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Clinical practice and effect of carbon dioxide on outcomes in mechanically ventilated acute brain-injured patients: a secondary analysis of the ENIO study

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Abstract

Purpose: The use of arterial partial pressure of carbon dioxide ($PaCO_2$) as a target intervention to manage elevated intracranial pressure (ICP) and its effect on clinical outcomes remain unclear. We aimed to describe targets for $PaCO_2$ in acute brain injured (ABI) patients and assess the occurrence of abnormal $PaCO_2$ values during the first week in the intensive care unit (ICU). The secondary aim was to assess the association of $PaCO_2$ with in-hospital mortality.

Methods: We carried out a secondary analysis of a multicenter prospective observational study involving adult invasively ventilated patients with traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracranial hemorrhage (ICH), or ischemic stroke (IS). $PaCO_2$ was collected on day 1, 3, and 7 from ICU admission. Normocapnia was defined as $PaCO_2 > 35$ and to 45 mmHg; mild hypocapnia as 32–35 mmHg; severe hypocapnia as 26–31 mmHg, forced hypocapnia as < 26 mmHg, and hypercapnia as > 45 mmHg.

Results: 1476 patients (65.9% male, mean age 52 ± 18 years) were included. On ICU admission, 804 (54.5%) patients were normocapnic (incidence 1.37 episodes per person/day during ICU stay), and 125 (8.5%) and 334 (22.6%) were mild or severe hypocapnic (0.52 and 0.25 episodes/day). Forced hypocapnia and hypercapnia were used in 40 (2.7%) and 173 (11.7%) patients. $PaCO_2$ had a U-shape relationship with in-hospital mortality with only severe hypocapnia and hypercapnia being associated with increased probability of in-hospital mortality (omnibus p value = 0.0009). Important differences were observed across different subgroups of ABI patients.

Conclusions: Normocapnia and mild hypocapnia are common in ABI patients and do not affect patients' outcome. Extreme derangements of $PaCO_2$ values were significantly associated with increased in-hospital mortality.

Keywords: Intensive care, Critical care, Brain injury, TBI, SAH, ICH, Stroke, Invasive ventilation, Carbon dioxide, $PaCO_2$, Hyperventilation

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Introduction

Changes in the arterial partial pressure of carbon dioxide ($PaCO_2$) can exert profound effects on cerebrovascular regulation, leading to adjustments in cerebrovascular tone, cerebral blood flow (CBF), and cerebral blood volume (CBV) in acute brain-injured (ABI) patients [1, 2]. Induced hypocapnia secondary to hyperventilation is utilized as a secondary intervention to control elevated intracranial pressure (ICP) that remains unresponsive to initial therapeutic measures [3–5]. Nevertheless, it is essential to exercise caution when employing induced hypocapnia, as some studies have demonstrated to cause cerebral hypoperfusion [1], particularly when reaching $PaCO_2$ levels < 25 mmHg.

Indeed, prophylactic or prolonged use of extreme hypocapnia is discouraged based on the most recent recommendations from the Brain Trauma Foundation Guidelines, supported by level IIB evidence [6], and it should be considered only in cases of life-threatening brain herniation. The most recent evidence-based Guidelines of the European Society of Intensive Care Medicine (ESICM) on ventilatory management of ABI patients have not provided definitive recommendations regarding target $PaCO_2$ levels in case of intracranial hypertension [7]. The lack of conclusive guidance is attributed to the limited quality of evidence available on this complex pathophysiological framework. Therefore, the optimal cutoffs for $PaCO_2$ in acute brain-injured patients, with and without intracranial hypertension, are currently under debate.

We performed a secondary analysis of a worldwide multicenter prospective observational study conducted in ABI patients who received invasive ventilation in the intensive care unit (ICU), with the aim to assess the incidence of abnormal $PaCO_2$ values on admission and during the first week of ICU stay. We also assessed the association between $PaCO_2$ values and in-hospital mortality in the entire population, as well as in different ABI subgroups.

Methods

Study design and ethics

This is a preplanned secondary analysis of a worldwide, multicenter, observational cohort study named "Extubation strategies in Neuro-Intensive care unit patients and associations with Outcomes" (ENIO) (registration number NCT03400904) conducted between June 2018 and November 2020 [8]. ENIO was endorsed by the PROtective VEntilation Network (PROVE Net), the ESICM, the French Society of Anesthesiology and Critical care (SFAR), and Colegio Mexicano de Medicina Critica (CMMC). The study protocol was approved by the International Review Board (IRB) of the Groupe Nantais d'Éthique dans le Domaine de la Santé, Nantes, France (IRB No. 7/11/2017), and then by each participating site. Informed consent was collected in accordance with the local regulations. Initial approval also included the secondary analysis, which underwent a preliminary evaluation and was approved by the Steering Committee of ENIO. This study was conducted according to the STROBE reporting guidelines for observational studies [9] (electronic supplementary material, ESM, Table S1).

Take-home message

Extreme values of hypo- and hypercapnia are associated with in-hospital mortality in acute brain injured patients, with mild hypocapnia being better tolerated, especially in the traumatic brain injured subpopulation.
The targets of carbon dioxide should take in consideration the type of acute brain injury as well as physiological/neuromonitoring data.

Patients

Inclusion criteria of the ENIO study were: (1) age ≥ 18 years; (2) patients receiving invasive ventilation ≥ 24 h; (3) admitted for ABI (including traumatic brain injury—TBI; subarachnoid hemorrhage—SAH; intracranial hemorrhage—ICH; ischemic stroke—IS) with a Glasgow Coma Scale (GCS) score ≤ 12; (4) having underwent an attempt to discontinue ventilation (defined as an extubation trial and/or tracheostomy). Pregnant patients, patients with spinal cord injury above T4, post-cardiac arrest patients, and Guillain–Barré syndrome patients were excluded. ENIO also excluded patients with withdrawal of life-sustaining treatment (WLST) in the first 24 h of ICU admission, patients with tracheostomy before ICU admission, and patients with major respiratory comorbidities or major chest trauma [10]. For this subanalysis, we additionally excluded patients for whom $PaCO_2$ data were missing at admission.

