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ORIGINAL

Management of arterial partial pressure of carbon dioxide in the first week after traumatic brain injury: results from the CENTER-TBI study

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Abstract

Purpose: To describe the management of arterial partial pressure of carbon dioxide ($PaCO_2$) in severe traumatic brain-injured (TBI) patients, and the optimal target of $PaCO_2$ in patients with high intracranial pressure (ICP).

Methods: Secondary analysis of CENTER-TBI, a multicentre, prospective, observational, cohort study. The primary aim was to describe current practice in $PaCO_2$ management during the first week of intensive care unit (ICU) after TBI, focusing on the lowest $PaCO_2$ values. We also assessed $PaCO_2$ management in patients with and without ICP monitoring (ICP_m), and with and without intracranial hypertension. We evaluated the effect of profound hyperventilation (defined as $PaCO_2 < 30$ mmHg) on long-term outcome.

Results: We included 1100 patients, with a total of 11,791 measurements of $PaCO_2$ (5931 lowest and 5860 highest daily values). The mean (± SD) $PaCO_2$ was 38.9 (± 5.2) mmHg, and the mean minimum $PaCO_2$ was 35.2 (± 5.3) mmHg. Mean daily minimum $PaCO_2$ values were significantly lower in the ICP_m group (34.5 vs 36.7 mmHg, $p < 0.001$). Daily $PaCO_2$ nadir was lower in patients with intracranial hypertension (33.8 vs 35.7 mmHg, $p < 0.001$). Considerable heterogeneity was observed between centers. Management in a centre using profound hyperventilation (HV) more frequently was not associated with increased 6 months mortality (OR = 1.06, 95% CI = 0.77–1.45, p value = 0.7166), or unfavourable neurological outcome (OR 1.12, 95% CI = 0.90–1.38, p value = 0.3138).

Conclusions: Ventilation is manipulated differently among centers and in response to intracranial dynamics. $PaCO_2$ tends to be lower in patients with ICP monitoring, especially if ICP is increased. Being in a centre which more frequently uses profound hyperventilation does not affect patient outcomes.

Keywords: Carbon dioxide, Hyperventilation, Traumatic brain injury, Intracranial pressure, Outcome

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CENTER-TBI ICU participants and investigators are listed as non-author contributors in the Acknowledgement section.

Introduction

Changes in the arterial partial pressure of carbon dioxide ($PaCO_2$), by modifying the extravascular pH, modulate cerebrovascular tone, and hence cerebral blood flow (CBF) and cerebral blood volume (CBV) [1, 2]. Hypercapnia results in perivascular acidosis, which causes cerebral vasodilation, and consequently, an increase in intracranial volume. In patients with poor intracranial compliance, this could raise intracranial pressure (ICP). On the other

hand, hyperventilation (HV) induced alkalosis reduces vascular calibre, and hence CBV, and can represent an effective measure to control intracranial hypertension, when ICP remains elevated despite first-line therapies [3–6]. However, hypocapnic cerebral vasoconstriction can also reduce CBF [7], thus posing the risk of secondary ischaemic insults [8]. In a survey across European trauma centers, the most frequently reported $PaCO_2$ target was 36–40 mmHg in the absence of intracranial hypertension, which was reduced to 30–35 mmHg when ICP was > 20 mmHg [9]. The most recent evidence-based guidelines on TBI management provide no definitive recommendations regarding target $PaCO_2$ levels due to the low quality of evidence available on this issue [10, 11].

Consequently, although many patients with severe TBI undergo several days of mechanical ventilation, there is little evidence-based guidance on $PaCO_2$ targets, and clinical practice remains highly variable. A recent consensus on mechanical ventilation in patients with acute brain injury suggested aiming for a physiologic range of $PaCO_2$ between 35 and 45 mmHg [12], and to only use hyperventilation (with an undefined $PaCO_2$ target) as a short-term therapeutic option in patients with evidence of brain herniation. However, the document was unable to provide a recommendation on the use of hyperventilation in patients who showed significant ICP elevation, but no evidence of herniation. A management algorithm for patients with intracranial hypertension, based on expert consensus, suggested the use of HV ($PaCO_2$ 32–35 mmHg) for controlling ICP only as a second-tier treatment, did not support lower $PaCO_2$ levels and recommended against routine hyperventilation to $PaCO_2$ below 30 mmHg [13].

The objectives of this study were to assess, in a real-world context, $PaCO_2$ management and the lowest target of $PaCO_2$ in a large cohort of mechanically ventilated TBI patients and practice variability between centres to evaluate the association between the use of profound HV and 6-month clinical outcomes.

Methods

Study design and patients

The Collaborative European NeuroTrauma Effectiveness in Research in Traumatic Brain Injury (CENTER-TBI study, registered at clinicaltrials.gov NCT02210221) is a longitudinal, prospective collection of data from TBI patients across 65 centers in Europe. The study was conducted between December 19th, 2014, and December 17th, 2017 and details regarding the design and the results of the screening and enrolment process have been previously described [14–16].

The CENTER-TBI study was approved by the Medical Ethics Committees in all participating centers, and informed consent was obtained according to local regulations (https://www.center-tbi.eu/project/ethical-approval). This project on $PaCO_2$ management was preregistered on the CENTER-TBI proposal platform and approved by the CENTER-TBI proposal review committee before starting the analysis (ESM Document 1). This report complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (ESM Table S1).

We included all patients in the CENTER-TBI Core study who had a TBI necessitating ICU admission, required tracheal intubation and mechanical ventilation, had at least two $PaCO_2$ measurements in the first 7 days and had been admitted to a study centre that enrolled at least ten patients.

