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

Giuseppe Citerio1,2*, Chiara Robba3,4, Paola Rebora1,5, Matteo Petrosino5, Eleonora Rossi6, Letterio Malgeri7, Nino Stocchetti8,9, Stefania Galimberti1,5, and David K. Menon10 on behalf of the Center-TBI participants and investigators

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Abstract

Purpose: To describe the management of arterial partial pressure of carbon dioxide (PaCO2) in severe traumatic brain-injured (TBI) patients, and the optimal target of PaCO2 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 PaCO2 management during the first week of intensive care unit (ICU) after TBI, focusing on the lowest PaCO2 values. We also assessed PaCO2 management in patients with and without ICP monitoring (ICPm), and with and without intracranial hypertension. We evaluated the effect of profound hyperventilation (defined as PaCO2 < 30 mmHg) on long-term outcome.

Results: We included 1100 patients, with a total of 11,791 measurements of PaCO2 (5931 lowest and 5860 highest daily values). The mean (± SD) PaCO2 was 38.9 (± 5.2) mmHg, and the mean minimum PaCO2 was 35.2 (± 5.3) mmHg. Mean daily minimum PaCO2 values were significantly lower in the ICPm group (34.5 vs 36.7 mmHg, p < 0.001). Daily PaCO2 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. PaCO2 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
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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{2} between 35 and 45 mmHg [12], and to only use hyperventilation (with an undefined PaCO\textsubscript{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\textsubscript{2} 32–35 mmHg) for controlling ICP only as a second-tier treatment, did not support lower PaCO\textsubscript{2} levels and recommended against routine hyperventilation to PaCO\textsubscript{2} below 30 mmHg [13].

The objectives of this study were to assess, in a real-world context, PaCO\textsubscript{2} management and the lowest target of PaCO\textsubscript{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/ethicalapproval). This project on PaCO\textsubscript{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\textsubscript{2} measurements in the first 7 days and had been admitted to a study centre that enrolled at least ten patients.

**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\textsubscript{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\textsubscript{2} ranging between 30 and 35 mmHg and profound for PaCO\textsubscript{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\texttextsubscript{m}, while those who did not receive ICP monitoring during ICU stay as no-ICP\texttextsubscript{m}. Intracranial hypertension was defined as ICP > 20 mmHg.

**Objectives**

The aims of this study are:

1. to describe the PaCO\textsubscript{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\textsubscript{2};
2. to assess at a center level the PaCO₂ 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 (± standard deviation, SD), medians (I–III quartiles, Q₁–Q₃) 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 PaCO₂ of 35–45 mmHg. MOR was obtained from a longitudinal logistic mixed-effect model on daily lowest PaCO₂ 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 PaCO₂ < 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 PaCO₂ 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 PaCO₂ 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 PaCO₂ at ICU admission was 39.1 (± 6) mmHg, and the no-ICP_m group had higher PaCO₂ mean values compared to the ICP_m patients (39.9 ± 6.8 vs 38.7 ± 5.6 mmHg, p < 0.002).

Lowest PaCO₂ targets according to centers
Daily minimum PaCO₂ distribution during the first week for the whole population, and separated by the centre, are presented in Fig. 1a. The overall mean lowest PaCO₂ 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 PaCO₂ value of 32.3 and 36.4 mmHg.

Only 144 (13%) patients had all PaCO₂ measurements between 35 and 45 mmHg, while 588 (53%) patients had at least half of the total PaCO₂ measurements in this range. Using MOR to quantify between-centre differences in targeting the suggested PaCO₂ 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 PaCO₂ 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 PaCO₂ measurements between 35 and 45 mmHg raised to 19% (111/593) and 64% (380/593), while MOR decreased to 1.4.
Lowest PaCO₂ targets in the presence or not of ICP monitoring

Mean minimum PaCO₂ values were significantly lower in ICPₘ patients compared to no-ICPₘ (34.7 ± 4.9 mmHg vs 36.8 ± 5.7 mmHg, \( p < 0.001 \)). Large variability was observed among centers in the management of PaCO₂ targets in both subgroups (Fig. 2 and ESM Fig. 2). Some centers showed no differences in target PaCO₂ when ICPₘ was used (i.e. data points near the line of identity in Fig. 2a), but most hospitals tended to adopt lower PaCO₂ 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 PaCO₂ when ICP monitoring was available (from 38–38.4 mmHg to 33.1–34.2 mmHg).