Management of acute brain injury

The primary care of brain damage, according to the main ENIO study, was specific to the initial pathology (trauma, subarachnoid hemorrhage, intracranial bleeding, etc.) and followed international guidelines [3, 5] as well as local practice. Neuromonitoring, brain imaging, and surgical approach were carried out in accordance with local procedures of each center [10].

Data collection

Data extracted from the ENIO dataset included: demographic and baseline characteristics [age, gender, height, weight, body mass index (BMI), previous comorbidities (chronic obstructive pulmonary disease, cardiovascular comorbidities, arterial hypertension, smoking, diabetes

mellitus, history of malignancy, etc.)]; type and severity of brain injury (as for GCS); neurosurgical and neurocritical care management, including tier three therapies (barbiturate coma, therapeutic hypothermia, ICP monitoring, and decompressive craniectomy) according to the Seattle Guidelines [3, 5]; airway and ventilatory management (i.e., tracheostomy, gag reflex, cough, spontaneous breathing trial, extubation, and reintubation); in-ICU events, in-hospital mortality, and in-ICU outcomes (need for and duration of IMV, ICU length of stay [LOS], mortality, need for non-invasive mechanical ventilation, and duration).

Definitions

Patients were initially binned in five $PaCO_2$ groups, according to the values on day 1 at ICU admission, according to previous literature [11] and on most recent guidelines [3, 5] as follows: normocapnia, $PaCO_2 > 35$–45 mmHg, mild hypocapnia 32–35 mmHg, severe hypocapnia as 26– < 32 mmHg, forced hypocapnia as $PaCO_2 < 26$ mmHg, and hypercapnia as $PaCO_2 > 45$ mmHg. Abnormal $PaCO_2$ was defined as a value < 35 mmHg and > 45 mmHg. Samples of $PaCO_2$ were obtained in the morning, at around 8 am, as for ENIO protocol.

Objectives

The primary objective was to describe the $PaCO_2$ values measured in ABI patients and assess the occurrence of abnormal $PaCO_2$ values on admission and during the ICU stay in the study cohort. The secondary objective was to assess the association between $PaCO_2$ values and in-hospital mortality in the entire population and according to different brain injury groups (i.e., TBI, SAH, ICH, and IS).

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD) or median (interquartile range [IQR]) as appropriate; discrete variables are presented as numbers and percentages. For continuous baseline characteristics, ANOVA was used for comparing $PaCO_2$ discrete categories (forced, severe, and mild hypocapnia, normocapnia, and hypercapnia); if the variable did not meet the normality assumption, Kruskal–Wallis test was used instead. For the comparison of discrete variables, a Chi-square test was used.

For descriptive purposes, $PaCO_2$ continuous ($PaCO_{2c}$) was log-transformed due to high skewness. As such, its trajectory over days 1, 3, and 7 was depicted using a locally weighted scatterplot smoothing (LOWESS) method [12]. We used longitudinal survival regression for inferential analysis. Using this method, we directly evaluated the association between $PaCO_2$ (continuous and categorized) and in-hospital mortality. For this analysis, $PaCO_{2c}$ was log-transformed due to high skewness. The model assumed a Weibull distribution for the baseline hazard and random intercept on patient identification (ID). Variable selection was carried out by backward elimination using a multivariable fractional polynomial (FP) procedure (see ESM for further details) [13]. The baseline variables selected (at day 1) by this method included: age (years), gender, history of hypertension, diabetes, and heart failure, treatment with midazolam, neuromuscular blockers, pentothal, propofol, and dexmedetomidine, ventilatory mode, respiratory rate (breaths/min), tidal volume (mL/kg of predicted body weight [PBW]), positive end-expiratory pressure (PEEP), arterial pH (pHa), GCS, and acute respiratory distress syndrome (ARDS). Results from the model of $PaCO_2$ with 5 discrete categories were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). Based on the U-shaped association suggested by the $PaCO_2$ categorical model, we decided to model $PaCO_{2c}$ with 5-df restricted cubic splines (RCS) to capture the non-linear trajectory [14]. Within this framework, the result was instead depicted through a graph where the HR on the *y*-scale was plotted against the continuum of $PaCO_{2c}$. To account for interdependence among centers, the models included a cluster-based adjustment of the standard error estimation.

As a second step, we used a linear mixed-effects model. We evaluated the differences in the log of $PaCO_{2c}$ over the 3 days (using day 1 as reference); the model included a random intercept on the study center and on patient ID to account for correlated measurements from the two clusters. In addition, the variable ICU days (1, 3, and 7) was included as a random coefficient with an unstructured covariance matrix. This model also included the same subset of covariates used in the longitudinal survival regression. Results were expressed as predicted means—also known as least square means (LSM).

Relative distribution analysis [15] evaluated the association between the continuum of $PaCO_{2c}$ and the cumulative proportion of in-hospital mortality with the results depicted as a figure, where the vertical axis shows the relative density of the two distributions (as a ratio) and the horizontal axis shows the percentiles of the reference group ($PaCO_{2c}$ values when in-hospital mortality = 0). Further details on statistical analysis are provided in ESM, Item S1. A significance level < 0.05 was used for all analyses. Stata 18.0 was used for data clean-up and preparation.

Results

Patients

Of the 1512 patients enrolled in the ENIO study, a total of 1476 were included in the analysis (36 patients were excluded for missing $PaCO_2$ data). The mean age of the study cohort was 52 (± 18) years, and 973 (65.9%) were male. Mean BMI was 26.3 (± 5.1) kg/m^2; 715 (48.4%) were admitted for TBI, 264 (17.9%) for SAH, 509 (34.5%) for ICH, and 132 (9.2%) for IS (Table 1 and Table S2 for additional data). Demographic characteristics, ventilator management, and arterial blood gas parameters according to neurologic status (GCS > 9 and ≤ 9), type of ABI, and different categories of $PaCO_2$ are presented in ESM, Tables S3–S9.

