Intensive Care Med (2023) 49:491–504
https://doi.org/10.1007/s00134-023-07012-z

ORIGINAL

Association between prehospital end-tidal carbon dioxide levels and mortality in patients with suspected severe traumatic brain injury

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Abstract

Purpose: Severe traumatic brain injury is a leading cause of mortality and morbidity, and these patients are frequently intubated in the prehospital setting. Cerebral perfusion and intracranial pressure are influenced by the arterial partial pressure of CO_2 and derangements might induce further brain damage. We investigated which lower and upper limits of prehospital end-tidal CO_2 levels are associated with increased mortality in patients with severe traumatic brain injury.

Methods: The BRAIN-PROTECT study is an observational multicenter study. Patients with severe traumatic brain injury, treated by Dutch Helicopter Emergency Medical Services between February 2012 and December 2017, were included. Follow-up continued for 1 year after inclusion. End-tidal CO_2 levels were measured during prehospital care and their association with 30-day mortality was analyzed with multivariable logistic regression.

Results: A total of 1776 patients were eligible for analysis. An L-shaped association between end-tidal CO_2 levels and 30-day mortality was observed ($p = 0.01$), with a sharp increase in mortality with values below 35 mmHg. End-tidal CO_2 values between 35 and 45 mmHg were associated with better survival rates compared to < 35 mmHg. No association between hypercapnia and mortality was observed. The odds ratio for the association between hypocapnia (< 35 mmHg) and mortality was 1.89 (95% CI 1.53–2.34, $p < 0.001$) and for hypercapnia (≥ 45 mmHg) 0.83 (0.62–1.11, $p = 0.212$).

Conclusion: A safe zone of 35–45 mmHg for end-tidal CO_2 guidance seems reasonable during prehospital care. Particularly, end-tidal partial pressures of less than 35 mmHg were associated with a significantly increased mortality.

Keywords: Ventilation, Traumatic brain injury, Critical care, Carbon dioxide, Endotracheal intubation

Introduction

Severe traumatic brain injury (TBI) is a leading cause of mortality and morbidity worldwide [1, 2]. Patients are at a substantial risk of developing secondary brain injury before even reaching the hospital, and prehospital treatment is considered a pivotal contributor to patient outcome [1, 3, 4]. Prehospital care commonly

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includes endotracheal intubation and ventilation to prevent airway obstruction and hypoxemia [5]. However, ventilation affects the arterial partial pressure of carbon dioxide ($PaCO_2$), which in turn modulates cerebral blood flow. Hypercapnia results in cerebral vasodilation and increased cerebral blood flow and may increase intracranial pressure, whereas hypocapnia causes cerebral vasoconstriction and a reduction of cerebral blood flow which may lead to cerebral ischemia [6]. Both cerebral vasodilatation and vasoconstriction might therefore aggravate the brain injury in TBI.

A recent systematic review as well as the international guideline on the prehospital management of patients with TBI recommend "normoventilation" [5, 7], but the evidence supporting this recommendation is weak. While various research groups have addressed the effects of hypo- and hypercapnia on the outcome of patients with TBI, results are conflicting and a clear understanding of the association between the CO_2 levels and outcomes is lacking [8]. Previous studies categorized CO_2 levels using inconsistent and arbitrary cut-offs or failed to adjust for key confounders [7, 9]. Moreover, blood gas analyses and measurements of $PaCO_2$ to guide "normoventilation" are generally not available during prehospital care, which is why end-tidal CO_2 ($ETCO_2$) concentrations are commonly used to guide ventilation. To account for the physiological gradient between end-tidal and arterial concentrations and bearing in mind that the gap can be markedly increased in trauma patients, prehospital providers often target $ETCO_2$ values below the "normal" range of 35–45 mmHg to maintain normocapnia [10]. Emergency medical services' (EMS) protocols also commonly specify target $ETCO_2$ values of ≤ 35 mmHg, typically in the range of 30–35 mmHg [11]. While in some protocols, the use of hyperventilation is relegated to cases of suspected cerebral herniation, other protocols do not specify such restrictions [11]. This common practice and existing protocols, however, may put the patient at risk of hypocarbia, and it is not yet clear which range of prehospital $ETCO_2$ values is associated with best outcomes.

To investigate the association between $ETCO_2$ levels and mortality, we performed analyses on the BRAIN-PROTECT data [12], a large observational cohort study in the Netherlands.

