ORIGINAL ARTICLE

Spontaneous Hyperventilation in Severe Traumatic Brain Injury: Incidence and Association with Poor Neurological Outcome

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Abstract

Background: Hypocapnia induces cerebral vasoconstriction leading to a decrease in cerebral blood flow, which might precipitate cerebral ischemia. Hypocapnia can be intentional to treat intracranial hypertension or unintentional due to a spontaneous hyperventilation (SHV). SHV is frequent after subarachnoid hemorrhage. However, it is understudied in patients with severe traumatic brain injury (TBI). The objective of this study was to describe the incidence and consequences on outcome of SHV after severe TBI.

Methods: We conducted a retrospective, observational study including all intubated TBI patients admitted in the trauma center and still comatose 24 h after the withdrawal of sedation. SHV was defined by the presence of at least one arterial blood gas (ABG) with both $\text{PaCO}_2 < 35$ mmHg and $\text{pH} > 7.45$. Patient characteristics and outcome were extracted from a prospective registry of all intubated TBI admitted in the intensive care unit. ABG results were retrieved from patient files. A multivariable logistic regression model was developed to determine factors independently associated with unfavorable outcome (defined as a Glasgow Outcome Scale between 1 and 3) at 6-month follow-up.

Results: During 7 years, 110 patients fully respecting inclusion criteria were included. The overall incidence of SHV was 69.1% (95% CI [59.9–77]). Patients with SHV were more severely injured (median head AIS score (5 [4–5] vs. 4 [4–5]; $p = 0.016$)) and exhibited an elevated morbidity during their stay. The proportion of patients with an unfavorable functional neurologic outcome was significantly higher in patients with SHV: 40 (52.6%) versus 6 (17.6%), $p = 0.0006$. After adjusting for confounders, SHV remains an independent factor associated with unfavorable outcome at the 6-month follow-up (OR 4.1; 95% CI [1.2–14.4]).

Conclusions: SHV is common in patients with a persistent coma after a severe TBI (overall rate: 69%) and was independently associated with unfavorable outcome at 6-month follow-up.

Keywords: Severe traumatic brain injury, Spontaneous hyperventilation, Hypocapnia, Respiratory alkalosis, Glasgow Outcome Scale

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Background

Carbon dioxide is a powerful modulator of the cerebral vasculature [1, 2]. Hypocapnia induces cerebral vasoconstriction leading to a decrease in cerebral blood flow (CBF) and a consequent decrease in intracranial pressure (ICP) [1, 3, 4]. Thus, in the past, intentional hyperventilation has been proposed as a treatment for intracranial hypertension (ICH) in patients with traumatic brain injury (TBI) [5, 6]. However, numerous recent studies demonstrated an association between hypocapnia and worse functional neurologic outcome [7–10]. In fact, hyperventilation induced reductions in CBF compromise oxidative metabolism, increase cerebral oxygen extraction, and then may precipitate or worsen cerebral ischemia [4, 9, 11–13]. It is for these reasons that current French and International guidelines advocate the avoidance of prolonged prophylactic hyperventilation, particularly during the first 24 h when CBF is more frequently already impaired [14–17]. Hyperventilation can be used as a temporizing measure for elevated ICP, ideally under the supervision of cerebral oxygenation monitoring (brain tissue oxygen tension [$P_{bt}O_2$] or jugular bulb venous oxygen saturation [SjO_2]) [14].

Central or neurogenic spontaneous hyperventilation (SHV) is frequent after a brain injury [18–21]. SHV can also occur in patients with severe TBI still comatose after the withdrawal of sedation. SHV leads to hypocapnia despite minimal or absent ventilator support and may have potential deleterious consequences. However, very little is known about its incidence or effects on functional neurologic outcomes.

The aim of this study was to determine the frequency of SHV in severe TBI patients still comatose after the withdrawal of sedation and its association with worse outcomes. We hypothesized that SHV is associated with poor neurologic functional outcome at 6 months after the trauma.