Carbon dioxide values on admission and during ICU stay

On admission, median $PaCO_2$ was 37 (34–41) mmHg; 804 (54.5%) patients presented with normocapnia on ICU admission, 125 (8.5%) patients were hypercapnic, and 334 (22.6%) and 173 (11.7%) were mild and moderate hypocapnic; forced hypocapnia was observed in 40 (2.7%) patients (Table 1). Significant differences were observed among different $PaCO_2$ categories according to the country of admission, gender, and type of ABI (Table 1, and ESM, Tables S2–S9). Normo- and mild hypocapnia were more frequently observed in the presence of ICP monitoring ($p < 0.001$), but not in patients who received tier three therapies or according to GCS and pupils' characteristics (Table 1). The occurrence of abnormal $PaCO_2$ values over time is shown in Fig. 1; only a minority experienced multiple events of abnormal $PaCO_2$ values, with mild hypocapnia being more common than other abnormalities.

The median $PaCO_2$ significantly increased over time in the whole population from day 1 to 3 (from 37 mmHg [34–41] to 38 mmHg [36–37]; $p < 0.001$) and from day 1 to 7 (from 37 mmHg [34–41] to 39 mmHg [39–40], $p < 0.001$) in the whole population (ESM, Figure S2) and in all ABI categories (except ischemic stroke, ESM, Figure S4). Figure 2 and supplemental Figure S3 present the transition of the different $PaCO_2$ categories from day 1 to day 3 and day 7. Most of the changes occurring in the hypocapnia group were toward normocapnia, and only a few were toward severe hypocapnia. Most patients with forced hypocapnia remained in the same category. Most patients with hypercapnia evolved toward normocapnia.

Effect of carbon dioxide on in-hospital mortality in the overall cohort

The overall in-hospital mortality in the population was 12.1% ($n = 178$ patients); trajectories of $PaCO_2$ values during ICU stay in survivors vs non-survivors are presented in supplemental Figures S6–S8. When modeled as a continuous variable, $PaCO_2$ had a U-shaped relationship with in-hospital mortality, with both hypo- and hypercapnia being independently associated with an increased probability of in-hospital mortality (omnibus $p = 0.0009$—Fig. 3a).

When $PaCO_2$ was modeled according to its discrete categories, the U-shaped curve persisted (Fig. 3b). Compared to normocapnia, patients with forced hypocapnia (adjusted hazard ratio [aHR] 4.31; 95% CI 1.56–11.87—$p = 0.005$) had the highest rate of in-hospital mortality, followed by hypercapnia (aHR 3.67; 95% CI = 1.75–7.71—$p = 0.001$), and severe hypocapnia (aHR 2.77; 95% CI 1.31–5.87—$p = 0.008$). Patients with mild hypocapnia had a borderline significant association with increased in-hospital mortality (aHR 2.07; 95% CI 1.02–4.12—$p = 0.049$).

Relative distribution analysis further confirmed the U-shaped association between hypo- and hypercapnia and in-hospital mortality (Fig. 4). In particular, a significant increase in the probability for in-hospital mortality for values > 45 mmHg and < 32 mmHg. Similar results were confirmed when $PaCO_2$ values were assessed separately on each day (Fig. 4b).

The relationship between $PaCO_2$ stratified according to neurologic status (GCS > 9 and ≤ 9) and according to the single time points of observation showed a consistent U-shaped curve (supplemental Figures S1 and S9).

Effect of carbon dioxide on in-hospital mortality in different ABI subgroups' population

In TBI patients (supplemental Figures S10 and S11), a statistically significant association with mortality was found only for severe hypocapnia (aHR 4.43; 95% CI 1.29–15.21—$p = 0.018$) and hypercapnia (aHR 4.58; 95% CI 1.81–11.58—$p = 0.001$), but not for other $PaCO_2$ categories. In patients with ICH (supplemental Figures S12 and S13), only hypercapnia was significantly associated with increased mortality (aHR 3.47; 95% CI 1.08–11.18—$p = 0.037$).

In patients with SAH (Figures S14 and S15), forced hypocapnia (aHR 46.76; 95% CI = 7.22–302.69—$p < 0.001$), severe (aHR = 7.04; 95% CI = 2.12–23.42—$p = 0.001$), and mild hypocapnia (HR 3.68; 95% CI = 1.12–12.05—$p = 0.032$) were independently associated with in-hospital mortality, whereas hypercapnia was not. In patients with IS (supplemental Figures S16 and S17), any of the $PaCO_2$ categories were significantly associated with in-hospital mortality, as compared with normocapnia.

Discussion

In this worldwide multicenter observational cohort of severe ABI patients, we found that—in the early days of

Table 1 Characteristics of the patients included in the cohort at admission and outcomes, considering the whole population and according to different subgroups of carbon dioxide ranges