Methods

BRAIN-PROTECT is a multicenter prospective observational study focusing on the prehospital treatment of patients with severe TBI in the Netherlands. Data from patients with suspected severe TBI (trauma mechanism or clinical findings suggestive of severe TBI and a prehospital Glasgow Coma Scale [GCS] score of 8 or lower) treated by any one of the four Dutch physician-staffed Helicopter Emergency Medical Services (HEMS) were included. HEMS services started patient inclusion between February 2012 and April 2014, and included patients until December 2017. Inclusion was based on suspected severe TBI rather than confirmed TBI, because prehospital treatment, including airway management and ventilation, is based on the suspected rather than the definite diagnosis [13]. After prehospital care, patients were transferred to one of the nine participating trauma centers. In-hospital and outcome data were collected up to 1 year after inclusion. Patients were excluded from the analysis if they were transported to a non-participating hospital (no follow-up data), if they underwent prehospital traumatic cardiopulmonary resuscitation (very high mortality regardless of treatment, with low $ETCO_2$ values), or if they did not receive prehospital advanced airway management. All other patients were considered for further analysis. Data were collected on the basis of the Utstein template for uniform reporting of major trauma data [14]. These data included patient and trauma characteristics, injuries, vital parameters, as well as prehospital treatments and interventions as described previously [12].

After advanced airway management, patients were usually mechanically ventilated with a respirator or manually ventilated with a self-inflating bag, depending on the availability of a mechanical ventilator in the ambulance, distance to hospital, and preference of the treating physician. $ETCO_2$ was routinely measured after airway management, and measurements were recorded from available capnography modules included in patient monitors provided by the regional ambulance medical services, such as Lifepak 15 (Physio-Control), Tempus Pro (Philips), Zoll X (Zoll), or Corpuls 3 (Corpuls) monitors. All-cause mortality was assessed at 30 days (primary outcome), and the functional neurologic outcome (Glasgow outcome scale) at discharge was recorded [15, 16]. Long-term mortality data up to 1 year after inclusion were collected from hospital records and the Dutch Personal Records Database.

A detailed protocol has been previously published [12]. The Medical Research Ethics Committees of the Amsterdam University Medical Center, location VUmc, and Erasmus MC Rotterdam concluded that this research

Take-home message

In this prospective observational multicenter study, post-intubation ventilation of patients with severe traumatic brain injury revealed a significant L-shaped association between end-tidal CO_2 levels and 30-day mortality.
Particularly, end-tidal partial pressures of CO_2 of less than 35 mmHg are associated with a significantly increased mortality.

project did not fall under the Dutch Medical Research in Human Subjects Act. Prehospital vital parameters, including $ETCO_2$, were recorded at three time points: after HEMS arrival, after initial stabilization and airway management, and before arriving at the emergency department. For this study, only $ETCO_2$ values measured at the second and third time point were considered, because most patients had not undergone advanced airway management before HEMS arrival, and $ETCO_2$ measurements were most often not available at the first time point.

Sample size considerations of the BRAIN-PROTECT project are comprehensively discussed in the study protocol and were based on the ability to detect an absolute 5% reduction in mortality for a binary exposure with 80% power [12]. In the present study, the exposure variable is continuous. At the given sample size and assuming a normal distribution of the exposure variable, logistic regression achieves > 80% power at a 0.05 alpha level to detect an odds ratio of 1.2.

Statistical analysis

Data were analyzed using Stata 17.0 (StataCorp, College Station, TX). The association between prehospital $ETCO_2$ levels and 30-day mortality was investigated using logistic regression. To allow for a non-linear association between $ETCO_2$ and the logit of mortality, $ETCO_2$ was modeled as a restricted cubic spline with four knots. The number of knots was based on Akaike's Information Criterion. After an initial explorative analysis (adjusting only for different $ETCO_2$ measurement timepoints), a multivariable model was built to account for potential confounders. Covariates were simultaneously forced into the model based on theoretical considerations and included demographic factors (age, sex, and American Society of Anesthesiologists [ASA] Physical Status Classification System score), vital parameters measured during prehospital care (systolic blood pressure, heart rate and oxygen saturation measured at the same time as $ETCO_2$, time point of $ETCO_2$ measurement), injury severity (Injury Severity Score and first GCS), and operational factors (HEMS provider involved in the treatment, distance between incident scene and trauma hospital). In addition to these analyses, in which $ETCO_2$ was considered a continuous variable, we performed analyses in which $ETCO_2$ was categorized into hypocapnia (< 35 mmHg), normocapnia (35–44 mmHg), and hypercapnia (≥ 45 mmHg). As planned subgroup analyses, these analyses were repeated for patients with confirmed TBI (head AIS ≥ 3) and isolated TBI (head AIS ≥ 3, all other AIS ≤ 2). Post hoc analyses were performed for patients with symptoms of intracerebral herniation, i.e., (A) patients with abnormal pupils (unequal or not reacting to light) and (B) patients with signs of elevated intracranial pressure on the initial CT scan (midline shift > 5 mm or compressed/absent basal cisterns). Moreover, we performed analyses in which only each patient's (A) first (B) second (C) lowest and (D) highest $ETCO_2$ value were considered. In addition to the logistic regression analyses that all model 30-day mortality, the relationship between $ETCO_2$ and the actual survival time (up to 1 year after the trauma) was modeled with Cox proportional hazards regression with cluster-robust standard errors and graphed with Kaplan–Meier curves [17].