Take-home message

The manipulation of arterial carbon dioxide levels ($PaCO_2$) is easy, and hyperventilation (HV) has been a common ICP-lowering strategy for over half a century. However, hyperventilation-induced vasoconstriction is a double-edged sword. It reduces cerebral blood volume and intracranial volume, and therefore, lowers ICP

We observed huge variability among centers in $PaCO_2$ values and use of HV. Although causal inferences cannot be drawn from these observational data, our results suggest that, in patients with severe intracranial hypertension, HV is not associated with worse long-term clinical outcome

Data collection and definitions

Detailed information on data collection is available on the study website (https://www.center-tbi.eu/data/dictionary). For the first week in ICU, the daily lowest and highest $PaCO_2$ values from arterial blood gases and, if an ICP device was inserted, the hourly ICP measures were used for analysis.

HV was defined as moderate for $PaCO_2$ ranging between 30 and 35 mmHg and profound for $PaCO_2$ < 30 mmHg [10, 13]. Therapy intensity level (TIL) was calculated according to the most recent TIL scale [17]. Patients with invasive ICP monitoring during the first week of ICU stay were classified as ICP_m, while those who did not receive ICP monitoring during ICU stay as no-ICP_m. Intracranial hypertension was defined as ICP > 20 mmHg.

Objectives

The aims of this study are:

1. to describe the $PaCO_2$ values in the first week from ICU admission in mechanically ventilated TBI patients, and to evaluate practice variability across centers, particularly focusing on the lowest targets of $PaCO_2$;

2. to assess at a center level the $PaCO_2$ management in patients with/without ICP monitoring and with/without intracranial hypertension;
3. to evaluate the association between patient outcomes and center propensity to use profound HV.

Outcomes

Mortality and functional outcome (measured as the Extended Glasgow Outcome Score, GOSE) were assessed at 6 months. All responses were obtained by study personnel from patients or from a proxy (where impaired cognitive capacity prevented patient interview), during a face-to-face visit, by telephone interview, or by postal questionnaire around 6 months after injury [18]. All evaluators had received training in the use of the GOSE. An unfavourable outcome was defined as GOSE ≤ 4, which includes both poor functional outcome and mortality.

Statistical methods

Patient characteristics were described by means ($\pm$ standard deviation, SD), medians (I–III quartiles, Q_1–Q_3) and counts or proportions, as appropriate. The comparison of baseline features according to ICP monitoring was performed using Mann–Whitney *U* test, *t* test and Chi-square test as appropriate. We used the median odds ratio (MOR) to estimate the between-centre heterogeneity in targeting a $PaCO_2$ of 35–45 mmHg. MOR was obtained from a longitudinal logistic mixed-effect model on daily lowest $PaCO_2$ adjusted for the IMPACT core covariates [19], ICP monitoring, and daily evidence of elevated ICP (at least one ICP > 20 mmHg during the day); and with a hierarchical random intercept effect's structure (i.e., patients within centers). The same model architecture was used to quantify between-centres heterogeneity in the use of profound HV.

We resorted to an instrumental variable approach to evaluate the association between HV and 6-month outcomes, trying to minimize the potential measured and unmeasured confounding acting in this complex observational study [20]. This was done by considering the propensity of centres to apply profound HV, measured as the proportion of daily lowest $PaCO_2 < 30$ mmHg, as an instrument in the logistic regression model with a random intercept for centers. This model was adjusted for some subject-specific covariates that included IMPACT core covariates at baseline, ICP monitoring and dose of intracranial hypertension, calculated as the area under the ICP profile above 20 mmHg, named AUC ICP > 20[21]. The assumptions underlying the IV approach were assessed (ESM-Statistical methods).

Tests were performed with a two-sided significance level of 5%. All analyses were conducted using R statistical software (version 4.03).

Results

Of the 4509 patients included in the CENTER-TBI dataset, 2138 patients with TBI from 51 centers in Europe were admitted to ICU. Among these, 1176 required mechanical ventilation and had at least two $PaCO_2$ measurements within the first 7 days from ICU admission. Excluding the centres that enrolled less than ten patients, 1100 patients from 36 centers were available for the analysis (ESM Fig. 1). During the first week of ICU admission, a total of 11,791 measurements of $PaCO_2$ were available (5931 lowest and 5860 highest daily values).

Patient characteristics

Patient characteristics at hospital admission in the overall population and stratified according to the presence ($n = 751$) or not ($n = 349$) of ICP monitoring, are summarized in Table 1. The median age was 48 years (Q1–Q3 = 29–64), and most patients were male (74%). 64.7% of patients presented with a severe TBI (Glasgow Coma Scale, GCS ≤ 8) and 12.5% of cases were complicated by thoracic trauma. In 727 (97%) ICP_m patients, ICP was inserted by the second day of ICU admission.

In the overall population, the mean $PaCO_2$ at ICU admission was 39.1 (± 6) mmHg, and the no-ICP_m group had higher $PaCO_2$ mean values compared to the ICP_m patients (39.9 ± 6.8 vs 38.7 ± 5.6 mmHg, $p < 0.002$).

Lowest $PaCO_2$ targets according to centers

Daily minimum $PaCO_2$ distribution during the first week for the whole population, and separated by the centre, are presented in Fig. 1a. The overall mean lowest $PaCO_2$ was 35.2 ± 5.4 mmHg with substantial heterogeneity between centres, whose means ranged from 32.3 (± 3.7) to 38.7 mmHg (± 5.9). This result seems to be related more to different management strategies at the centre level, rather than reflecting national policies (Fig. 1b). For example, among the UK centers (in yellow), two centers had a mean $PaCO_2$ value of 32.3 and 36.4 mmHg.