	Total $n = 1476$ (100)	Forced hypocapnia ($PaCO_2 < 26$ mmHg) $n = 40$ (2.7%)	Severe hypocapnia ($PaCO_2$ 26 to < 32 mmHg) $n = 173$ (11.7%)	Mild hypocapnia ($PaCO_2$ 32 to 35 mmHg) $n = 334$ (22.6%)	Normocapnia ($PaCO_2 > 35$ to 45 mmHg) $n = 804$ (54.5%)	Hypercapnia ($PaCO_2 > 45$ mmHg) $n = 125$ (8.5%)	*P* value
Demographics at ICU admission							
Age, years, mean (SD)	52 (18)	50 (18)	52 (19)	51 (18)	51 (18)	52 (19)	0.965
Gender (male), *n* (%)	973 (65.9)	22 (55)	98 (56.6)	206 (61.7)	553 (68.8)	94 (75.2)	0.001
BMI, kg/m^2, mean (SD)	26.3 (5.1)	25.8 (5.4)	25.9 (4.3)	26.0 (4.7)	26.4 (5.4)	27.1 (5.2)	0.198
Study country, *n* (%)							0.001
The Netherlands	52 (3.5)	5 (12.5)	5 (2.9)	12 (3.6)	27 (3.4)	3 (2.4)	
France	646 (43.8)	8 (20)	62 (35.8)	152 (45.5)	373 (46.4)	51 (40.8)	
United Kingdom	50 (3.4)	0 (0)	2 (1.2)	10 (3)	33 (4.1)	5 (4)	
India	78 (5.3)	6 (15)	17 (9.8)	19 (5.7)	32 (4)	4 (3.2)	
Mexico	202 (13.7)	15 (37.5)	41 (23.7)	50 (15)	82 (10.2)	14 (11.2)	
Argentina	45 (3)	0 (0)	1 (0.6)	12 (3.6)	32 (4)	0 (0)	
Belgium	20 (1.4)	0 (0)	1 (0.6)	1 (0.3)	13 (1.6)	5 (4)	
Italy	131 (8.9)	2 (5)	12 (6.9)	29 (8.7)	67 (8.3)	21 (16.8)	
Uruguay	33 (2.2)	0 (0)	4 (2.3)	6 (1.8)	21 (2.6)	2 (1.6)	
Canada	11 (0.7)	0 (0)	6 (3.5)	2 (0.6)	3 (0.4)	0 (0)	
Spain	27 (1.8)	0 (0)	3 (1.7)	7 (2.1)	15 (1.9)	2 (1.6)	
Switzerland	77 (5.2)	3 (7.5)	8 (4.6)	14 (4.2)	46 (5.7)	6 (4.8)	
Greece	33 (2.2)	0 (0)	1 (0.6)	7 (2.1)	21 (2.6)	4 (3.2)	
Japan	30 (2)	1 (2.5)	4 (2.3)	5 (1.5)	17 (2.1)	3 (2.4)	
United States	7 (0.5)	0 (0)	0 (0)	2 (0.6)	5 (0.6)	0 (0)	
Other	34 (2.3)	0 (0)	6 (3.5)	6 (1.8)	17 (2.1)	5 (4)	
Medical history, n (%)							
Pulmonary disease	49 (3.3)	0 (0)	4 (2.3)	9 (2.7)	23 (2.9)	13 (10.4)	< 0.001
Heart failure	43 (2.9)	2 (5)	4 (2.3)	9 (2.7)	24 (3)	4 (3.2)	0.919
Hypertension	436 (29.6)	11 (27.5)	58 (33.5)	99 (29.7)	232 (28.9)	36 (28.8)	0.805
Active smoking	324 (22.1)	3 (7.5)	33 (19.2)	62 (18.7)	194 (24.2)	32 (25.8)	0.025
Diabetes	179 (12.1)	3 (7.5)	25 (14.5)	40 (12)	94 (11.7)	17 (13.6)	0.721
Malignancy	65 (4.4)	6 (15)	7 (4)	14 (4.2)	35 (4.4)	3 (2.4)	0.018
Neurological status at ICU admission							
Lowest GCS motor, median (IQR)	4 (2; 5)	4 (3; 5)	4 (2; 5)	4 (2; 5)	4 (2; 5)	4 (2; 5)	0.827
Lowest GCS, median (IQR)	7 (5; 9)	7 (6; 8)	7 (4; 8)	7 (5; 9)	7 (5; 9)	7 (5; 9)	0.984
Episode of anisocoria, n (%)	406 (27.6)	9 (23.1)	43 (24.9)	95 (28.6)	219 (27.3)	40 (32)	0.649
Type of brain injury, n (%)							
TBI	715 (48.4)	19 (47.5)	69 (39.9)	159 (47.6)	394 (49)	74 (59.2)	0.026
SAH	264 (17.9)	5 (12.5)	29 (16.8)	70 (21)	148 (18.4)	12 (9.6)	0.059
ICH	509 (34.5)	17 (42.5)	69 (39.9)	115 (34.4)	268 (33.3)	40 (32)	0.382
IS	136 (9.2)	3 (7.5)	17 (9.8)	26 (7.8)	73 (9.1)	17 (13.6)	0.416
CNS infection	74 (5)	5 (12.5)	6 (3.5)	20 (6)	38 (4.7)	5 (4)	0.156
Brain tumor	68 (4.6)	1 (2.5)	16 (9.2)	14 (4.2)	33 (4.1)	4 (3.2)	0.040
Other	29 (2)	0 (0)	2 (1.2)	5 (1.5)	20 (2.5)	2 (1.6)	0.555

Table 1 (continued)