Lowest PaCO₂ 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 centers showed no differences in target PaCO₂ when ICP was elevated (i.e. data points near the line of identity in Fig. 2b), but most hospitals tended to adopt lower PaCO₂ targets when ICP was monitored (i.e. data points that deviate substantially from the line of identity in Fig. 2b). The mean minimum PaCO₂ 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 PaCO₂, both in the absence and presence of intracranial hypertension (ESM Fig. 3).
Profound hyperventilation

An episode of profound HV (PaCO₂ < 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 ICPₘ 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...

| Characteristic                          | Overall (n = 1100) | no-ICPₘ (n = 349) | ICPₘ (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)     | 0.929   |
| Thoracic trauma, n (%)                  | Yes                | 138 (12.5)       | 42 (12)       | 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)     | 0.936   |
|                                        | Not available      | 78               | 10            | 68      |
| Hypoxia, n (%)                          | Yes                | 182 (17.9)       | 53 (15.6)     | 0.217   |
|                                        | Not available      | 82               | 10            | 72      |
| Severity TBI, n (%)                     | GCS ≤ 8            | 367 (35.3)       | 147 (44.3)    | < 0.001 |
|                                        | GCS > 8            | 674 (64.7)       | 185 (55.7)    |         |
|                                        | Not available      | 59               | 17            | 42      |
| Pupillary reactivity, n (%)             | Both reactive      | 799 (75.8)       | 280 (82.8)    | 0.001   |
|                                        | One reactive       | 89 (8.4)         | 22 (6.5)      |         |
|                                        | Both unreactive    | 166 (15.7)       | 36 (10.7)     |         |
|                                        | Not available      | 47               | 11            | 35      |
| GCS motor, n (%)                        | None               | 460 (42.7)       | 129 (37.7)    | < 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) |
|                                        |                      | 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 PaCO₂ (mmHg), mean (SD)         | 39.10 (6)          | 39.93 (6.8)      | 38.72 (5.6)   | 0.027   |
| Lowest PaCO₂ (mmHg), mean (SD)          | 34.66 (5.98)       | 35.92 (6.67)     | 34.09 (5.56)  | < 0.001 |
| Highest PaCO₂ (mmHg), mean (SD)         | 43.68 (8.1)        | 44.07 (8.6)      | 43.5 (7.86)   | 0.287   |

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

Hypotension was defined as a documented systolic blood pressure < 90 mmHg; hypoxia was defined as a documented partial pressure of oxygen (PaO₂) < 8 kPa (60 mmHg), oxygen saturation (SaO₂) < 90%, or both; PaCO₂ data refer to values at ICU admission

PaCO₂ 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, ICPₘ intracranial pressure monitored, ICU intensive care unit
used frequently. No differences were found in their use in patients receiving profoundly HV (jugular bulb venous oxygen saturation, SjvO2: 2.4% vs profound HV 3.5%, \( p\) value = 0.380; brain tissue oxygenation, PbtO2: 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 \( \leq 4\)). 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 PaCO2 < 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 PaCO2 management during mechanical ventilation at a centre level in prospectively collected
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 PaCO₂ levels and the lowest PaCO₂ adopted in TBI patients;
- patients who received ICP monitoring were managed at lower PaCO₂ 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 PaCO₂ 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 (PaCO₂ < 30 mmHg).

Appropriate management of PaCO₂ 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 PaCO₂ values in the hypocapnic range (35 mmHg), and the HV utilized was
profound (PaCO₂ 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 PaCO₂ 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 PbtO₂ [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, PaCO₂ reduction is still widely used in the clinical setting for ICP control. The most common PaCO₂ 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 PaCO₂ 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 PaCO₂ 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 PaCO₂ measurements in the first week were < 35 mmHg. Moreover, in presence of ICP monitoring, clinicians use a lower target of PaCO₂. However, we also saw wide variability in PaCO₂ levels between centres, both in terms of the overall values, and the lowest levels of PaCO₂ 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,

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                              |                                 |                                    |
| 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          |
| **Pupilar reactivity**                       |                                 |                                    |
| Both reacting                                |                                 |                                    |
| One reacting                                 |                                 |                                    |
| Both unreacting                              |                                 |                                    |
| **ICP monitoring**                           |                                 |                                    |
| No                                           |                                 |                                    |
| 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          |

* Centre HV propensity is calculated as the percentage of daily lowest PaCO₂ < 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

OR Odds ratio, CI confidence intervals, SD standard deviation

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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 (PaCO₂: 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 PaCO₂ and outcome: further randomized controlled studies are needed to assess the effect of PaCO₂ 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 is missing, and hence unavailable to strengthen our analysis. Data on the incidence and timing of pulmonary complications would have been desirable. Fourth, we did not specifically take into consideration the temperature management of the patients, which can importantly affect PaCO₂ values. However, the measurements of PaCO₂ are automatically corrected for temperature from the arterial blood gases machines, and we aimed to assess the targets of PaCO₂ achieved, regardless of the effects of different factors on its final value.

