF could be measured.

In patients with ICP values remaining close to the critical threshold for therapy (i.e., 20–22 mmHg), international guidelines recommended the use of controlled hyperventilation only as "tiers 2" therapy, after the failure of increased sedation and osmotics infusion (78); indeed, controlled hyperventilation produced similar effects on ICP but more metabolic disturbances of cerebral metabolism than mannitol in TBI patients (61). In these patients, it is recommended to set $PaCO_2$ around 33–36 mmHg and avoid values <30 mmHg (49). In the absence of other neuromonitoring than ICP and cerebral perfusion pressure (CPP), CTP scan and TCD are helpful to suggest normal or high (i.e., hyperemia) CBF values, which would logically respond to hyperventilation. However, in case of oligemia, physicians could decide to avoid hypocapnia and move to "tiers 3" therapy, such as barbiturates, hypothermia, or decompressive craniectomy, to treat ICHT as hypocapnia would result in additional cerebral hypoperfusion.

In our opinion, invasive neuromonitoring should be also considered in severe TBI patients and ICHT to optimize overall management and, in particular, to assess the effects of low $PaCO_2$ values on cerebral oxygenation and metabolism. As such, $PaCO_2$ values and hyperventilation could be adjusted to the brain tolerance and therapeutic targets individualized on the patients' need. In case of the need for low $PaCO_2$ values and concomitant lung injury, other interventions aiming at reducing CO_2 production, such as increasing sedation or hypothermia, could be considered to induce hypocapnia and avoid lung stress and VILI. However, this strategy should be further evaluated in clinical studies.

If controlled $PaCO_2$ values are mandatory in severe TBI patients because of the significant effects on brain hemodynamics and compliance, high doses of sedatives, often in association with neuromuscular blocking agents (NMBAs), are required to adjust ventilatory parameters to obtain desired $PaCO_2$ targets. As such, in the absence of aggressive therapies for ICHT, it remains unknown when it would be safe to discontinue sedatives and eventually tolerate spontaneous hyperventilation in these patients. If this occurs after several (i.e., >7–10) days from injury, the risk of oligemia would be probably limited. Also, spontaneous hyperventilation after acute brain injury is often triggered by local acidosis (i.e., low pH surrounding the respiratory center located in the brainstem), which result in vascular dilation and would probably compensate from vasoconstriction induced by hyperventilation. In these cases, non-invasive (i.e., TCD) and invasive (i.e., $PbtO_2$) monitoring would again be helpful to individualize therapeutic decisions.

In conclusions, controlled hyperventilation is effective in reducing ICP but it also reduces CBF and might have both cerebral and systemic serious side effects. As such, normal $PaCO_2$ values should be maintained in the early phase after TBI if ICP remains within acceptable values. Controlled hyperventilation (i.e., never below $PaCO_2$ of 30 mmHg) should be used as a temporary life-saving intervention in case of severe intracranial hypertension; $PaCO_2$ levels should be also adjusted and individualized in each patient using CTP and cerebral ultrasound of, whenever possible, advanced multimodal neuromonitoring.

AUTHOR CONTRIBUTIONS

EG, LP, JC, and FT contribute equally to the elaboration of this manuscript. All authors contributed to the article and approved the submitted version.

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OPINION
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Hyperventilation in Severe Traumatic Brain Injury Has Something Changed in the Last Decade or Uncertainty Continues? A Brief Review