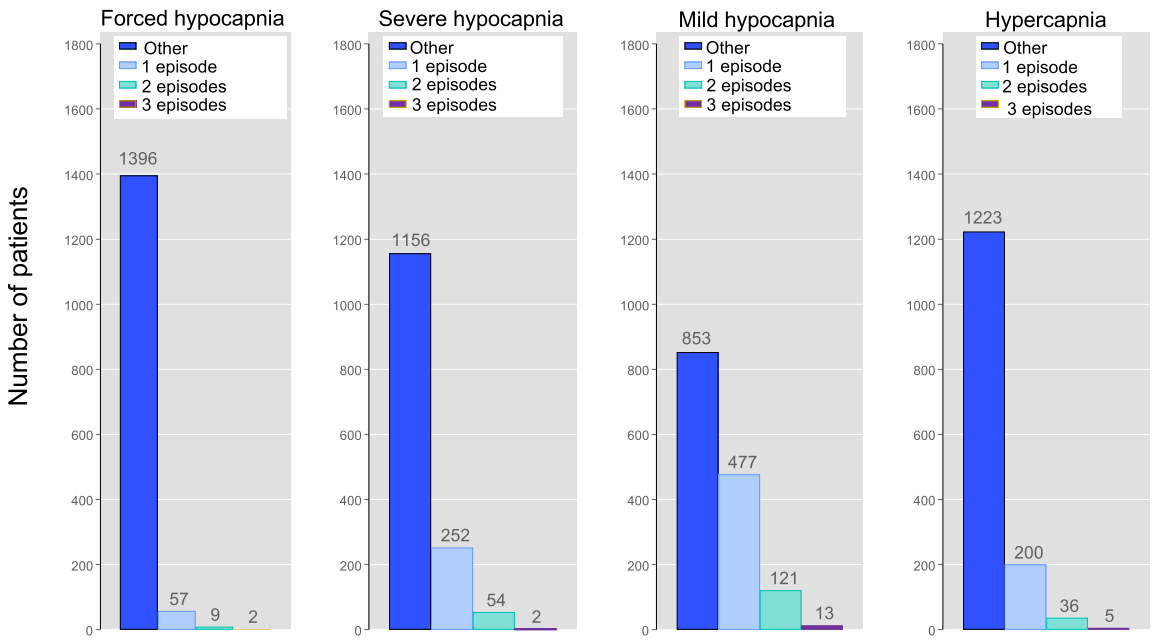
	Total $n = 1476$ (100)	Forced hypocapnia ($PaCO_2 < 26$ mmHg) $n = 40$ (2.7%)	Severe hypocapnia ($PaCO_2$ 26 to < 32 mmHg) $n = 173$ (11.7%)	Mild hypocapnia ($PaCO_2$ 32 to 35 mmHg) $n = 334$ (22.6%)	Normocapnia ($PaCO_2 > 35$ to 45 mmHg) $n = 804$ (54.5%)	Hypercapnia ($PaCO_2 > 45$ mmHg) $n = 125$ (8.5%)	*P* value
Neurosurgical management in ICU, n (%)							
ICP monitoring	626 (42.5)	5 (12.5)	61 (35.3)	143 (43.1)	370 (46.0)	47 (37.6)	< 0.001
EVD	428 (29)	9 (22.5)	56 (32.4)	101 (30.3)	237 (29.5)	25 (20)	0.132
Therapeutic hypothermia	59 (4)	0 (0)	6 (3.5)	14 (4.2)	34 (4.2)	5 (4)	0.747
Barbiturate coma	83 (5.6)	0 (0)	8 (4.6)	24 (7.2)	42 (5.2)	9 (7.2)	0.277
Need for neurosurgery	593 (40.2)	15 (37.5)	71 (41)	153 (45.9)	314 (39.1)	40 (32)	0.071
Decompressive craniectomy	284 (19.3)	10 (25)	31 (17.9)	75 (22.5)	146 (18.2)	22 (17.6)	0.383
ICU events and outcomes							
VAP, n (%)	584 (40)	12 (30)	60 (35.1)	143 (43.1)	319 (40.2)	50 (40.3)	0.319
Tracheo bronchitis, n (%)	136 (9.4)	3 (7.7)	12 (7.1)	29 (8.9)	86 (11)	6 (4.9)	0.177
ARDS, n (%)	135 (9.3)	1 (2.5)	10 (5.8)	29 (8.8)	18 (9.8)	17 (13.7)	0.096
Mild	24 (17.8)	1 (100)	4 (36.4)	7 (24.1)	8 (10.4)	4 (23.5)	
Moderate	54 (40.0)	0 (0)	5 (45.5)	11 (37.9)	33 (42.9)	5 (29.4)	
Severe	57 (42.2)	0 (0)	2 (18.2)	11 (37.9)	36 (46.8)	8 (47.1)	
Withdrawal life-sustaining treatments, n (%)	85 (5.9)	0 (0)	12 (7.1)	14 (4.3)	49 (6.2)	10 (8.1)	0.227
ICU mortality, n (%)	94 (6.5)	2 (5.1)	12 (7.1)	24 (7.3)	48 (6.1)	8 (6.5)	0.942
Hospital mortality, n (%)	178 (12.1)	6 (15)	28 (16.2)	41 (12.3)	85 (10.6)	18 (14.4)	0.245
LOS in ICU, median (IQR)	14 (8; 24)	12 (6.8; 16.2)	12 (7; 23)	15 (9; 25)	14 (8; 25)	14 (7; 28)	0.099
Tracheostomy required, n (%)	409 (28.0)	15 (37.5)	60 (34.9)	88 (26.5)	212 (26.6)	34 (27.6)	0.138

LOS, lengths of stay, *ICU*, intensive care unit, *IQR*, interquartile range, *SD*, standard deviation, *ICP*, intracranial pressure, *EVD*, extra ventricular drainage, *TBI*, traumatic brain injury, *SAH*, subarachnoid hemorrhage, *IS*, ischemic stroke, *ICH*, intracerebral hemorrhage, *CNS*, central nervous system, *GCS*, Glasgow Coma scale, *BMI*, body mass index, *PaCO2*, arterial partial pressure of carbon dioxide; *VAP*, ventilator-associated pneumonia; *ARDS*, acute respiratory distress syndrome

ICU admission—$PaCO_2$ values were generally maintained within normal to mild hypocapnia ranges, and that both profound hypo- and hypercapnia were associated with mortality. However, the prevalence and the effect of $PaCO_2$ on in-hospital mortality importantly change according to the type of ABI, with mild hypocapnia being better tolerated in the TBI and ICH population, when compared to the SAH and IS.

Current European Guidelines on mechanical ventilation in ABI patients are inconclusive regarding the optimal target of $PaCO_2$ [7]; the Seattle algorithm suggests maintaining normocapnia as the first instance, and then target to a value of 35–38 mmHg as tier 1 and eventually 32–35 mmHg (mild hypocapnia) as tier 2, avoiding profound hypocapnia except for life-threatening conditions and risk of brain herniation. Although low $PaCO_2$ values can lead to a reduction in ICP, and possibly improve cerebral autoregulation, the consequent vasoconstriction related to hypocapnia can potentially lead to a transitory reduction of CBF and oxygenation [16–18].

Some authors demonstrated an increase of cerebral hypoperfused areas using positron emission tomography (PET) following hyperventilation [19], as well as important changes in cerebral metabolism or microdialysis data, suggesting a higher risk of cerebral ischemia [20, 21]. However, other studies [22, 23] suggested that mild and short-term hypocapnia can be safe on cerebral function, causing minimal and not clinically important changes in brain oxygenation and metabolism [23, 24].