Patients and Methods

Study Design and Patient Selection

This 7-year retrospective, observational, single-center study was conducted at the Sainte Anne Military Hospital of Toulon (France). Patients with severe TBIs were eligible when they were intubated and admitted to the intensive care unit (ICU) between January 2007 and December 2013. Inclusion criteria were: age ≥ 18 years; severe TBI with a Glasgow Coma Scale (GCS) score ≤ 8 after initial resuscitation; still comatose 24 h after the withdrawal of sedation. Patients were excluded when they died before the withdrawal of sedation, had quick extubation (within 6 h) after the withdrawal of sedation, or no arterial blood gas (ABG) results available in the wake-up period.

All patients were sedated, intubated, and mechanically ventilated in accordance with international guidelines [17]. The institutional therapeutic management approach is presented in Fig. 1 and remained constant throughout the study period.

The Institutional Review Board approved the study and waived the requirement for informed consent from patients and their relatives, given the observational nature of the study.

Definition and Diagnosis of Spontaneous Hyperventilation (SHV)

ABG results were retrieved from patient files for all included subjects during a 7-day period after the withdrawal of sedation. Included subjects had to have at least one ABG that was obtained while ventilated in a pressure support ventilation (PSV) mode or not mechanically ventilated (through a T-tube or extubation). ABGs were collected before or following a delay of at least 30 min after nursing care or other painful procedure.

SHV was defined by the presence of at least one ABG with both $PaCO_2 < 35$ mmHg and $pH > 7.45$. Severe SHV was defined by the presence of both $PaCO_2 < 30$ mmHg and $pH > 7.50$. Patients with SHV not meeting the requirement for severe SHV were considered to have moderate SHV [21].

Data Collected

We accessed a registry of data prospectively collected on all patients intubated for TBIs and admitted to the ICU. The registry reported data on patient characteristics, mechanism of injury, pre-hospital assessment, whole-body computed tomography scan results, evolution in the ICU, in-hospital mortality, and neurologic functional outcome at 6 months according to the Glasgow Outcome Scale (GOS). The GOS score is a 5-point scale, where 1 = death, 2 = persistent vegetative state, 3 = severe disability, 4 = moderate disability, and 5 = good recovery [22]. A senior intensivist or a senior physical medicine and rehabilitation physician assessed the GOS by clinic visits (preferentially) or a phone call to patient or relatives with standardized, structured interviews [23].

Endpoints

The primary endpoint of the study was the GOS at 6 months post-TBI, which was prospectively collected in our registry. GOS was dichotomized to unfavorable neurologic functional outcome (GOS between 1 and 3) and favorable outcome (GOS 4 and 5). Secondary endpoints were in-hospital length of stay and in-hospital mortality.

Fig. 1 Stages of therapeutic management. *CPP* cerebral perfusion pressure, *EEG* electroencephalogram

Statistical Analysis

All statistical analyses were performed with XLSTAT, version 2015.3.01 (Addinsoft, Paris, France). Continuous data are reported as the mean $\pm$ SD. Data that were not normally distributed are expressed as the median and interquartile range [25th–75th percentiles]. Nominal variables are reported as number and proportions (%).

To compare differences in baseline characteristics and evolution between the groups of patients with and without SHV, the χ^2 test or Fisher's exact test was used for categorical variables, and the Mann–Whitney test or Student *t* test was used for continuous variables, as appropriate.

To examine association between SHV and unfavorable functional neurologic outcome (GOS 1–3), we used a simple logistic regression. All parameters with *p* value < 0.1 in the simple logistic regression analysis were included in multivariable logistic regression model to identify independent factors associated with an unfavorable neurologic outcome at 6 months. The Hosmer–Lemeshow goodness-of-fit test and the area under the receiver operating characteristic (ROC) curve were used to evaluate the overall final model fit and the model discrimination, respectively. To detect multicollinearity, we calculated the Variance Inflation Factors of each variable included in the model. Final model results were expressed as the odds ratio (OR) and 95% confidence intervals (95% CI). For all tests, a two-side *p* < 0.05 was considered statistically significant.