Finally, in our dataset only the daily lowest and highest PaCO₂ values were collected, thus missing possible changes in PaCO₂ and pulmonary function parameters that may occur suddenly and repeatedly during the day. However, our analysis includes data on daily PaCO₂, thus providing a longitudinal view of PaCO₂ management over time.

Conclusions

In a large cohort of mechanically ventilated TBI patients, we found substantial between-centre variations in PaCO₂, but with a large proportion of patients being managed at PaCO₂ levels below those suggested by expert consensus statements. On average, patients who had ICP monitors in place had significantly lower PaCO₂ levels than those that did not, and amongst ICP monitored patients, PaCO₂ levels were lower in patients who had episodes of intracranial hypertension—suggesting that HV is still used for ICP management. Profound hyperventilation (PaCO₂ < 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 PaCO₂ targets in patients with TBI.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06470-7.

Abbreviations

AUC CO₂: Area below the value of 30 mmHg as a benchmark and the interpolation of the PaCO₂ 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; CO₂: 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; ICPₚ: ICP monitored, No-ICPₚ: No-ICP monitored, ICU: Intensive care unit; ISS: Injury severity score; LOS: Length of stay; MDR: Median odds ratio; OR: Odds ratio; PaCO₂: Partial pressure of carbon dioxide; PbtO₂: Brain tissue oxygenation; SaO₂: Oxygen saturation; SjvO₂: 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.

Author details

1 School of Medicine and Surgery, University of Milano - Bicocca, Monza, Italy.
2 Neurointensive Care Unit, Ospedale San Gerardo, Azienda Socio-Sanitaria
We acknowledge the CENTER-TBI ICU Participants and Investigators listed here as non-authors contributors: Cecilia Åkerlund, Kristina Armean, Nada Andelic, Lasse Andressen, Audny Anke, Anna Antoni, Gérard Audibert, Philippe Aouzou, Maria Laura Azzolinis, Ronald Bartels, Pål Barzó, Romuald Beauvais, Ronny Beer, Bo-Michael Bellander, Cristina Maria Tudora, Andreas Unterberg, Peter Vajkoczy, Aarno Palotie, Paul M. Parizel, Jean-François Payen, Natascha Peter, Camilla Brooker, Camilla Brosson, Andreas Buki, Monika Bullinger, Manuel Cabeleira, Alessio Cacciapuoti, Emilia Calapppi, Maria Rosa Calvi, Peter Cameron, Guillermo Carbayo Lozano, Marco Carbonara, Simona Cava, Giorgio Cavallari, Arturo Cherepoga, Giuseppe Citro, Hans Clusmann, Mark Coburn, Jonathan Coles, Jamie Cooper, Jamie D. Cooper, Thomas Cooper, Dick Tibboel, Marjolein Timmers, Christos Tolias, Tony Trapani, Cristina Vargiolu, Emmanuel Vega, Kimberly Velt, Jan Verheyden, Paul M. Vesper, Anne Vik, Rematas Vilcins, Victor Volotcji, Nicole von Steinbuchel, Daphne Voorsmolen, Petar Vulekove, Kevin K.W. Wang, Eveline Wiegers, Gun Williams, Lindsay Wilson, Stefan Winzek, Stefan Wolf, Zhihuai Yang, Peter Ylen, Alexander Young, Frederik A. Zeiler, Veronika Zelinkova, Agate Ziverte.