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INTRODUCTION

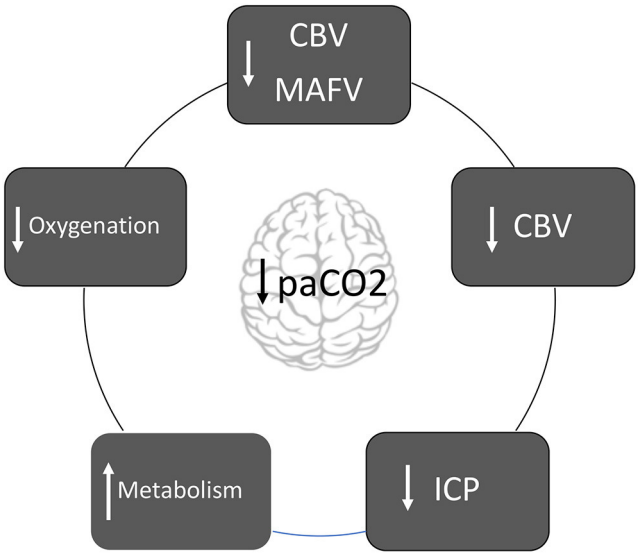
Induced hypocapnia through hyperventilation is a second-line measure to control intracranial pressure (ICP) when it remains elevated despite first line therapies (1). However, is not exempt of severe complications. Current recommendations of the Brain Trauma Foundation based on a level IIB evidence suggested against the use of hyperventilation up to a profound level ($paCO_2$ < 25 mmHg), nor prophylactically and neither for a long period of time (2). Additionally, hyperventilation should be avoided during the first days after trauma when cerebral blood flow (CBF) is critically reduced (2). Lastly, when hyperventilation is necessary, a brain oxygen monitoring is mandatory (2). Focal brain oxygen monitoring is not the only adjunctive monitoring technique that can provide reassurance of the safety of hypoventilation. Jugulovenous oxygen saturation monitoring, for instance, is a much less expensive intervention with a fairly strong evidenciary base (2).

Since these recommendations are based on a low level of evidence, it is clear that certain controversies persist. A literature search of PubMed, Medline, Current Controlled Trials, and EMBASE was performed. The following search terms were used: hyperventilation and severe traumatic brain injury. Details of the studies were recorded using a dedicated data-extraction form. Titles, abstracts, or both, of studies retrieved using the search strategy and those from additional sources were screened independently, and the full text of potentially eligible studies was retrieved and assessed independently for eligibility. Disagreement over eligibility was resolved through open discussion.

Some questions are not yet answered with certainty and the results of recent studies motivate the following points of view:

WHAT HAPPENS TO THE BRAIN PHYSIOLOGY DURING HYPERVENTILATION?

Cerebral blood vessels (< 50 μm) are able to change their diameter when $paCO_2$ levels change through the phenomenon called "CO2 reactivity" (3). Dilatation occurs with hypercapnia



GRAPHICAL ABSTRACT | Diagram about the mechanisms in which hyperventilation affects the brain pathophysiology.

($paCO_2$ >44 mmHg), and constriction occurs with hypocapnia ($paCO_2$ <35 mmHg) (3). This vascular activity occurs when $paCO_2$ levels are between 20 and 60 mmHg, although the upper limit is not well defined. The response of CBF to changes in $paCO_2$ resembles a sigmoid curve (3).

Changes in vessel diameter elicited by hypocapnia and hypercapnia are not proportional (4, 5). If $paCO_2$ increases above 80 mmHg, vasodilation increases CBF around 100–200%, triggering catecholamines release and increase of metabolism. During hypocapnia, for every mmHg of $paCO_2$ decrease, CBF decreases by 3%; thus, $paCO_2$ levels between 20 and 25 mmHg are associated with a CBF reduction of 40–50% (4, 5).

Regarding vascular reactivity, the endothelium reacts to changes in perivascular pH by releasing mediators that regulate the state of smooth muscles (6). These vasoactive mediators include nitric oxide, prostaglandins, cyclic nucleotides, potassium, and calcium (6).

CBF is heterogeneous and changes according to the metabolic activity of each cerebral region (7). In fact, CO_2 reactivity is not uniform (7). During the early phases of severe TBI, CO_2 reactivity is exacerbated, especially in the areas adjacent to contusions or subdural hematomas. For these reasons, changes in normal levels of CO_2 are potentially dangerous secondary insults that can drastically impact on brain physiology.