Results

Study Population

During the study period, 228 patients with severe TBIs were admitted to the ICU. One-hundred and eighteen patients were excluded, due to death while sedated (*n* = 45), rapid awakening after withdrawal of sedation (*n* = 36), no ABG available (*n* = 34), no evaluation of the 6-month GOS (*n* = 3) (Fig. 2). Among the 110 patients included in the study, the most common mechanism of injury was a motorcycle crash (31%). There were 85 male (77%) and 25 female (23%) patients. These patients had a median age of 38 [22–60] years, a median injury severity score of 23 [16–29], a median abbreviated injury scale (AIS) score for head injury of 5 [4–5], and a median minimal GCS score of 6 [4–8].

Spontaneous Hyperventilation

We collected a total of 473 ABGs: 381 (67.2%) during PSV mode and 155 (32.8%) without mechanical ventilation. The median level of support was 12 cmH₂O (10–14), and

the median tidal volume was 7.3 ml/kg (6.2–9.1) (Additional Table).

SHV was diagnosed in 76 patients with severe TBIs still comatose after the withdrawal of sedation (overall incidence, 69.1%; 95% CI [59.9–77]). The SHV started within the 3 days after the withdrawal of sedation for 72 patients (95%) (2 patients developed SHV at day 4 and 2 patients at day 7). SHV started at a median of 11 (7–16) days after the TBI. Twenty-five of 76 patients with SHV (32.9%) were classified as having a severe SHV. The remaining 51 (67.1%) were considered to have moderate SHV.

At the onset of SHV, 35 patients (46.1%) had an ongoing infection (31 early- or late-onset ventilator-associated pneumonia [88.6%] and 4 nosocomial meningitis [11.4%]). Eighteen of them (49.6%) were already treated with antibiotics for more than 48 h before the start of SHV.

General characteristics of patients with SHV are compared to those without SHV in Table 1. In comparisons of patients without SHV, those with SHV had a more severe TBI, in terms of median initial GCS score (6 [4–8] vs. 8 [6–10]; *p* = 0.006), rate of pupillary abnormality (46.1% vs. 14.7%; *p* = 0.002), and median head AIS score (5 [4–5] vs. 4 [4–5]; *p* = 0.016). There were no significant differences in age, gender, injury severity score, and thoracic AIS score.

SVH patients were significantly more likely to experience at least one episode of ICH before the withdrawal of sedation (52.6% vs. 23.5%, *p* = 0.005), and thus, they more frequently received therapeutic hypothermia (50% vs. 23.5%, *p* = 0.009), barbiturate infusion (18.4% vs. 8.8%, *p* = 0.015), and/or decompressive craniectomy (31.6% vs. 2.9%, *p* = 0.001).

Functional Neurologic Outcome at 6 months

The GOS score distribution was more favorable among patients without SHV (*p* = 0.0007) (Fig. 3). Based on our dichotomization, the proportion of patients with an unfavorable functional neurologic outcome was significantly higher in patients with SHV: 40 (52.6%) versus 6 (17.6%), *p* = 0.0006.

In simple logistic regression analysis, we found that patients with SHV had five times the odds of unfavorable outcome (OR 5.2; 95% CI [1.9–14]). Other factors significantly associated with unfavorable outcome were age above 65 years (OR 4.7; 95% CI [1.6–13.3]), minimal GCS score < 6 (OR 3; 95% CI [1.4–6.7]), pupillary abnormalities (OR 5.6; 95% CI [2.4–13]), Marshall category ≥ 3 (OR 4; 95% CI [1.8–8.9]), and hypernatremia (> 155 mEq/L) (OR 2.7; 95% CI [1.2–6.3] (Table 2).

After adjustment in the multivariable logistic regression model, SHV remained significantly associated with unfavorable outcome (OR 4.1; 95% CI [1.2–14.4]).