Analyses were primarily performed as complete-case analyses, i.e., in patients with non-missing $ETCO_2$ data and non-missing mortality data (and in multivariable models, additionally with non-missing data for all independent variables in the model). To gauge whether missing data affect our conclusions, 20 data sets were imputed using chained equations with an imputation model including the outcome variables, all independent variables included in the analysis models, as well as auxiliary variables. In all regression models, standard errors were adjusted for clustering of $ETCO_2$ values measured at two time points within the same patients using generalized estimating equations (GEE) with independent correlation structure and robust Huber–White standard error estimates. Two-sided P values < 0.05 were considered statistically significant.

Results

Of the 2589 patients with suspected severe traumatic brain injury included in the BRAIN-PROTECT database, 1776 were eligible for analysis (Fig. 1). The remainder were excluded due to transport to a non-participating trauma center ($n = 472$), due to prehospital cardiopulmonary resuscitation ($n = 290$) or due to absence of prehospital advanced airway management ($n = 51$).

Of the patients eligible for further analysis, the majority were male (70%), had a median age of 45 [23, 65] years and an initial GCS of 4 [3, 7] (Table 1). Thirty days after injury, 66.8% of patients were still alive, of which 40.6% recovered with moderate or good recovery at discharge (GOS 4 & 5).

In total, the results of 2649 CO_2 measurements were available for further analyses ($n = 1295$ after initial stabilization and advanced airway management, $n = 1354$ before arriving at the emergency department of the participating hospitals). The measurements at these two time points showed a moderate correlation, and correlation between the last $ETCO_2$ measurement and first in-hospital PaO2 was weak (Supplemental Figs 1 and 2) [18]. The distribution of $ETCO_2$ measurements is shown in Supplemental Fig. 3.