Only 144 (13%) patients had all $PaCO_2$ measurements between 35 and 45 mmHg, while 588 (53%) patients had at least half of the total $PaCO_2$ measurements in this range. Using MOR to quantify between-centre differences in targeting the suggested $PaCO_2$ range of 35–45 mmHg, we found that, after correction for patient and trauma characteristics, there was a 1.72-fold difference in the odds of having a $PaCO_2$ range of 35–45 mmHg between centres with the highest and lowest rates. After excluding 390 patients with intracranial hypertension, the percentage of patients with all and at least half of the total $PaCO_2$ measurements between 35 and 45 mmHg raised to 19% (111/593) and 64% (380/593), while MOR decreased to 1.4.

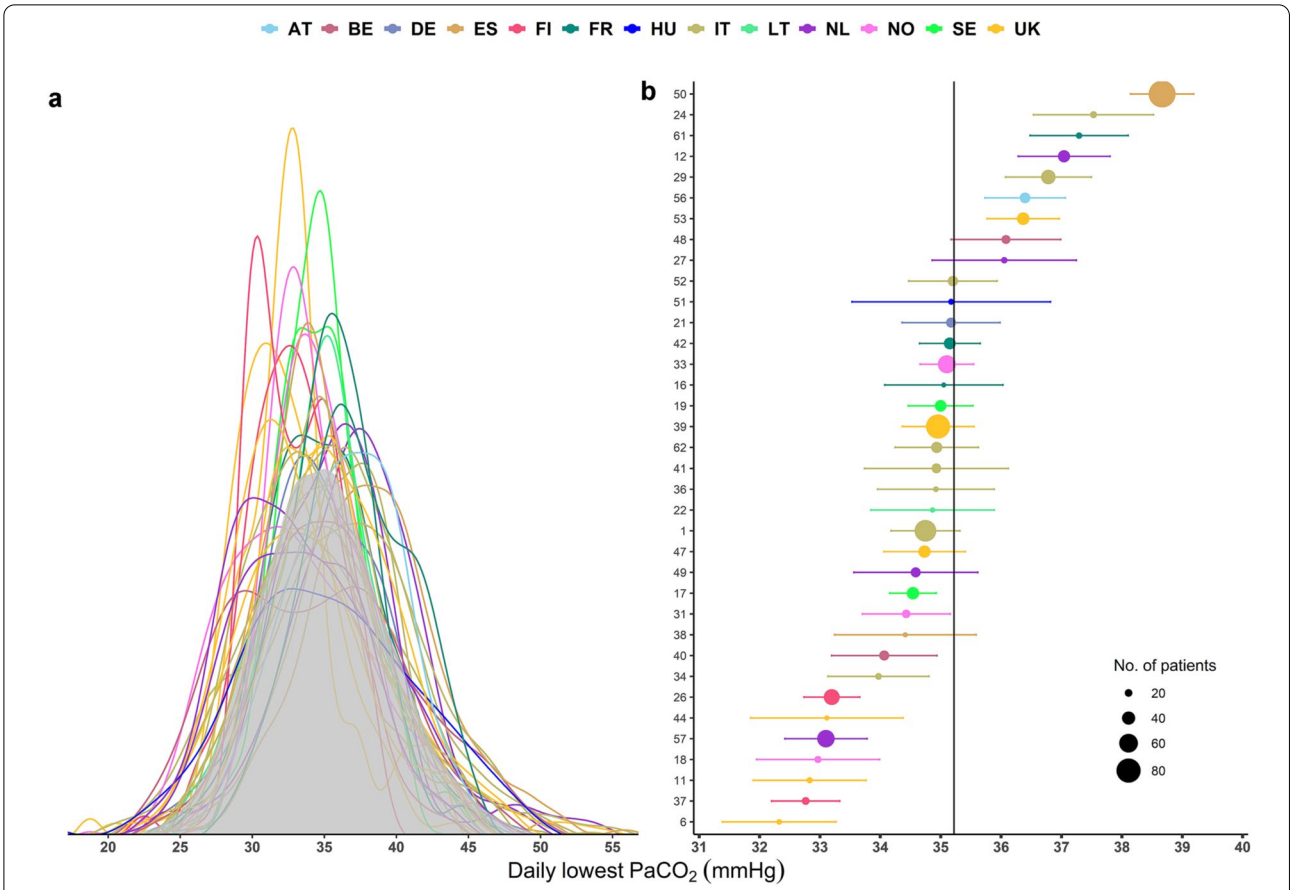

Fig. 1 (**a**) Distributions of the daily lowest $PaCO_2$ recorded in the first 7 days of ICU in each participating centre (coloured by country) and overall (grey area). These distributions were estimated by a Gaussian kernel density. (**b**) Centre-specific mean values (coloured by country) of daily lowest $PaCO_2$ with the corresponding 95% confidence intervals. The solid vertical line represents the overall mean of daily lowest $PaCO_2$ values, and the size of the dots is proportional to the number of patients in the centre. *$PaCO_2$* the partial pressure of carbon dioxide, *AT* Austria, *BE* Belgium, *DE* Germany, *ES* Spain, *FI* Finland, *FR* France, *HU* Hungary, *IT* Italy, *LT* Lithuania, *NL* Netherlands, *NO* Norway, *SE* Serbia, *UK* United Kingdom

Lowest $PaCO_2$ targets in the presence or not of ICP monitoring

Mean minimum $PaCO_2$ values were significantly lower in ICP_m patients compared to no-ICP_m (34.7 ± 4.9 mmHg vs 36.8 ± 5.7 mmHg, $p < 0.001$). Large variability was observed among centers in the management of $PaCO_2$ targets in both subgroups (Fig. 2 and ESM Fig. 2). Some centres showed no differences in target $PaCO_2$ when ICP_m was used (i.e. data points near the line of identity in Fig. 2a), but most hospitals tended to adopt lower $PaCO_2$ targets when ICP was monitored (i.e. data points that deviate substantially from the line of identity in Fig. 2a). For example, three centers showed a reduction greater than 4 mmHg in the mean daily lowest $PaCO_2$ when ICP monitoring was available (from 38–38.4 mmHg to 33.1–34.2 mmHg).