$PaCO_2$ category	IR	95% CI	P-value
Forced Hypocapnia	0.056	0.034 - 0.093	< 0.001
Severe Hypocapnia	0.252	0.204 - 0.313	< 0.001
Mild Hypocapnia	0.520	0.470 - 0.574	< 0.001
Normocapnia	1.367	1.266 - 1.476	< 0.001
Hypercapnia	0.199	0.155 - 0.256	< 0.001

Fig. 1 Number of patients experiencing abnormally low and high partial pressure of carbon dioxide-$PaCO_2$-episodes during the ICU stay. The bars indicate the number of patients with 0, 1, 2, and 3 episodes of abnormal $PaCO_2$. Incidence rates (as number of episodes per 1 person-day) of hypocapnia and hypercapnia during ICU stay are provided. IR, incidence rate; CI, Confidence Interval

The only randomized-controlled trial on this topic [25] was performed on a small group of patients more than 30 years ago, explored the effect of prophylactic hypocapnia, and the results were inconclusive because of important methodological limitations. A recent CENTER-TBI study [4] suggested that large variability across countries still exists regarding $PaCO_2$ targets, but clinicians tend to use mean values of $PaCO_2$ of 38.9 (SD ± 5.2) mmHg, with mean minimum $PaCO_2$ of 35.2 (SD ± 5.3) mmHg, and even lower values are generally used in patients receiving ICP and having intracranial hypertension.

Our study confirms these results regarding the use of relatively low values of $PaCO_2$ adopted in the clinical practice, as in the whole population the median value was 37 mmHg on day 1, and only slightly increased over the following days. Mild hypocapnia was commonly observed and was more frequently used when an ICP probe was inserted and in TBI patients vs. other pathologies. This suggests that clinicians tend to target $PaCO_2$ to a normo-/mild hypocapnia in ABI and especially in TBI patients where a higher number of evidence/recommendations are available, and especially in the early phase of ICU admission when patients have more important issues in controlling ICP.

Interestingly, in the above-mentioned CENTER-TBI study, centers where profound hyperventilation was used did not present worsened outcomes [4]. On the other hand, a recent study from the BRAIN-PROTECT group [26], including a cohort of 1776 TBI patients with end-tidal (ET) CO_2 levels measured during prehospital care,

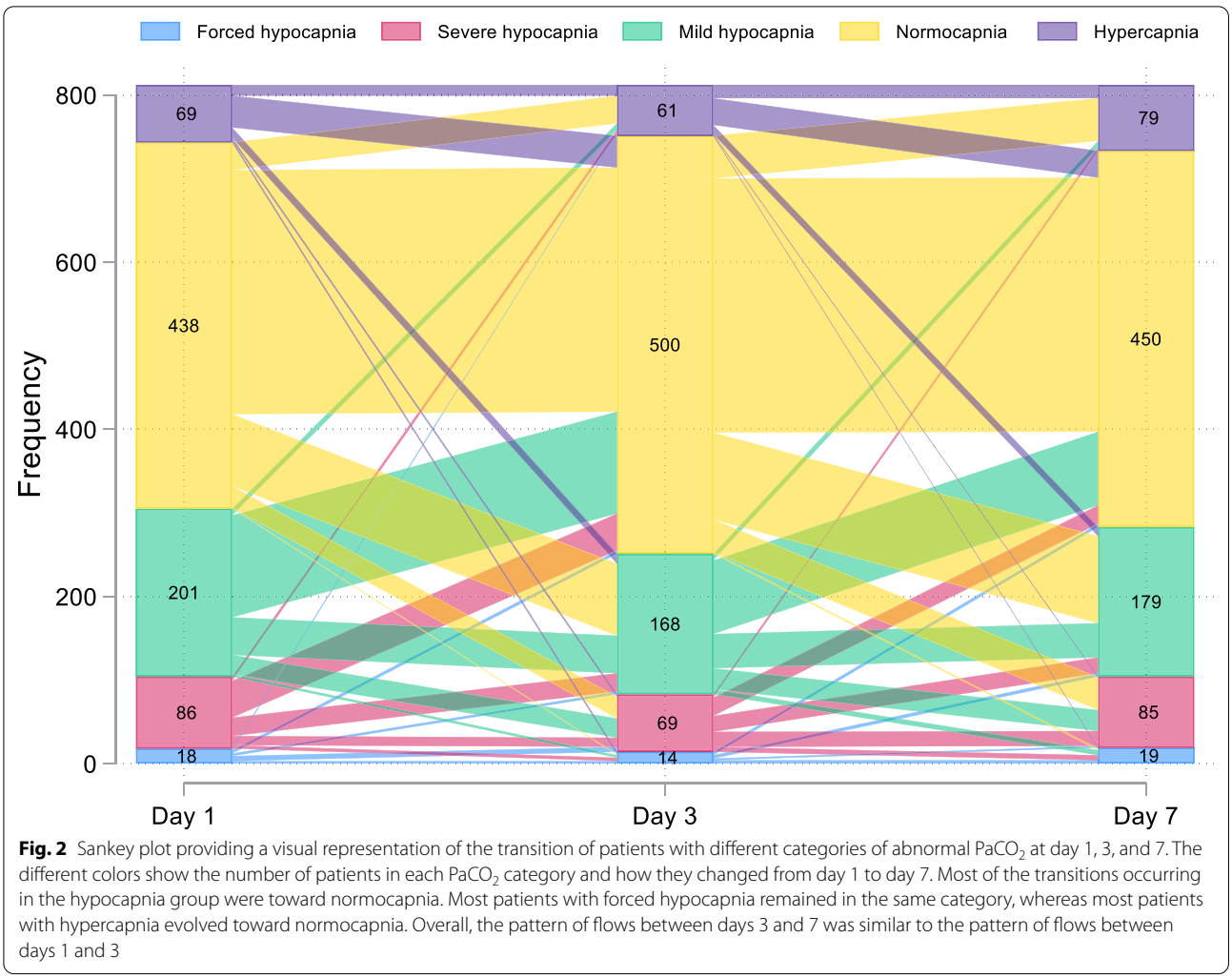


Fig. 2 Sankey plot providing a visual representation of the transition of patients with different categories of abnormal $PaCO_2$ at day 1, 3, and 7. The different colors show the number of patients in each $PaCO_2$ category and how they changed from day 1 to day 7. Most of the transitions occurring in the hypocapnia group were toward normocapnia. Most patients with forced hypocapnia remained in the same category, whereas most patients with hypercapnia evolved toward normocapnia. Overall, the pattern of flows between days 3 and 7 was similar to the pattern of flows between days 1 and 3