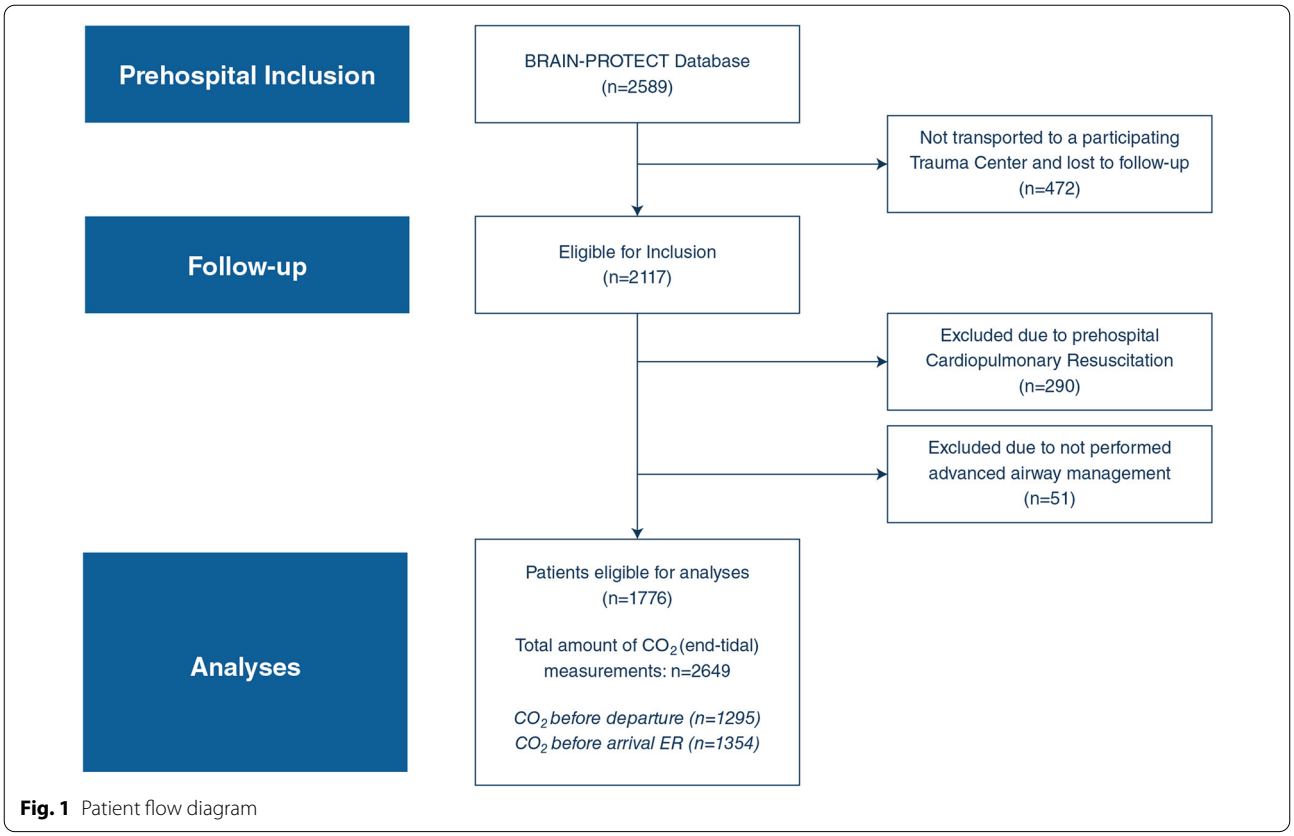

Fig. 1 Patient flow diagram

Most patients were endotracheally intubated, with only few patients receiving a supraglottic airway device or coniotomy (Table 1). Of those patients with available information about how they were ventilated after airway management ($n=941$), 61.4% were mechanically ventilated with a respirator and 35.4% were manually ventilated with a self-inflating bag.

For a total of 1342 patients, 30-day mortality data as well as at least one $ETCO_2$ measurement were available to study the relationship between $ETCO_2$ levels and 30-day mortality. Analyses of the unadjusted association between $ETCO_2$ levels and predicted mortality revealed an L-shaped association, with a marked increase in mortality with $ETCO_2$ levels below 35 mmHg and a flat portion with $ETCO_2$ levels above 35 mmHg ($p<0.001$ for the overall association between $ETCO_2$ and mortality, Fig. 2).

After adjusting for confounders in multivariable logistic regression, the L-shaped association between hypocapnia and predicted mortality persisted ($p=0.01$ for the overall association, Fig. 3, Supplemental Table 1). As in the unadjusted analysis, $ETCO_2$ levels below 35 mmHg were associated with markedly increased mortality, whereas values above 35 mmHg were associated with lower and rather constant mortality, with no evident increase in mortality for high $ETCO_2$ levels. However, the precision of the estimated association declined above 45 mmHg, such that the uncertainty on how mortality changes with high $ETCO_2$ values increases.

After stratification into the three categories normocapnia (1302 measurements), hypocapnia (976 measurements), and hypercapnia (371 measurements), hypocapnia was associated with an approximately 90% increased odds of mortality (OR 1.89, 95% CI 1.53–2.34, $p<0.001$, Table 2) compared to normocapnia. No significant association between hypercapnia and mortality was observed (OR 0.83, 95% CI 0.62–1.11, $p=0.212$). Likewise, survival analysis demonstrated an increased hazard of mortality with hypocapnia (HR 1.65, 95% CI 1.42–1.92, $p<0.001$), whereas no relationship between hypercapnia and mortality was observed compared to normocapnia (HR 0.82, 95% CI 0.65–1.04, $p=0.095$, Table 3, Fig. 4). Considering only the lowest and highest $ETCO_2$ values per patient, nadir values < 35 mmHg (hypocapnia observed at least once) were associated with a higher mortality in logistic regression and survival analyses (both $p<0.001$), whereas no association between peak values ≥ 45 mmHg (hypercapnia observed at least once) and mortality was observed (both $p>0.05$, Tables 2, 3).

Table 1 Patient characteristics

Characteristics ($n = 1776$)	median [quartiles] / *n* (percentage)	*N* missing
Demographic data and Injury Severity		
Age (years)	45 [23, 65]	20 (1.1%)
Male sex [*N* (%)]	1247 (70.3%)	3 (0.2%)
Mechanism of injury		29 (1.6%)
Traffic—motor vehicle	311 (17.8%)	
Traffic—motorcycle	163 (9.3%)	
Traffic—bicycle	389 (22.3%)	
Traffic—pedestrian	123 (7%)	
Traffic—other	53 (3%)	
Fall from height	600 (34.3%)	
Gunshot or stab injury	34 (2%)	
Other	74 (4.2%)	
Injury Severity Score	26 [19, 35]	202 (11.4%)
Glasgow Coma Scale (GCS) at arrival of HEMS	4 [3, 7]	0 (0%)
Motor response component of the CGS	2 [1, 4]	0 (0%)
Pupils equal and reactive to light (N (%))	756 (49.8%)	258 (14.5%)
Abbreviated Injury Scale Score—Head		202 (11.4%)
No head injury	74 (4.7%)	
1	68 (4.3%)	
2	92 (5.8%)	
3	222 (14.1%)	
4	456 (29%)	
5	650 (41.3%)	
6	12 (0.8%)	
Abbreviated Injury Scale Score—Face		
< 3 or no injury	1460 (92.8%)	
≥ 3	114 (7.2%)	
Abbreviated Injury Scale Score—Neck		
< 3 or no injury	1547 (98.3%)	
≥ 3	27 (1.7%)	
Abbreviated Injury Scale Score—Spine		
< 3 or no injury	1418 (90.1%)	
≥ 3	156 (9.9%)	
Abbreviated Injury Scale Score—Thorax		
< 3 or no injury	974 (61.9%)	
≥ 3	600 (38.1%)	
Abbreviated Injury Scale Score—Abdomen		
< 3 or no injury	1461 (92.8%)	
≥ 3	113 (7.2%)	
Abbreviated Injury Scale Score—Upper extremity		
< 3 or no injury	1513 (96.1%)	
≥ 3	61 (3.9%)	
Abbreviated Injury Scale Score—Lower extremity		
< 3 or no injury	1344 (85.4%)	
≥ 3	230 (14.6%)	
Prehospital observations and Airway management		
Respiratory rate at primary survey		101 (5.7%)
Normal	1242 (74.2%)	
Tachypnea (> 29/min)	68 (4.1%)	