Lowest $PaCO_2$ in the presence of intracranial hypertension

In the subgroup of patients with ICP monitoring, we also explored the attitude of centres in response to episodes of intracranial hypertension ($n = 3646$). Some centres showed no differences in target $PaCO_2$ when ICP was elevated (i.e. data points near the line of identity in Fig. 2b), but most hospitals tended to adopt lower $PaCO_2$ targets when ICP was monitored (i.e. data points that deviate substantially from the line of identity in Fig. 2b). The mean minimum $PaCO_2$ was significantly lower in 398 patients with at least one episode of intracranial hypertension compared to the 240 who did not experience increased ICP (34.1 vs 35.6 mmHg, $p < 0.001$). Within the group of patients with ICP monitoring in place, significant inter-centre differences were observed in the mean lowest $PaCO_2$, both in the absence and presence of intracranial hypertension (ESM Fig. 3).

Table 1 Baseline demographic and clinical characteristics, including trauma characteristics, clinical presentation, and neuroimaging features at ICU admission in the overall population and stratified according to the presence or not of ICP monitoring

Characteristic		Overall ($n=1100$)	no-ICP_m ($n=349$)	ICP_m ($n=751$)	*P* value
Age (years), median (Q1–Q3)		48 (29–64)	53 (31–69)	46 (28–61)	< 0.001
Sex, *n* (%)	Female	284 (25.8)	89 (25.5)	195 (26)	0.929
Thoracic trauma, *n* (%)	Yes	138 (12.5)	42(12)	96 (12.8)	0.802
ISS, median (Q1–Q3)		34 (25–48)	34 (25–43)	34 (25–48)	0.011
Hypotension, *n* (%)	Yes	178 (17.4)	60 (17.7)	118 (17.3)	0.936
	Not available	78	10	68	
Hypoxia, *n* (%)	Yes	182 (17.9)	53 (15.6)	129 (19)	0.217
	Not available	82	10	72	
Severity TBI, *n* (%)	GCS ≤ 8	367 (35.3)	147 (44.3)	220 (31)	< 0.001
	GCS > 8	674 (64.7)	185 (55.7)	489 (69)	
	Not available	59	17	42	
Pupillary reactivity, *n* (%)	Both reactive	799 (75.8)	280 (82.8)	519 (72.5)	0.001
	One reactive	89 (8.4)	22 (6.5)	67 (9.4)	
	Both unreactive	166 (15.7)	36 (10.7)	130 (18.2)	
	Not available	47	11	35	
GCS motor, *n* (%)	None	460 (42.7)	129 (37.7)	331 (45)	< 0.001
	Extension	51 (4.7)	9 (2.6)	42 (5.7)	
	Abnormal flexion	60 (5.6)	10 (2.9)	50 (6.8)	
	Normal flexion	89 (8.3)	30 (8.8)	59 (8)	
	Localizes/obeys	418 (38.8)	164 (48)	254 (34.5)	
	Not available	22	7	15	
Marshall CT classification, *n* (%)	1	63 (6.5)	48 (15.6)	15 (2.3)	0.0005
	2	416 (42.9)	167 (54.2)	249 (37.7)	
	3	98 (10.1)	17 (5.5)	81 (12.3)	
	4	19 (2)	3 (1)	16 (2.4)	
	5	6 (0.6)	2 (0.6)	4 (0.6)	
	6	367 (37.9)	71 (23.1)	296 (44.8)	
	Not available	131	41	90	
Overall $PaCO_2$ (mmHg), mean (SD)		39.10 (6)	39.93 (6.8)	38.72 (5.6)	0.002
Lowest $PaCO_2$ (mmHg), mean (SD)		34.66 (5.98)	35.92 (6.67)	34.09 (5.56)	< 0.001
Highest $PaCO_2$ (mmHg), mean (SD)		43.68 (8.1)	44.07 (8.6)	43,5 (7.86)	0.287

Hypotension was defined as a documented systolic blood pressure < 90 mmHg; hypoxia was defined as a documented partial pressure of oxygen (PaO_2) < 8 kPa (60 mmHg), oxygen saturation (SaO_2) < 90%, or both; $PaCO_2$ data refer to values at ICU admission

$PaCO_2$ the partial pressure of carbon dioxide, *SD* standard deviation, *Q1–Q3* I and III quartiles, *ISS* injury severity score, *TBI* traumatic brain injury, *GCS* Glasgow Coma Scale, *ICP_m* intracranial pressure monitored, *ICU* intensive care unit

Profound hyperventilation

An episode of profound HV ($PaCO_2$ < 30 mmHg) was recorded on 727 occasions during the first week of ICU admission in 397 (36%) patients (57% had one, 22% two and 10% three occurrences). Results from the longitudinal mixed-effects model show notable heterogeneity between centres on the use of HV, even after adjusting for patient and trauma characteristics, with a MOR of 2.04 (Fig. 3, ESM Table 1). We found a significant positive association between the occurrence of increased ICP and the use of HV. Among ICP_m patients, even after correction for covariates, the odds of HV in a day with elevated ICP was nearly three times that in a day with controlled ICP (OR = 4.34 95% CI = 4.25-4.44, *p* value < 0.0001 vs OR = 1.47 95% CI = 0.97-2.22, *p* value = 0.03167). Finally, HV was less applied from day 1 to 7 (OR of HV per day = 0.83; 95% CI = 0.82–0.84, *p* value < 0.0001).