found a L-shaped association between $ETCO_2$ levels and 30-day mortality, with important increase in mortality for values below 35 mmHg. However, this study presents important limitations, as it refers only to a limited timeframe setting (prehospital) and does not totally take in account confounding physiological factors which can have influenced decreases in $ETCO_2$. Our results are importantly different; we found a clear U-shaped curve in the whole population, with a steeper part of the curve for hypercapnia, and a tendency to a better outcome for normocapnia or mild hypocapnia. Interestingly, this curve had different shapes when comparing different types of ABIs. In addition, when stratifying for the severity of ABI ($GCS \leq 9$ vs > 9), the U-shaped relationship between $PaCO_2$ and in-hospital mortality was consistent. This suggests that both hypocapnia and hypercapnia are associated with increased in-hospital mortality, regardless of GCS status. However, the risk related to forced hypocapnia is more pronounced in patients with $GCS \leq 9$, implying that patients with more severe brain injuries are more vulnerable to aggressive reductions in $PaCO_2$.

In TBI patients, and similarly in ICH, $PaCO_2$ between 32 mmHg and 42 mmHg had lower rates of hospital mortality as compared with other acute neurological conditions, suggesting that maintaining these values is associated with better outcomes in this group. In contrast, hypocapnia had a stronger effect on mortality risk in the context of subarachnoid hemorrhage and ischemic stroke, whereas hypercapnia appears less harmful. We can speculate that in TBI and ICH patients, where the main issue pivots on the mass effect

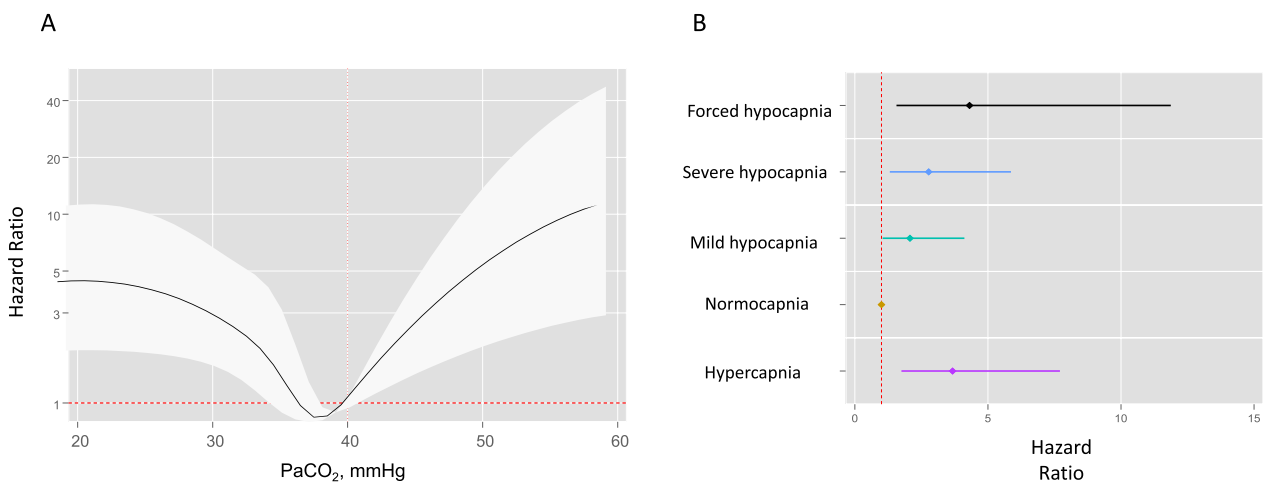


Fig. 3 **A** Association between $PaCO_2$ (modeled as a continuous variable) and in-hospital mortality using a longitudinal survival regression. $PaCO_{2c}$ was modeled with 5-df restricted cubic splines (RCS). For esthetic purposes, $PaCO_2$ distribution was trimmed between 20 mmHg and 60 mmHg. The graph shows the adjusted hazard ratio (aHR) for in-hospital mortality on the y-axis across the full range of $PaCO_2$ values on the x-axis. The solid line represents the hazard ratio and the shaded area is the 95% confidence interval. **B** The association between categorical $PaCO_2$ values and in-hospital mortality risk using a longitudinal survival regression. The graph shows the hazard ratios with 95% confidence intervals using normocapnia a reference category

related to cerebral edema and bleeding, lower values of $PaCO_2$ can help in managing intracranial hypertension and can mitigate secondary brain damage; on the contrary, in patients with SAH or IS patients who are at risk of vasospasm or cerebral hypoperfusion, hypocapnia can further cause cerebral vasoconstriction and lead to secondary brain damage.

Strengths of our study include the preplanned design, and the use of a large database prospectively collected involving different centers worldwide, which can provide important insights into the state of the art on this topic across different centers. We believe that our results may be of great importance as these provide novelty and deep insights into the optimal values that could potentially be recommended for achieving ventilatory targets [27] in the ABI population with the ultimate goal of improving clinical outcomes. In particular, our results confirm the large use of mild hypocapnia across different centers, and the safety in the use of cutoffs of $PaCO_2$ 32–35 mmHg in TBI patients as suggested by Seattle Guidelines [5].

Limitations

This study has several limitations that need to be mentioned. Although our results were obtained from a pre planned secondary analysis, data from the ENIO study are observational and therefore do not allow causality to be inferred from our findings.

In our study, we have used a snapshot approach, with data on $PaCO_2$ available only on days 1, 3, and 7. We acknowledge that this methodology only provides a cross-sectional view of the patients' $PaCO_2$ status at those specific time points and may not reflect the actual time-weighted exposure to different $PaCO_2$ levels. Although continuous monitoring of $PaCO_2$ would be ideal for capturing the duration of exposure, this granularity of data is often not available in multicenter observational studies due to practical constraints; it is also a clinical snapshot of real daily practice, where $PaCO_2$ is typically not monitored continuously.