Cerebral blood volume (CBV) is 3–4 ml per 100 grams of cerebral parenchymal. Seventy percent of the total blood volume is contained in the venous system that does not react to changes in $PaCO_2$ (7). Modifications in CBV are attributed only to blood contained in the arterial system (30%). For each mmHg of $paCO_2$ reduction, CBV decreases by approximately CBV decreases by ∼0.049 ml/100 grams of parenchyma. Therefore, if hypocapnia induces 30% of CBF decrease, CBV decreases only 7% (7). In summary, decrease in the $paCO_2$ decreases CBF, but has little effect on CBV and ICP7. Finally, CBV response to hypocapnia is exacerbated when arterial hypotension is present (7).

Following the Monro-Kellie doctrine, if hypocapnia induces vasoconstriction and CBV decrease, ICP decrease consequently (8). Hypercapnia triggers vasodilation, which leads to an increase in CBV and a subsequent increase in ICP (8).

The ability of cerebral vessels to modify their diameter to keep a constant CBF across a range of perfusion pressures, called "cerebral autoregulation," is a natural survival mechanism that works within certain limits. Preliminary studies with the evaluation of indices obtained from transcranial doppler (Mx, Prx) have shown that cerebral autoregulation improves with hyperventilation; however, this relationship is transient and works only with moderate levels of hypocapnia (8–11).

Hypocapnia induces the release of excitatory amino acids (*N*-Methyl-D-aspartate and glutamate) and increases both glucose consumption, and metabolic rate of O_2 (CMRO2) (1). It also potentiates neuronal excitability and prolongs convulsive activity (1).

WHY IS HYPERVENTILATION POTENTIALLY DANGEROUS?

Hyperventilation-induced hypocapnia is a potent stimulus, which causes vasoconstriction, therefore decreasing CBF and can potentially cause cerebral ischemia (1, 8).

Tissue hypoxia is defined when the amount of oxygen supplied to the cells is insufficient or when the cells—despite an adequate supply—are not able to metabolize it (8). Several clinical studies have showed that hyperventilation significantly reduces CBF and oxygen delivery (12–14).

Positron emission tomography (PET) was applied in some studies (15, 16) in patients without intracranial hypertension, decreasing $paCO_2$ levels from 36 to 29 mmHg. Results from these studies demonstrated that hyperventilation decreased CBF and increased the number and volume of hypoperfused areas. However, these changes were not associated with changes in global (SjvO2, AVDO2) or local (pbtO2) oxygenation reduction. Zones in the range of hypoperfusion showed less reserve capacity to extract oxygen, which increased the risk of ischemic damage (15, 16).

In another study, the 28% of hyperventilated individuals showed a marked decrease in cerebral metabolic rate of oxygen (CMRO2) (17).

Similarly, Marion et al. (18) analyzed regional CBF and tissue hypoxia markers before and after hyperventilation at a target of 24.6 mmHg in individuals without intracranial hypertension. "Apparently healthy areas" adjacent to contusions or subdural hematomas were analyzed at 24–36 h and 3–4 days post-trauma. After hyperventilation, CBF decreased and an increase in glutamate, lactate, and lactate/pyruvate relationship was observed (18). The author's conclusion was that in brain parenchyma adjacent to analyzed areas, even brief periods of

hyperventilation in the acute phase of trauma can significantly increase the risk of secondary brain injury (18).

Diringer et al. (19, 20) tested PET variables after hyperventilation ($paCO_2$ 30 mmHg) in patients with and without ICP increase. CBV, CBF, and cerebral venous oxygen were decreased; however, there was no ischemia or energy dysfunction since CMRO2 remained unchanged at the expenses of oxygen extraction fraction (OEF) increase (19, 20) (**Table 1**).

Hyperventilation-induced hypocapnia is one of the avoidable cerebral secondary insults. Multiple clinical studies have shown the direct relationship between low levels of $paCO_2$ and decrease in global, such as saturation in the jugular bulb (SvjO2) or local parameters, such as tissue oxygen pressure (ptiO2) (21–25).

Hyperventilation can cause hypoxia through various mechanisms: (a) decrease CBF; (b) compromise of pulmonary ventilation-perfusion relationship; (c) deviation to the left of the oxygen-hemoglobin dissociation curve and (d) increased metabolic demands (1, 8). This phenomenon is not limited to brain vessels. The myocardial, intestinal, or renal vasculature are also affected; therefore, hyperventilation also has a negative systemic impact (1, 8).