Neuromonitoring

Indirect CBF monitoring, using jugular bulb venous oxygen saturation or brain tissue oxygenation, was not

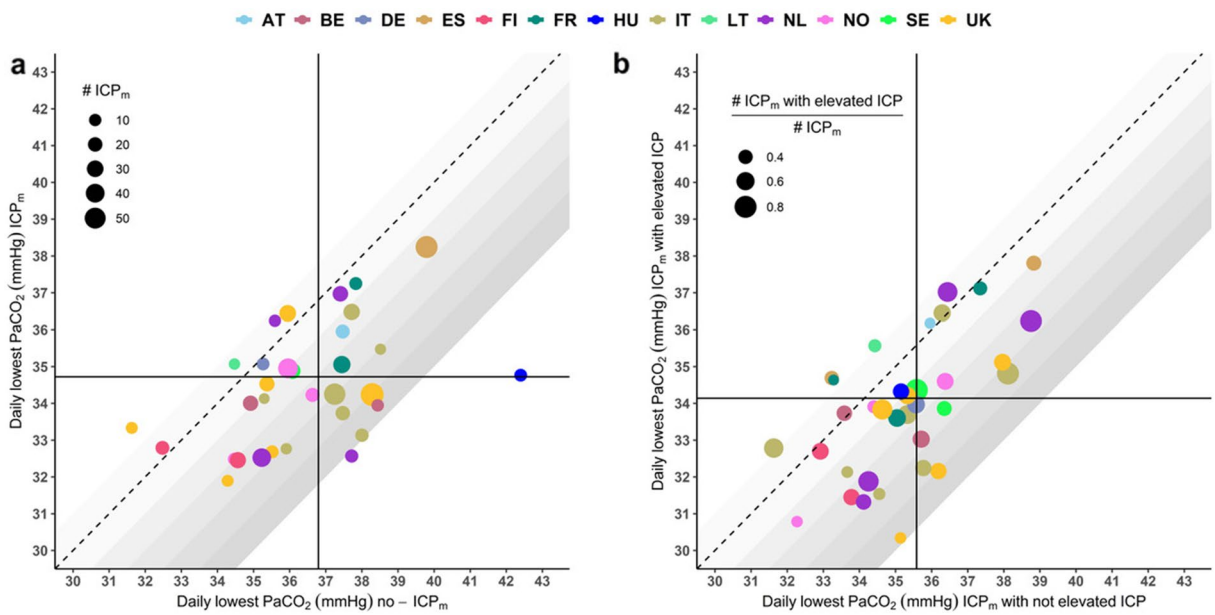

Fig. 2 (**a**): Scatterplot of the mean daily lowest $PaCO_2$ values in no-ICP_m vs ICP_m patients in each participating centre (coloured by country). The dashed line represents the line of identity, and a data point on or close to the line indicates that $PaCO_2$ targets in that centre were not affected by the presence of ICP monitoring. The gradient of grey zones on either side of the grey area indicates increasing deviations from this line of identity between values in no-ICP_m vs ICP_m patients. Each gradation in shade representing one unit change (mmHg). The size of the dots is proportional to the number of ICP_m patients at a centre. The outlier centre from Hungary included only two no-ICP_m patients, out of a total of 12 patients, with only two measurements each before ending ventilation. (**b**) Mean of the daily lowest $PaCO_2$ values in ICP_m patients with no episodes of elevated ICP (ICP ≤ 20 mmHg) vs ICP_m patients with at least one episode of elevated ICP (> 20 mmHg) in each participating centre (coloured by country). The dashed line represents the line of identity, and the size of the dot is proportional to the number of ICP_m patients with elevated ICP. *$PaCO_2$* the partial pressure of carbon dioxide, *AT* Austria, *BE* Belgium, *DE* Germany, *ES* Spain, *FI* Finland, *FR* France, *HU* Hungary, *IT* Italy, *LT* Lithuania, *NL* Netherlands, *NO* Norway, *SE* Serbia, *UK* United Kingdom

used frequently. No differences were found in their use in patients receiving profoundly HV (jugular bulb venous oxygen saturation, $SjvO_2$: 2.4% vs profound HV 3.5%, *p* value = 0.380; brain tissue oxygenation, $PbtO_2$: 14.2% vs profound HV 13.9%, *p* value = 0.937). However, the use of profound HV was associated with significantly higher use of more aggressive treatment, expressed as mean TIL (9.7 vs 6.3 *p* value < 0.001). In particular, patients who received profound hyperventilation were more likely to have decompressive surgery (8.6 vs 4.8, *p* value < 0.001) and hyperosmolar therapy (low dose 12.7 vs 5.5, *p* value < 0.001; high dose 16.8 vs 5.7, *p* value < 0.001).