In addition, the ENIO collected outcome data on in-hospital and ICU mortality, length of stay, and ICU-related complications. No data on Glasgow Outcome Scale extended (GOSE), modified Rankin scale (mRS), and quality of life were available from the main study. Finally, according to the study design, it is not possible to fully understand whether hypo- or hypercapnia was related to an intentional treatment or the patients' clinical conditions. In this context, a more specific analysis evaluating the association with the outcome of ventilatory variables, such as mode of ventilation, is ongoing and will provide more insights on this topic.

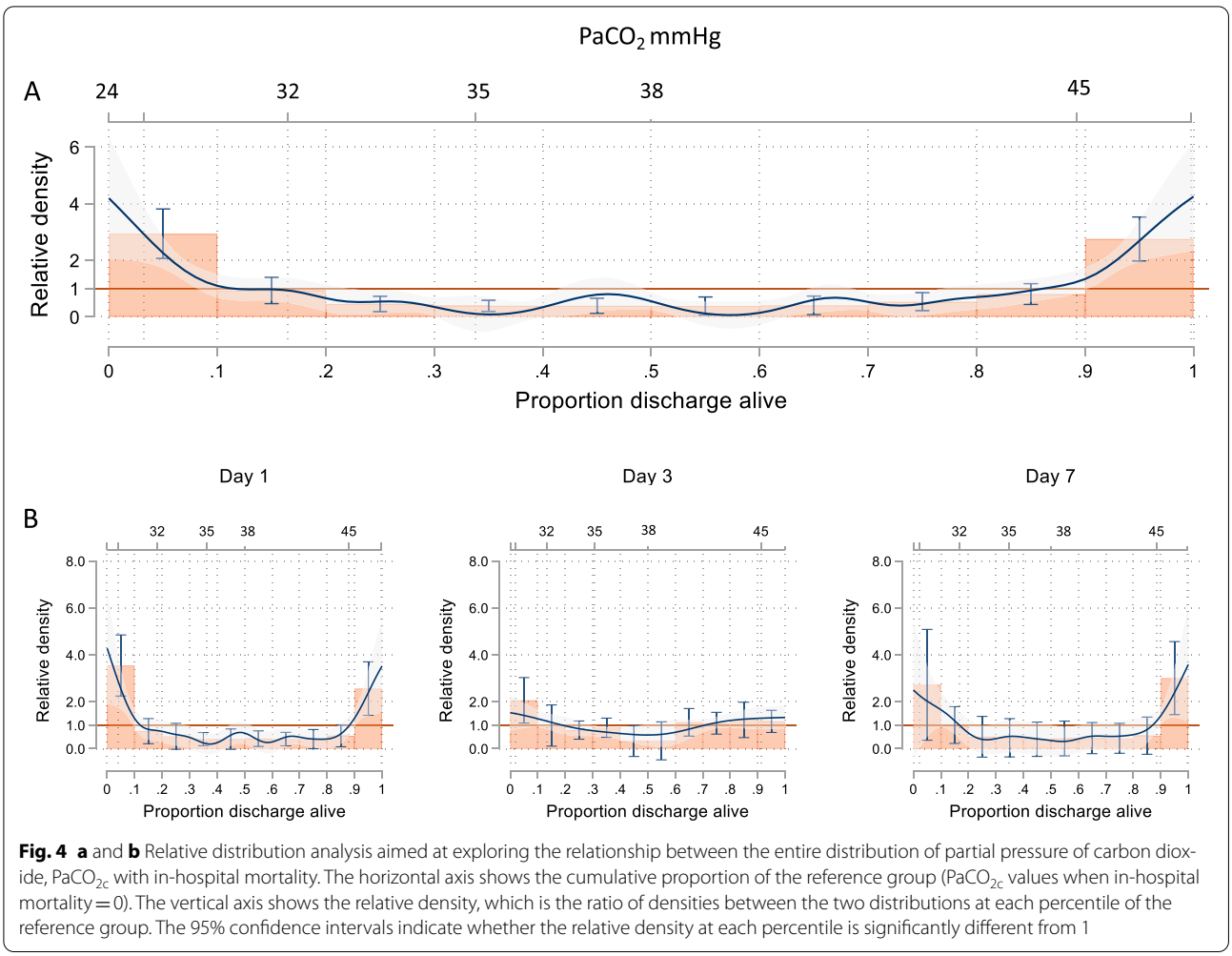


Fig. 4 **a** and **b** Relative distribution analysis aimed at exploring the relationship between the entire distribution of partial pressure of carbon dioxide, $PaCO_{2c}$ with in-hospital mortality. The horizontal axis shows the cumulative proportion of the reference group ($PaCO_{2c}$ values when in-hospital mortality = 0). The vertical axis shows the relative density, which is the ratio of densities between the two distributions at each percentile of the reference group. The 95% confidence intervals indicate whether the relative density at each percentile is significantly different from 1

Conclusions

Both hypo- and hypercapnia are associated with in-hospital mortality when considering the whole cohort. However, mild hypocapnia seemed not to be harmful, especially in the TBI subpopulation. Specific targets should be considered according to the type of ABI. Randomized-controlled trials are warranted to confirm our preliminary observational results.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-023-07305-3.

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Author contributions

CR and RB conceived and designed the manuscript. CR and RB interpreted the data and drafted the manuscript. RB, MS, FT, GC, and CR supervised the work. All authors were involved in critical revision of the manuscript and approved the final version of the manuscript.

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Availability of data and materials

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

Declarations

Conflicts of interest

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethics approval and consent to participate

Approval to conduct this sub-analysis was not necessary. Approval to enroll patients in the ENIO main study was obtained from the International Review Board (IRB) of the promoter center (Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7/11/2017), and from the local IRB for each participating center.

Consent for publication

Informed consent was generally waived in accordance with the observational nature of the ENIO study, but if necessary was collected in accordance with the local regulations of each IRB involved. Informed consent was obtained from the patient or from the patient's neck of kin if the patient was unable to give the consent at the time of enrollment.

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