IS THERE A SOLID EVIDENCE THAT ASSOCIATES THE HYPERVENTILATION WITH A POOR OUTCOME?

Only one prospective, controlled, and randomized study evaluated the association of hyperventilation with outcome (26). Three groups were analyzed: group 1: normoventilation ($paCO_2$ 35 mmHg); group 2: hyperventilation ($paCO_2$ 25 mmHg), and group 3 hyperventilation and THAM (tromethamine). Favorable outcome at 3 and 6 months from the event were significantly lower in the hyperventilation group; however, after 12 months, the differences between the groups were not significant. Of note, there was no evidence of ischemia in any of the three groups (26).

The conclusions of this study should be interpreted with caution. In fact, clinical and imaging characteristics were not well-balanced between the groups. Also, there was a small number of patients per group (type α error). The control group was hyperventilated ($paCO_2$ 31 mmHg), and only 14% of the individuals in groups 1 and 2 respectively and 5% of group 3 had intracranial hypertension. Finally, when analyzing the final outcome at 12 months post-trauma, the best results correspond to hyperventilation + THAM group (26).

IS THERE NEW EVIDENCE ABOUT THE ROLE OF HYPERVENTILATION IN THE MANAGEMENT OF SEVERE TRAUMATIC BRAIN INJURY (TBI)?

Recently, two manuscripts were published regarding the use of hyperventilation in TBI (27, 28). In the first one, Wettervik et al. in a retrospective series concluded that hyperventilation in a mild range ($paCO_2$: 30–34 mmHg) is safe and can improve cerebrovascular reactivity (27). Some considerations deserve to be expressed not to misunderstand the results. First, hyperventilation was induced in the absence of intracranial hypertension (mean ICP between 11 and 14 mmHg). Second, the study lacks monitoring of CBF, cerebral oxygenation, and neuroimaging follow-up that would allow to rule out the occurrence of ischemic complications; therefore, this study does not allow to demonstrate the safety of hyperventilation. Also, the analyzed population showed space-occupying lesions <25 cc with open basal cisterns (Marshall II) and does not specify the location of the microdialysis catheter, which is of extreme importance, since it only obtains data from an area no larger than 1.5 cm^2 in a pathology characterized by dynamism and heterogeneity.

Additionally, prophylactically hyperventilated patients fluctuated during the first 3 days between making up 25 and 33% of the total of the analyzed population, while the mean $paCO_2$ levels of all patients remained in the normoventilation range (35–37 mmHg) throughout the period of study (27). Although the energy metabolism is not modified, this can be explained in different ways. First, the absence of intracranial hypertension.

Second, the position of the microdialysis catheter, which perhaps was implanted in a healthy area without major metabolic compromise. Third, the population that was studied did not specifically direct to those truly hyperventilated (25–33% of total). Of note, the relationship between $paCO_2$ levels and cerebral autoregulation is interesting, although the data should be interpreted with caution in the context of the above-mentioned limitations (27).

In the another study, Brandi et al. concluded that moderate hyperventilation ($paCO_2$: 30–35 mmHg), for a short duration period, does not induce alterations in metabolism or cerebral oxygenation in a cohort of severe TBI (28). The study reaffirms previous pathophysiological concepts about hyperventilation; however, certain reflections are important. First, moderate hyperventilation was utilized in absence of ICP increase (average ICP 16 mmHg) (28). Second, probes were placed in the white matter of the most damaged cerebral hemisphere, in regions of normal appearance on the CT scan. We agree with the decision regarding the monitoring site, but as the authors signaled, PbrO2 only measures local interstitial oxygen availability of a very small area (28). Severe TBI is a heterogeneous condition, and not all areas respond in the same way to HYPERVENTILATION (9). Ischemic volume increases during hyperventilation, inclusive without detection of cerebral oxygen monitoring (17, 18).

Third, patients were included on average at 23 hours after trauma (28).