6 months mortality and neurological outcome

Overall, of the 1100 patient cohort, 165 died before ICU discharge (15%). Of the 970 patients for whom 6-month outcomes were available, 246 (25.4%) died, and 529 (54.5%) experienced unfavourable functional outcomes (GOSE ≤ 4). The 6 months mortality rate was 29% in patients who had at least one episode of profound HV and 23% in those who did not (*p* value = 0.045), while the rates of unfavourable GOSE were 64% vs 49% in the two groups, respectively (*p* value < 0.001). The percentage of patients who received profound HV in the first seven days from admission ranged from 1 to 30% between hospitals. In the IV analysis, the propensity to apply profound HV (defined by the use of $PaCO_2$ < 30 mmHg) did not significantly increase mortality or unfavourable functional outcome, after adjusting for the dose of intracranial hypertension. Patients in hospitals that used 10% more profound HV had 1.06 higher odds of mortality compared to hospitals where profound HV was applied less often (95% CI = 0.77–1.45, *p* value = 0.7166) and the OR for the same comparison was 1.12 (95% CI = 0.90–1.38, *p* value = 0.3138) for an unfavourable functional outcome (Table 2).

Discussion

The current literature is inconclusive regarding the optimal ventilatory strategy to adopt in patients with TBI and, though there is increasing caution surrounding the use of HV, the translation of expert consensus recommendations into clinical practice remains uncertain. This study examined the $PaCO_2$ management during mechanical ventilation at a centre level in prospectively collected

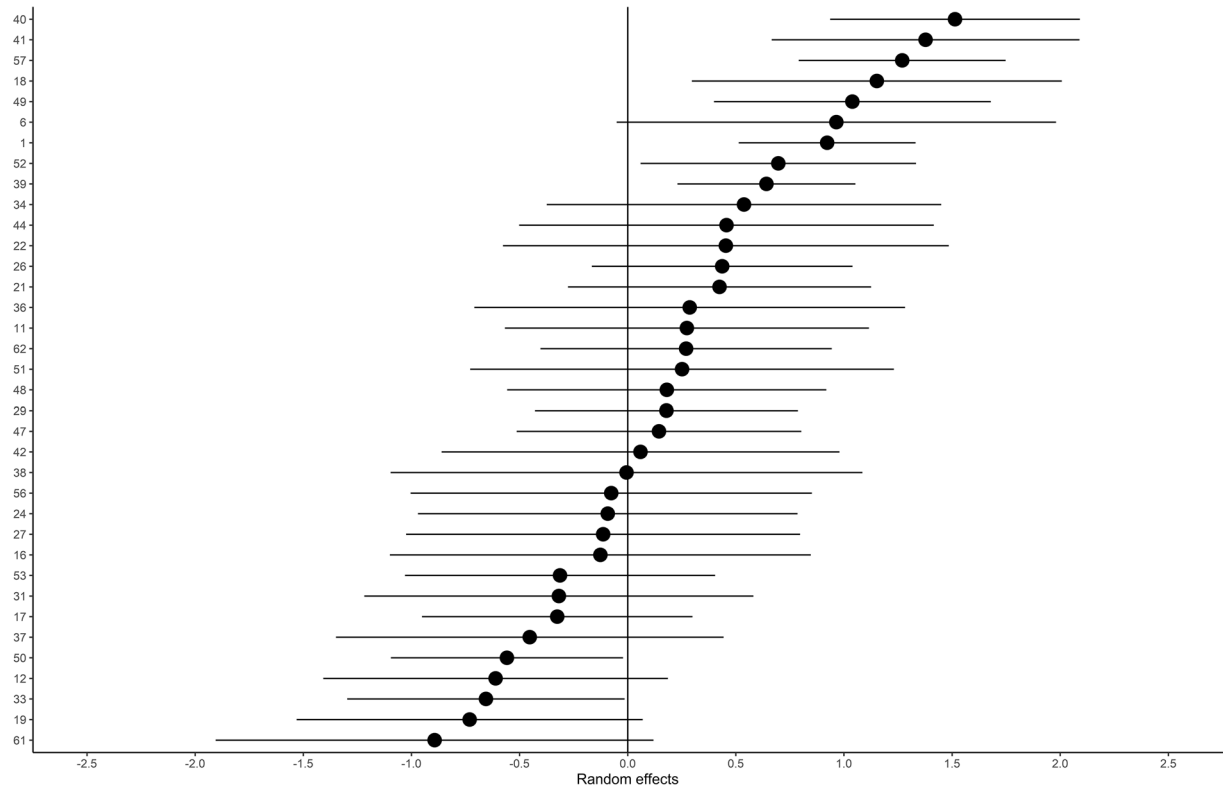

Fig. 3 Caterpillar plot of between-centre variation in using profound HV. The figure shows the predicted random intercepts for each centre, on the log-odds scale, along with their 95% prediction intervals. Higher values indicate a higher propensity to use profound HV. A longitudinal random effect logistic model was used to correct for random variation and adjusted for the core IMPACT covariates and elevated ICP. The MOR summarises the between-centre variation: a MOR = 1 indicates no variation, while the larger the MOR is, the larger the variation present. The median odds ratio (MOR = 2.04) refers to the odds of using profound HV between two randomly selected centres for patients with the same covariates and (comparable) random effects

observational data from a large multicentre cohort of TBI patients, focusing on the use of HV.

Our main findings are:

- there is substantial practice variation among countries and centers regarding $PaCO_2$ levels and the lowest $PaCO_2$ adopted in TBI patients;
- patients who received ICP monitoring were managed at lower $PaCO_2$ compared to patients in whom such monitoring was not used;
- patients who did receive ICP monitoring and experienced episodes of increased ICP were managed at lower $PaCO_2$ levels than those who did not have ICP elevations; profound HV was commonly used in such patients;
- we observed no association between the risk of mortality or unfavourable functional outcome and more frequent use of profound hyperventilation ($PaCO_2 < 30$ mmHg).