Table 1 Characteristics and clinical follow-up variables among patients with and without spontaneous hyperventilation

Variable	Patients without SHV (n = 34)	Patients with SHV (n = 76)	p value
Age (years)	39 [24–59]	38 [22–60]	0.87
Male sex	25 (74%)	60 (79%)	0.53
SAPS II	35 [26–43]	42 [36–49]	0.005
ISS	18 [11–32]	25 [16–29]	0.10
Head AIS ≥ 3	33 (97%)	76 (100%)	0.31
Thorax AIS ≥ 3	16 (47%)	37 (49%)	0.92
Minimal GCS score	7 [5–8]	6 [4–7]	0.11
Lateralizing deficit	9 (26%)	41 (54%)	0.008
Pupillary abnormalities	5 (14.7%)	35 (46.1%)	0.002
Marshall category ≥ 3	9 (26%)	37 (49%)	0.03
Admission Hb (g/dl)	13.6 [12.0–14.8]	12.4 [11.4–14.1]	0.12
Pre-hospital hemodynamic shock	7 (21%)	16 (21%)	1.00
Intracranial hypertension frequency	8 (24%)	40 (53%)	0.005
Therapeutic hypothermia use	8 (24%)	38 (50%)	0.009
Barbiturate use	3 (9%)	24 (32%)	0.02
Decompressive craniectomy use	1 (3%)	24 (32%)	0.001
Total of RBC units transfused	0 [0–5]	3 [1–7]	0.03
Day of sedation interruption	4 [2–7]	9 [4–14]	<0.001
Duration of MV (days)	6 [4–10]	15 [10–21]	<0.001
Tracheostomy	5 (15%)	64 (84%)	<0.001
ICU length of stay (days)	8 [6–13]	19 [14–28]	<0.001
Hospital length of stay (days)	14 [10–32]	33 [25–49]	<0.001
In-hospital mortality	3 (9%)	7 (9%)	1.00

Data are presented as the number (%) or the median [25th–75th]

AIS abbreviated injury scale, GCS Glasgow Coma Scale, Hb hemoglobin level, ICU intensive care unit, ISS injury severity score, MV mechanical ventilation, RBC Red Blood Cell, SAPS II Simplified Acute Physiology Score, SHV spontaneous hyperventilation

Table 2 Factors associated with unfavorable neurologic functional outcome at 6 months

Variable	Odds ratio	95% CI	p value
Age > 65 years	4.68	1.65–13.26	0.004
Head AIS ≥ 5	1.65	0.76–3.61	0.21
Minimal GCS score < 6	3.02	1.35–6.72	0.007
Pupillary abnormalities	5.57	2.39–12.99	< 0.001
Marshall category ≥ 3	3.97	1.78–8.89	< 0.001
Pre-hospital hemodynamic shock	0.69	0.26–1.79	0.44
Pre-hospital hypoxia	0.75	0.23–2.39	0.62
Intracranial hypertension during stay	1.34	0.62–2.88	0.45
Spontaneous hyperventilation	5.19	1.93–13.96	0.001
Natremia max ≥ 155 mEq/l	2.75	1.20–6.31	0.02
Transfusion of RBC unit	2.31	0.97–5.46	0.057

AIS abbreviated injury scale, CI confidence interval, GCS Glasgow Coma Scale, RBC Red Blood Cell

Table 3 Multivariate logistic regression model of factors associated with unfavorable neurologic functional outcome at 6 months

Variable	Odds ratio	95% CI	p value	VIF
Age > 65 years	10.37	2.68–40.19	< 0.001	1.27
Minimal GCS score < 6	3.59	1.24–10.36	0.02	1.23
Pupillary abnormalities	2.60	0.91–7.38	0.07	1.15
Marshall category ≥ 3	3.10	1.09–8.80	0.03	1.21
Spontaneous hyperventilation	4.08	1.15–14.44	0.03	1.14
Natremia max ≥ 155 mEq/l	1.21	0.43–3.40	0.72	1.11
Transfusion of RBC unit	1.50	0.46–4.82	0.50	1.11

Area under the ROC curve: 0.84. Hosmer–Lemeshow test: $\chi^2 = 9.8$, $df = 8$, $p = 0.28$

CI confidence interval, GCS Glasgow Coma Scale, RBC Red Blood Cell, VIF Variance Inflation Factors

Other variables included in the model are shown in Table 3. The area under the ROC curve was 0.84. The Hosmer–Lemeshow test demonstrated a good model fit ($\chi^2 = 9.8$, $df = 8$, $p = 0.28$).