Fourth, there are some considerations about ventilatory management that need to be mentioned: (a) Due to the risk of alveolar distention, increased intrathoracic pressure, and decreased cerebral venous return with consequent ICP increase, hyperventilation with tidal volume increase is not recommended (1, 2, 8). (b) On the other hand, the patients were in supranormal pa02 values (147 mmHg), which contributes to masking possible declines in PbrO2 (29). In this context, Dellazio et al. described the usefulness of the pbtO2/paO2 relationship to detect episodes of hidden

TABLE 1 | Effect of hyperventilation on cerebral blood flow and metabolic parameters.

Author	Method	Moment of study post Trauma (n/time)	ICP (mmHg)	$paCO_2$ target (mmHg)	Findings
Cold et al. (5)	Xe-CT	15/2 days 16/3–7 days 8/2 week 6/3 week	19	26	Decrease rCBF
Coles et al. (15)	PET	4/24 h 21/2–4 days 8/5–7 days	19.5	29	Decrease ICP/CBF Increase CPP SvJO2/AVO2 without changes
Menon et al. (16)	PET	37–160 h	15	29	Decrease CBF/pvO2 Increase OEF CMRO2/CBV without changes
Coles et al. (17)	PET	15–240 h	17	29	Decrease CBF Increase OEF/CMRO2/ischemic brain volume 28% CMRO2 decrease
Marion et al. (18)	Thermodiffusion Microdialysis	24–36 h 3–4 days	16 19.6	26.1 24.9	Decrease CBF Increase glutamate, lactate, L/P
Diringer et al. (19)	PET	11.3 (8–14) h	14 (6–26)	30	Decrease CBF/CBV/CvO2 Increase OEF CMRO2 without changes
Diringer et al. (20)	PET	11.3 (8–14) h 1–5 days	14 24	30 25	Decrease CBF/CBV/CvO2 Increase OEF CMRO2 without changes

Xe-CT, xenon-computed tomography; PET, positron emission tomography; ICP, basal intracranial pressure; rCBF, regional cerebral blood flow; CBF, cerebral blood flow; CPP, cerebral perfusion pressure; $SvJO_2$, venous saturation of jugular bulb; AVO_2, oxygen arteriovenous difference; pvO_2, oxygen venous pressure; OEF, oxygen extraction fraction; $CMRO_2$, cerebral metabolic rate of oxygen; CBV, cerebral blood volume; L/P, lactate-piruvate relationship; CvO_2, venous content of oxygen.

hypoxia, defined by a ratio below 0.10 (29). In the analyzed Brandi's cohort, the PbtO2/paO2 ratio was 0.20, close to the mentioned value.

Fifth, mean arterial blood pressure (MABP) and cerebral perfusion pressure (CPP) were 92 and 77 mmHg, respectively. Mean CBF velocity of both mean cerebral arteries was 80 cm/s, while the mean PbrO2 value was 32 mmHg (27). In our opinion, these values are unusually elevated for patient's requirement, so, this could explain why moderate hyperventilation did not induce ischemic changes.

DO THE RESULTS OF THE RECENT STUDIES JUSTIFY CHANGING OUR USUAL CLINICAL PRACTICE?

According to the available evidence, our point of view is not to change the current practice of avoiding hyperventilation in the context of severe TBI in the absence of ICP elevation. All efforts should be directed to avoid hypocapnia especially the first 24 h of trauma (30).

ARE THERE CIRCUMSTANCES THAT ALLOW THE USE OF HYPERVENTILATION?

Hyperventilation in the setting of imminent increases in ICP is not explored fully—should we really even be doing that? This is the real question because it is common practice to avoid hyperventilation otherwise.

We cannot afford to easily discard anything useful of HYPERVENTILATION (1, 2). By contrast, we believe that hyperventilation could be used for a short period of time with brain oxygenation monitoring when ICP is not controlled with first line therapies and in certain emergency situations (herniation syndromes, plateau waves, intracranial hypertension associated to hyperemia) as a "bridge" pending definitive solution (1, 2).

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DG, RB, CR, and FM drafting the article, critical revision of the article, and final approval of the version to be published.

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