Appropriate management of $PaCO_2$ is a critical requirement in mechanically ventilated patients with TBI, since carbon dioxide is one of the major determinants of cerebral vascular physiology, and therefore cerebral blood flow and volume. The effect of the interplay between carbon dioxide and perfusion pressure on the cerebral circulation results in a sophisticated modulation of cerebrovascular resistance and tone, with hypercapnia causing cerebral vasodilation, and hypocapnia, vasoconstriction.

The only randomized controlled trial [22] addressing the benefit of prophylactic hyperventilation was conducted thirty years ago, and randomised TBI patients into three categories: control ($n = 41$), hyperventilation ($n = 36$), and HV + tromethamine (an H^+ acceptor used to treat metabolic acidosis; $n = 36$). This setting is different from the current context, as the putatively normoventilated controls had $PaCO_2$ values in the hypocapnic range (35 mmHg), and the HV utilized was

Table 2 Results of the logistic mixed-effect model on 6-month outcomes by the instrumental variable approach with complete data (*n* = 919)

Outcome	6-month GOSE OR (95% CI) *p* value	6-month mortality OR (95% CI) *p* value
Centre HV tendency (per 10% change)*	1.12 (0.9–1.38) 0.3138	1.06 (0.77–1.45) 0.7166
Age	1.04 (1.03–1.05) < 0.0001	1.05 (1.04–1.06) < 0.0001
GCS Motor Score		
None	2.08 (1.46–2.95) < 0.0001	2.28 (1.44–3.62) 0.0004
Extension	5.47 (2.39–12.51) < 0.0001	1.82 (0.74–4.48) 0.1886
Abnormal flexion	3.29 (1.63–6.65) 0.0009	1.69 (0.65–4.37) 0.2794
Normal flexion	1.45 (0.82–2.56) 0.1980	1.2 (0.55–2.64) 0.6421
Localizes/obeys	1	1
Pupilar reactivity		
Both reacting	1	1
One reacting	1.98 (1.14–3.43) 0.0146	2.18 (1.16–4.11) 0.0154
Both unreacting	3.29 (2.05–5.27) < 0.0001	6.04 (3.69–9.87) < 0.0001
ICP monitoring		
No	1	1
Yes	1.79 (1.27–2.51) 0.0008	1.00 (0.65–1.54) 0.9948
AUC ICP > 20 (per one SD change)°	3.72 (1.94–7.15) < 0.0001	5.15 (2.86–9.25) < 0.0001

OR Odds ratio, *CI* confidence intervals, *SD* standard deviation

* Centre HV propensity is calculated as the percentage of daily lowest $PaCO_2$ < 30 mmHg out of all available measures

°Standardized AUC ICP > 20 is the dose of intracranial hypertension calculated as the area under the ICP profile above 20 mmHg

profound ($PaCO_2$ 25 mmHg). These discordances with current practice, the limited number of patients, and the low incidence of episodes of intracranial hypertension make the results difficult to interpret.

A recent consensus still recommends targeting a normal range of $PaCO_2$ values in the absence of increased ICP [12]. However, in the case of increased ICP, no agreement was achieved regarding the role of HV, providing evidence of the current uncertainty in this area [12]. Although induced hypocapnia is considered an efficient second line measure to reduce ICP, clinicians remain worried about potential cerebral ischemic complications of hyperventilation [8, 23]. Coles et al. used positron emission tomography in a cohort of 30 patients to show that the acute application of HV resulted in a reduction of cerebral blood flow and an increase in oxygen extraction fraction and the ischemic brain volume [23]. These results have left an indelible imprint on the way HV is perceived by intensivists, but they do not represent a randomized trial. Other authors suggest that mild HV may reduce ICP without leading to pathological changes of brain metabolism and oxygenation measured through cerebral microdialysis and $PbtO_2$ [24] or energy failure. Moreover, Diringer et al. demonstrated that HV reduces global cerebral blood flow while increased oxygen extraction fraction leaving cerebral metabolic rate for oxygen unchanged, concluding that it is unlikely that HV causes neurological injury [25, 26].

Although some concerns still exist, $PaCO_2$ reduction is still widely used in the clinical setting for ICP control. The most common $PaCO_2$ target declared by clinicians in the absence of intracranial hypertension (35–40 mmHg) is higher than in the case of raised ICP (30–35 mmHg) [9]. Similarly, in a retrospective study of 151 patients with TBI, the $PaCO_2$ target adopted in clinically stable ICP was 36 ± 5.7 mmHg, whereas in the case of increased ICP it was 34 ± 5.4 mmHg [27]. Besides, a recent consensus on ICP treatment suggested considering HV to $PaCO_2$ of 30–32 mmHg when ICP is elevated in patients not responding to Tier 1 and 2 treatment [13].

Our data document a divergence between suggestions from literature and practice: nearly half of the daily lowest $PaCO_2$ measurements in the first week were < 35 mmHg. Moreover, in presence of ICP monitoring, clinicians use a lower target of $PaCO_2$. However, we also saw wide variability in $PaCO_2$ levels between centres, both in terms of the overall values, and the lowest levels of $PaCO_2$ observed. These differences were seen not just across the whole study cohort, but also in subgroups of patients with and without ICP monitoring, and those with and without episodes of intracranial hypertension in the first week. HV in presence of high ICP was frequently used,

particularly in the first few days after admission, and was often combined with other ICP-lowering therapies such as osmotic agents and decompressive craniectomy. Interestingly, centres that used HV more frequently were not more likely to routinely apply more advanced neuromonitoring techniques for early detection of impaired cerebral blood flow and cerebral oxygen availability.

There is no strong evidence regarding the possible benefits or harms of profound HV on patient outcomes. However, a single retrospective analysis of 251 brain-injured patients [28] reported that, when compared to controls, patients who underwent prolonged HV ($PaCO_2$: 25–30 mmHg; mean duration = 10, min–max = 5–41 h) experienced lower mortality (9.8 vs. 32.8%) but a higher rate of poor functional outcome.