Table 1 (continued)

Prehospital observations and Airway management		
Bradypnea (6–9/min)	296 (17.7%)	
Gasping (1–5/min)	56 (3.3%)	
No breathing	13 (0.8%)	
Type of airway management		23 (1.3%)
Endotracheal intubation	1733 (98.9%)	
Laryngeal mask	13 (0.7%)	
Supraglottic device other than LMA	1 (0.1%)	
Coniotomy	6 (0.3%)	
Prehospital systolic blood pressure < 90 mmHg	187 (10.9%)	67 (3.8%)
Prehospital SpO_2 < 90% or documented cyanosis	332 (19.6%)	79 (4.5%)
Distance from incident scene to hospital (km)	24.6 [14.2, 40.4]	289 (16.3%)
Time from HEMS dispatch to patient arrival at the hospital (minutes)	56 [46, 69]	94 (5.3%)
In-hospital data		
First arterial pCO_2 (mmHg)	45 [40, 51]	203 (11.4%)
Systolic blood pressure < 90 mmHg at hospital arrival	144 (8.9%)	166 (9.4%)
SpO_2 < 90% at hospital arrival	67 (4.5%)	294 (16.6%)
First cerebral CT scan, Rotterdam classification		351 (19.8%)
Basal cisterns		
Normal	911 (63.9%)	
Compressed	270 (19%)	
Absent	244 (17.1%)	
Midline shift		
No shift or ≤ 5 mm	1106 (77.6%)	
> 5 mm	319 (22.4%)	
Epidural mass lesion		
Present	200 (14%)	
Absent	1225 (86%)	
Intraventricular blood or traumatic SAH		
Present	885 (62.2%)	
Absent	539 (37.9%)	
Emergency neurosurgical intervention (first 48 h)	521 (36.4%)	343 (19.3%)
Emergency extracranial surgery (first 48 h)	241 (16.8%)	345 (19.4%)
Hospital LOS (days)*	16 [6, 33]*	10 (1%)*
Follow-up and outcome		
Follow-up time (days)	365 [5; 365] (range 1–365)	109 (6.1%)[‡]
Death at 30 days	554 (33.2%)	109 (6.1%)[$]
Death at 1 year	610 (40.2%)	258 (14.5%)
GOS at discharge [N(%)]		
Death	564 (35%)	166 (9.3%)
Vegetative state	38 (2.4%)	
Severe disability	583 (36.2%)	
Moderate disability	170 (10.6%)	
Good recovery	255 (15.8%)	

Demographic, treatment, and outcome data of included patients. Numbers presented as median [quartiles] or n (percentage). For the calculation of percentages, the number of non-missing cases was used as the denominator. * Of surviving patients past hospital discharge (see GOS at discharge for the number of patients known to have survived past discharge). The total number of missing data for LOS was 134/1776 = 7.5%. [‡]These patients could not be followed up, and thus, the follow-up time was coded as 0 in the database. Here, these patients are considered to have a missing follow-up time, and the follow-up time is reported only for those patients who were actually followed up. [$]The 109 patients with missing data for 30-day mortality are the same as those with also missing follow-up and thus are also missing all mortality data including survival time