1 Department of Physiology and Pharmacology, Section of Perioperative Medicine and Intensive Care, Karolinska Institutet, Stockholm, Sweden
2 Department of Neurosurgery & Anesthesia & intensive care medicine, Karolinska Universitetssjukhuset, Stockholm, Sweden
3 Department of Neurosurgery, University of Pecs, Pécs, Hungary
4 Department of Diversion of Surgery and Neurosciences, Department of Physical Medicine and Rehabilitation, Oslo University Hospital and University of Oslo, Oslo, Norway
5 Department of Neurosurgery, University Hospital Northern Norway, Tromsø, Norway
6 Department of Physical Medicine and Rehabilitation, University Hospital Northern Norway, Tromsø, Norway
7 Trauma Surgery, Medical University Vienna, Vienna, Austria
8 Department of Neurology, University Hospital Nancy, Nancy, France
9 Department of Neurology and Intensive Care Medicine, University Hospital of Innbruck, Innbruck, Austria
10 Department of Neurosurgery & Anesthesia & Intensive care medicine, Karolinska University Hospital, Stockholm, Sweden
11 NIHR Surgical Reconstruction and Microbiology Research Centre, Birmingham, UK
12 Anesthesia-Réanimation, Assistance Publique – Hopitaux de Paris, Paris, France
13 Department of Anesthesiology & Intensive Care, Aachen, Germany
14 Department of Neurosurgery, University of Szeged, Szeged, Hungary
15 Department of Neurology, University of Milan, Torino, Italy
16 Anesthesie-Réanimation, Assistance Publique – Hopitaux de Paris, Paris, France
17 Department of Neurosurgery, Torino—Orthopedic and Trauma Center, Torino, Italy
18 Department of Neurology, Odense University Hospital, Odense, Denmark
19 BehaviourWorks Australia, Monash Sustainability Institute, Monash University, Victoria, Australia
20 Department of Public Health, Faculty of Health Sciences and Social Work, Trnava University, Trnava, Slovakia
21 Queensens Systems Inc, Burlingame, California, USA
22 Australian & New Zealand Intensive Care Research Centre, Department of Epilepidology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
23 Department of Surgery and Perioperative Science, Umeå University, Umeå, Sweden
24 Department of Neurosurgery, Medical School, University of Pecs, Hungary and Neurotrauma Research Group, János Szentágothai Research Centre, University of Pécs, Pécs, Hungary
25 Department of Medical Psychology, Universitätshôpital Zürich-Horn-Baden, Switzerland
26 Australian & New Zealand Intensive Care Research Centre, Department of Epilepidology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
27 Brain Physics Lab, Division of Neurosurgery, Dept of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
28 Neuro ICU, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy
29 Department of Anesthesiology & Intensive Care Medicine, University Hospital Bonn, Bonn, Germany
30 Department of Anesthesia & Neurocritical Care Medicine, University Hospital NHS Foundation Trust, Cambridge, UK
sachusetts General Hospital, Boston MA, USA
114 National Trauma Research Institute, The Alfred Hospital, Monash University, Melbourne, Victoria, Australia
115 Department of Neurosurgery, Odense University Hospital, Odense, Denmark
116 International Neurotrauma Research Organisation, Vienna, Austria
117 Klinik für Neurochirurgie, Klinikum Ludwigsburg, Ludwigsburg, Germany
118 Division of Biostatistics and Epidemiology, Department of Preventive Medicine, University of Debrecen, Debrecen, Hungary
119 Department of Health and Prevention, University Greifswald, Greifswald, Germany
120 Department of Anaesthesiology and Intensive Care, AUA Trauma Hospital, Salzburg, Austria
121 Department of Neurology, Elisabeth-TweeSteden Ziekenhuis, Tilburg, the Netherlands
122 Department of Neuroanesthesia and Neurointensive Care, Odense University Hospital, Odense, Denmark
123 Department of Neuromedicine and Movement Science, Norwegian University of Science and Technology, NTNU, Trondheim, Norway
124 Department of Physical Medicine and Rehabilitation, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
125 Department of Neurosurgery, University of Pécs, Pécs, Hungary
126 Division of Neuroscience Critical Care, John Hopkins University School of Medicine, Baltimore, USA
127 Department of Neuropathology, Queen Elizabeth University Hospital and University of Glasgow, Glasgow, UK
128 Dept. of Department of Biomedical Data Sciences, Leiden University Medical Center, Leiden, The Netherlands
129 Department of Pathophysiology and Transplantation, Milan University, and Neuroscience ICL, Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, Milano, Italy
130 Department of Radiation Sciences, Biomedical Engineering, Umeå University, Umeå, Sweden
131 Perioperative Services, Intensive Care Medicine and Pain Management, Turku University Hospital and University of Turku, Turku, Finland
132 Department of Neurosurgery, Kaunas University of Health Sciences, Kaunas, Lithuania
133 Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
134 Department of Neurosurgery, Kings college London, London, UK
135 Neurologie, Neurochirurgie und Psychiatrie, Charité – Universitätsmedizin Berlin, Berlin, Germany
136 Department of Intensive Care Adults, Erasmus MC–University Medical Center Rotterdam, Rotterdam, the Netherlands
137 iCoMetrix NV, Leuven, Belgium
138 Movement Science Group, Faculty of Health and Life Sciences, Oxford Brookes University, Oxford, UK
139 Psychology Department, Antwerp University Hospital, Edegem, Belgium
140 Director of Neurocritical Care, University of California, Los Angeles, USA
141 Department of Neurosurgery, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway
142 Department of Emergency Medicine, University of Florida, Gainesville, Florida, USA
143 Department of Neurosurgery, Charité – Universitätsmedizin Berlin, corporate member of Free Universitats Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany
144 YTT Technical Research Centre, Tampere, Finland
145 Section of Neurosurgery, Department of Surgery, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

Author contributions
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 and PR analysed the data, drafted the manuscript, and the supplementary material. UM, ER, DKM, and NS were 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
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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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