We found that being treated in a centre where profound hypocapnia is more frequently used compared to centers where it is rarely used was not significantly associated with a higher rate of mortality or poor functional outcome.

In summary, our results suggest that moderate HV is widely used in severely brain-injured patients, especially when ICP is monitored, and in case of elevated ICP.

Limitations

Although our results may provide useful context with an important clinical message for physicians, we believe they should be interpreted with caution for several reasons. First, 6 months GOSE and mortality are influenced by several other factors, such as systemic and ICU complications, as well as post-ICU events. Therefore, based on observational data, it is speculative to draw a direct causal relationship between $PaCO_2$ and outcome: further randomized controlled studies are needed to assess the effect of $PaCO_2$ more precisely and in particular HV, on the outcome. Second, this is an analysis of data from a large study, which primarily addressed the epidemiology, clinical care and outcome of TBI. However, as respiratory management was not a primary focus of the study, more specific data on ventilatory management of these patients are missing, and hence unavailable to strengthen our analysis. Data on the incidence and timing of pulmonary complications such as acute respiratory distress respiratory syndrome and ventilator-associated pneumonia, the use of ventilatory strategies used to manipulate $PaCO_2$, and the ventilator settings used in our study population are unavailable. Third, the outcome was evaluated at 6 months, which can be considered as an early measurement of outcome after TBI, and further long-term evaluations would have been desirable. Fourth, we did not specifically take into consideration the temperature management of the patients, which can importantly affect $PaCO_2$ values. However, the measurements of $PaCO_2$ are automatically corrected for temperature from the arterial blood gases machines, and we aimed to assess the targets of $PaCO_2$ achieved, regardless of the effects of different factors on its final value.

Finally, in our dataset only the daily lowest and highest $PaCO_2$ values were collected, thus missing possible changes in $PaCO_2$ and pulmonary function parameters that may occur suddenly and repeatedly during the day. However, our analysis includes data on daily $PaCO_2$, thus providing a longitudinal view of $PaCO_2$ management over time.

Conclusions

In a large cohort of mechanically ventilated TBI patients, we found substantial between-centre variations in $PaCO_2$, but with a large proportion of patients being managed at $PaCO_2$ levels below those suggested by expert consensus statements. On average, patients who had ICP monitors in place had significantly lower $PaCO_2$ levels than those that did not, and amongst ICP monitored patients, $PaCO_2$ levels were lower in patients who had episodes of intracranial hypertension—suggesting that HV is still used for ICP management. Profound hyperventilation ($PaCO_2 < 30$ mmHg) was not uncommon. However, a centre that had a greater propensity to use profound HV did not worsen 6-month mortality or functional outcome. Notwithstanding this, we believe that the available evidence still makes the case for caution in the use of HV, with careful consideration of risks and benefits on a case-by-case basis. Our data provide no basis for dismissing continuing concerns regarding prophylactic or profound hyperventilation. We need randomized controlled trials and high-level evidence guidelines to support rational choices regarding optimal ventilation management and $PaCO_2$ targets in patients with TBI.

Supplementary Information

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Abbreviations

AUC CO_2i: Area below the value of 30 mmHg as a benchmark and the interpolation of the $PaCO_2$ profile in time; AUC ICP > 20: Area under ICP profile above 20 mmHg; CBF: Cerebral blood flow; CENTER-TBI: Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury; CI: Confidence interval; CO_2: Carbon dioxide; CT: Computed tomography; ESM: Electronic supplementary material; GCS: Glasgow coma scale; GOSE: Glasgow outcome scale extended; HP: Hypocapnia; HR: Hazard rate; HV: Hyperventilation; ICP: Intracranial pressure; ICP_m: ICP monitored; No-ICP_m: No-ICP monitored; ICU: Intensive care unit; ISS: Injury severity score; LOS: Length of stay; MOR: Median odds ratio; OR: Odds ratio; $PaCO_2$: Partial pressure of carbon dioxide; $PbtO_2$: Brain tissue oxygenation; SaO_2: Oxygen saturation; $SjvO_2$: Jugular bulb venous oxygen saturation; SD: Standard deviation; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology; TBI: Traumatic brain injury; TIL: Therapy intensity level.

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GC conceived and supervised the project, participated in the data analysis, revised the first version of the manuscript the manuscript, and the supplementary tables. CR participated in the data analysis, drafted the manuscript, the supplementary tables and collected the COIs. SG, MP, and PR analysed the data, drafted the manuscript, and the supplementary material. LM, ER, DKM, and NS were an active part of the manuscript drafting and revision. GC, CR, SG, MP, PR have verified the underlying data. DKM was one of the two coordinators of the CENTER-TBI study, and GC and NS were Work Package leaders. GC, CR, SG and DKM discussed the findings with all the authors. All co-authors gave substantial feedback on the manuscript and approved the final version of it.

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Declarations

Conflict of interest
GC reports grants, personal fees as Speakers' Bureau Member and Advisory Board Member from Integra and Neuroptics. DKM reports grants from the European Union and UK National Institute for Health Research, during the conduct of the study; grants, personal fees, and non-financial support from GlaxoSmithKline; personal fees from Neurotrauma Sciences, Lantmaanen AB, Pressura, and Pfizer, outside of the submitted work. The other authors declare that they have no competing interests.

Ethics approval and consent to participate
The Medical Ethics Committees of all participating centers approved the CENTER-TBI study, and informed consent was obtained according to local regulations. (https://www.center-tbi.eu/project/ethical-approval).

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