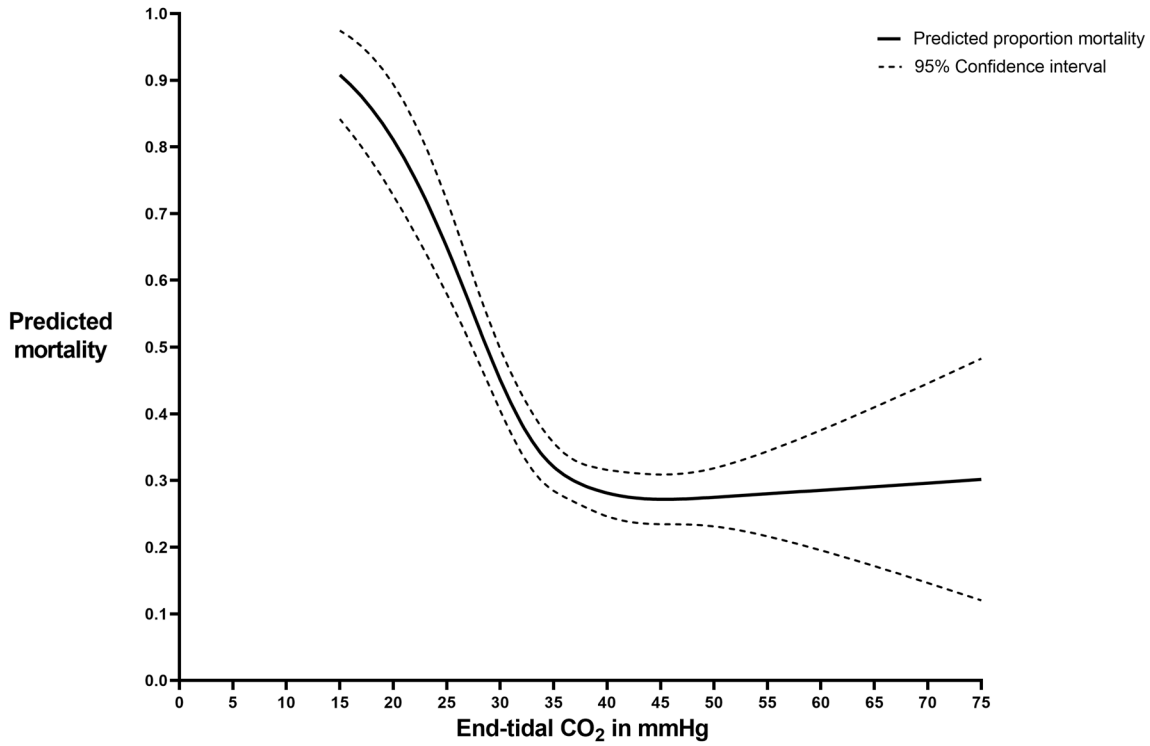

Fig. 2 Prehospital $ETCO_2$ values and predicted mortality—unadjusted analysis. Association between prehospital end-tidal CO_2 values (regression model based on 2505 $ETCO_2$ values observed after advanced airway management at two time points in 1342 patients; see text for details) and predicted 30-day mortality. This analysis does not adjust for confounders but does adjust for the time point of the end-tidal CO_2 measurement. The figure can be interpreted as the expected probability of mortality given the first recorded $ETCO_2$ value during prehospital ventilation. The curve for the second measurement time point is virtually identical (not shown)

In subgroup analyses, $ETCO_2$ values < 35 mmHg were associated with increased mortality in patients with confirmed TBI (OR 1.90 versus normocapnia, 95% CI 1.51–2.39, $p < 0.001$) and with isolated TBI (OR 2.14, 95% CI 1.55–2.97, $p < 0.001$). Likewise, $ETCO_2$ values < 35 mmHg were associated with an increased mortality in patients with signs of cerebral herniation. Consistent results were found in survival analyses and after multiple imputation (Tables 2, 3).

Discussion

The BRAIN-PROTECT study prospectively addressed the prehospital care of patients with severe TBI in the Netherlands. We observed an L-shaped association between $ETCO_2$ levels and 30-day mortality, and that a "safe zone" of 35–45 mmHg CO_2 seems to be a reasonable target range for prehospital ventilation.

Prehospital care of patients with severe TBI focuses on the prevention of secondary brain injury, and often involves advanced airway management and ventilation [19]. While guidelines recommend "normoventilation", evidence for specific ventilation targets is lacking and clinical practice regarding ventilation of patients with TBI broadly varies, both in the prehospital setting [11] as well as in hospital [20]. "Normoventilation" implies normocapnia, commonly defined as an arterial CO_2 partial pressure in the range between 35 and 45 mmHg. Notably, a previous study observed that only 36% of ventilated patients present to the emergency department with normocapnia [21], suggesting that prehospital normoventilation is often not delivered.

Previous data on the association between arterial CO_2 partial pressures and cerebral oxygenation/metabolism or clinical outcomes have been conflicting and often derive from studies performed in the intensive-care unit rather than in the prehospital setting. On the one hand, for example, Brandi et al. did not find negative effects of hypocapnia on cerebral metabolism [22], whereas Coles