Others Endpoints

Patients that developed SHV exhibited elevated morbidity during their stay (Table 1). Notably, compared to patients without SHV, those with SHV had significantly longer sedation durations (9 [4–14] days vs. 3.5 [2–6.5] days, $p = 0.0002$), significantly longer mechanical ventilation durations (14.5 [10–21] days vs. 5.5 [4–10] days, $p < 0.0001$), and significantly longer hospital lengths of stay (33 [25–49] days vs. 14 [10–32] days, $p = 0.0001$). In-hospital mortality was not different: 7 (9.2%) vs. 3 (8.8%), $p = 1.00$.

Discussion

This retrospective analysis of a prospective observational cohort of 110 patients with severe TBIs still comatose after interruption of sedation showed a high occurrence of SHV (approximately of 69%) including almost 33% of severe SHV. This occurrence is consistent with similar findings in other types of brain injury [20, 21]. Notably, in subarachnoid hemorrhage (SAH), the frequency of SHV varies from 55 to 92% [20, 21]. The pathophysiology of this condition after TBI is not completely established, but multiples hypotheses can be discussed. First, TBI may induce SHV by disrupting the cortical inhibition on the brainstem respiratory centers, liberating them and thereby triggering hyperventilation [24]. Second, SHV may be a part of the paroxysmal sympathetic hyperactivity (PSH), which is also associated elevated heart rate, elevated blood pressure, hyperthermia, and sweating [25]. PSH is common in neurointensive care units, with a reported prevalence ranging from 8 to 33% [25]. Finally, SHV could be simply due to other factors indirectly related to the TBI and its care, such as pain, discomfort from endotracheal tube, fever due to infection or analgesic and sedative drugs withdrawal syndrome.

The second and probably main finding of the present work is the independent association between SHV and unfavorable functional neurologic outcome at 6 months. Indeed, severe TBI patients developing SHV had four times the odds of unfavorable outcome. However, whether the SHV just reflected severity of cerebral damage or contributed to its aggravation is still unclear. It is well established that hypocapnia, especially if it occurs in the first days following the TBI, is associated with unfavorable outcome by causing or aggravating brain ischemia [4, 9]. Indeed, hypocapnia results in a cerebrospinal fluid alkalosis triggering multiples neurologic effects [4, 26]. Firstly, cerebrospinal fluid alkalosis reduces CBF and, to a lesser extent, cerebral blood volume via cerebral arterial vasoconstriction, leading to a decrease in oxygen delivery [4, 9, 12]. In patients with TBI, CBF decreases by approximately 3% per mm Hg change in PaCO_2 [27]. Coles et al. [12] demonstrated that an induced moderate hypocapnia (from 36 to 29 mm Hg) significantly reduces global CBF (from 31 to 23 mL/100 g/min) and results in a significant increase in the volume of critically hypoperfused tissue. However, some studies have demonstrated that prolonged hyperventilation is associated with a tachyphylaxis of the effect of hypocapnia and, therefore, prolonged cerebral arterial vasoconstriction may be unlikely [28]. Secondly, hypocapnia increases cerebral oxygen demand through an increased neuronal excitability or induction of seizures [13, 29]. In 2007, Coles and colleagues using positron emission

tomography and somatosensory evoked potentials showed that hypocapnia is associated with an increase in cerebral oxygen metabolism (CMRO₂) [13]. Both of these mechanisms (i.e., decreased oxygen delivery by reduction of CBF and increased CMRO₂) deteriorate the flow–metabolism balance and may contribute to a switch to anaerobic metabolism or, even worse, precipitate a brain ischemia, especially in regions with preexisting impairment of CBF [4, 12, 13]. Finally, cerebrospinal fluid alkalosis may induce neurotoxicity, notably by the production of excitatory amino acids, like *N*-methyl-D-aspartate, that are locally cytotoxic [30, 31].

Although patients with SHV have more severe disease in the present work (in terms of initial GCS score, rate of pupillary abnormalities, need for advanced therapeutics as decompressive craniotomy or barbiturate infusion), two elements may argue in favor of a direct negative impact of SHV on outcome. Firstly, after adjustment on age and markers of TBI severity in the multivariable analysis, SHV remains associated with unfavorable functional neurologic outcome at 6 months. Secondly, Carrera et al. [32] demonstrated that SHV may negatively affect brain tissue oxygenation monitored with brain tissue oxygen tension (PbtO₂) in patients with severe brain injury (SAH, intracranial hemorrhage, or TBI). Compared with normocapnia, the percentage of hourly data with PbtO₂ < 15 mm Hg was significantly higher for patients with hypocapnia (15.7% in patients with normal EtCO₂ to 33.9% in patients with EtCO₂ < 25 mm Hg). Moreover, EtCO₂ and PbtO₂ were strongly correlated in patients with TBI. It was already proved that a PbtO₂ < 15 mm Hg is associated with an increased risk of brain ischemia leading to secondary cerebral insults and, therefore, poor functional neurologic outcome [33, 34]. Thus, the work of Carrera et al. supports our opinion that SHV may induce cerebral hypoxic events that may alter the prognosis.

Even if the present work demonstrated an independent association between SHV and poor functional neurologic outcome, further studies are necessary to determine whether a treatment of SHV is effective or leads to improved outcome. Overall, the level of evidence is too low to recommend any intervention to treat SHV. Moreover, therapeutic options in this kind of patients to minimize hyperventilation are limited, either mechanical by adding dead space to the ventilator circuit in order to reduce hypocapnia, or pharmacological with sedatives, opioids or more specific molecules acting on the PSH like α_2 agonists (clonidine for example) [25]. However, both of these options have side effects like an increase in the work of breathing or an interference with clinical monitoring [25, 35].

Study Limitations

Our study had several limitations. First, it was a single-center study; therefore, the results are not generalizable to all patient populations. Second, since this is an observational study, it was not possible to account for all confounders leading to an association between SHV and unfavorable functional neurologic outcome. Nonetheless, the final logistical regression model included most of the well-established parameters classically associated with poor outcome (age, GCS score, radiological severity with Marshall category etc.). Additionally, given the historic nature of the data, it is possible that temporal changes in clinical practice may have impacted the results. For example, over the course of the time frame of the study, practitioners became more aware of the potential adverse effects of SHV, leading to increased usage of medications targeting PSH (propranolol, clonidine), since PSH was thought to cause some cases of SHV. Thus, the incidence of SHV and its consequences could have been artificially decreased. Finally, we excluded patients quickly extubated after the withdrawal of sedation. This leads to a very high occurrence of SHV (69.1%; 95% CI [59.9–77]). However, we hope that this study may help clinicians to determine which patients will have a poor outcome, and this question seems more relevant in patients still comatose after the initial phase of TBI.

Conclusions

The present work showed that patients with severe TBI had a high incidence of SHV. We found that SHV starts quickly after the withdrawal of sedation for the majority of patients. In addition, our results suggested that SHV was associated with an unfavorable functional neurologic outcome.

Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s12028-018-0639-0>) contains supplementary material, which is available to authorized users.

Abbreviations

TBI: Traumatic brain injury; GCS: Glasgow Coma Scale; CPP: Cerebral perfusion pressure; PbtO₂: Brain tissue oxygen tension; ICU: Intensive care unit; ICP: Intracranial pressure; FiO₂: Oxygen inspired fraction; GOS: Glasgow Outcome Scale; ROC: Receiver operating characteristic; 95% CI: 95% confidence intervals.

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Authors' contributions

PE, JR, and CJ contributed to the study concept and design. PE, JR, MC, ED, AM, PJC, and AS contributed to the acquisition of data. PE, PG, AD, and BP contributed to the analysis and interpretation of data. PE, PG, JB, and EM contributed to the drafting of manuscript and critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Source of support

None.

Compliance with Ethical Standards

Conflict of interest

The authors have no conflicts of interest to report.

Ethical Approval and Consent to Participate

Institutional Review Board of the Sainte Anne Military Hospital, Toulon (France), approved the study and waived the requirement for informed consent from the patients or patient's kin given the observational nature of the study.

Published online: 1 November 2018

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