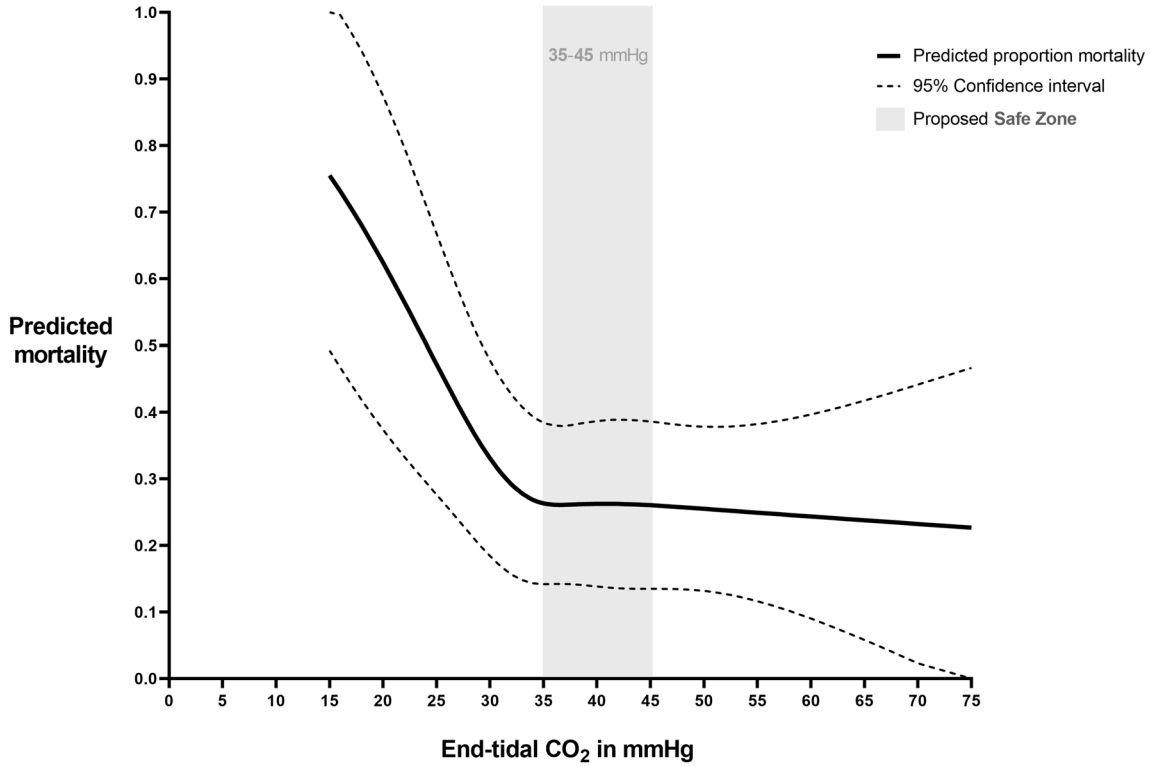

Fig. 3 Prehospital $ETCO_2$ values and predicted mortality—multivariable analysis. Prehospital end-tidal CO_2 values measured after advanced airway management versus predicted 30-day mortality, after multivariable correction. The multivariable model is based on 1504 $ETCO_2$ measurements in 836 patients and included the time point of the end-tidal CO_2 measurement, age (*spline variable*), sex, ASA score, systolic blood pressure (*spline variable)*, heart rate (*spline variable)*, oxygen saturation (*spline variable*), Injury Severity Score (*spline variable*), first Glasgow Coma Scale score, HEMS service involved in the treatment, and distance between incident scene and trauma hospital (*spline variable)*. As the plotted curve depends on the levels or values of all covariates in the model, this figure is just an example in which covariates were fixed at their mode (categorical variables) or mean (continuous variables) to obtain an estimate for the "average" patient, namely male gender, age 45 years, ISS 27, systolic blood pressure 131 mmHg, heart rate 95 beats per minute, ASA I, GCS 3, distance to hospital 28.6 km, and treated by the HEMS service that contributed most patients to the dataset. Moreover, as the time point of $ETCO_2$ measurement was also included in the model, the figure shows the expected adjusted probability of mortality given the first recorded $ETCO_2$ value after airway management. The curve for the second measurement time point is virtually identical (not shown)

et al. report adverse effects of hyperventilation [23]. With respect to clinical outcomes, Citerio et al. did not observe worse outcomes in patients treated in centers that use profound hyperventilation more often [20]. In contrast, in the only randomized trial to date performed more than 30 years ago, hyperventilation adversely affected the neurologic outcome at 3 and 6 months in a subgroup of patients with relatively good motor scores (4—5) of the GCS score [24].

While it is thus not even clear what $PaCO_2$ values are optimal for TBI patients, prehospital ventilation is further complicated by the fact that $PaCO_2$ measurements are generally not available to guide (normo-) ventilation, such that $ETCO_2$ levels are commonly used as a surrogate. Several studies have addressed the correlation between end-tidal and arterial CO_2 levels in severe TBI [10, 25–27]. Overall, they reported mixed correlations, from good to poor. The physiological gap between $PaCO_2$ and $ETCO_2$ can be markedly increased in trauma patients [10], for example due to thoracic injury or circulatory shock. Therefore, guiding ventilation by $ETCO_2$ is challenging, and prehospital healthcare personnel often target low-normal or subnormal $ETCO_2$ values to account for this potentially increased PaCO2-$ETCO_2$ gap, to achieve normoventilation. A recent study that observed a substantial gap

Table 2 Logistic regression analyses for the association between hypo- and hypercapnia on 30-day mortality

	Hypocapnia (< 35 mmHg)		Hypercapnia (≥ 45 mmHg)		Number of $ETCO_2$ measurements/patients/mortality events
Complete case analysis	**OR**	**95% CI**	**OR**	**95% CI**	
Overall	1.89	1.53–2.34	0.83	0.62–1.11	2505/1342/459
Confirmed TBI	1.90	1.51–2.39	0.91	0.66–1.24	2051/1094/424
Isolated TBI	2.14	1.55–2.97	0.92	0.60–1.41	1069/567/231
Patients with symptoms of cerebral herniation					
Absence of PEARL$^{\pm}$	1.72	1.27–2.32	0.81	0.54–1.20	1113/598/296
Signs of elevated ICP on CT$^{\$}$	1.87	1.31–2.67	0.96	0.60–1.54	871/461/297
Only considering a single CO_2 value per patient					
First $ETCO_2$	2.05	1.56–2.69	0.83	0.60–1.14	1224/1224/420
Second $ETCO_2$	1.78	1.40–2.27	0.90	0.53–1.52	1281/1281/435
Nadir $ETCO_2$	1.86	1.47–2.36	1.00	0.58–1.71	1342/1342/459
Peak $ETCO_2$	1.86	1.43–2.42	0.87	0.64–1.18	1342/1342/459
After multiple imputation	**OR**	**95% CI**	**OR**	**95% CI**	**(NA)**
Overall	1.89	1.57–2.29	0.78	0.59–1.03	
Confirmed TBI	1.83	1.50–2.24	0.84	0.63–1.13	
Isolated TBI	2.00	1.49–2.60	0.85	0.56–1.30	
Patients with symptoms of cerebral herniation					
Absence of PEARL$^{\pm}$	1.70	1.33–2.17	0.79	0.55–1.13	
Signs of elevated ICP on CT$^{\$}$	1.83	1.34–2.48	0.89	0.59–1.35	
Only considering a single CO_2 value per patient					
First $ETCO_2$	2.02	1.57–2.60	0.77	0.57–1.04	
Second $ETCO_2$	1.80	1.44–2.26	0.86	0.51–1.45	
Nadir $ETCO_2$	1.93	1.52–2.45	0.63	0.33–1-22	
Peak $ETCO_2$	2.06	1.58–2.68	0.77	0.57–1.03	
Confounder adjusted	**OR**	**95% CI**	**OR**	**95% CI**	**(NA)**
Overall	1.57	1.22–2.03	0.85	0.61–1.19	
Confirmed TBI	1.54	1.19–2.00	0.87	0.61–1.22	
Isolated TBI	1.59	1.03–2.45	0.79	0.46–1.37	
Patients with symptoms of cerebral herniation					
Absence of PEARL$^{\pm}$	1.64	1.17–2.30	0.87	0.55–1.37	
Signs of elevated ICP on CT$^{\$}$	1.46	1.00–2.12	0.79	0.49–1.26	
Only considering a single CO_2 value per patient					
First $ETCO_2$	1.53	1.09–2.17	0.84	0.57–1.25	
Second $ETCO_2$	1.62	1.19–2.23	0.85	0.44–1.65	
Nadir $ETCO_2$	1.50	1.10–2.06	0.77	0.36–1.64	
Peak $ETCO_2$	1.81	1.26–2.60	0.86	0.59–1.25	

Logistic regression analyses (complete-case analyses as well as after multiple imputation performed on all 1776 patients that had been selected from the BRAIN-PROTECT database) on hypo- and hypercapnia versus normocapnia for the overall population, as well as in subgroups of patients with confirmed and isolated TBI as well as in patients with signs of cerebral herniation. Additional sensitivity analyses consider only one measurement per patient, i.e., either the first or second measurement, as well as nadir and peak $ETCO_2$ values per patient. The outcome variable was 30-day mortality for all analyses. $^{\pm}$At arrival of HEMS; $^{\$}$midline shift > 5 mm or compressed/absent basal cisterns. All analyses including multiple $ETCO_2$ values per patient were adjusted for the measurement time point. Confounder adjusted analyses adjust for age (*spline variable*), sex, ASA score, systolic blood pressure (*spline variable)*, heart rate (*spline variable)*, oxygen saturation (*spline variable*), Injury Severity Score (*spline variable*), first Glasgow Coma Scale score, HEMS service involved in the treatment and distance between incident scene and trauma hospital (*spline variable)* after multiple imputation of missing variables

between $PaCO_2$ and $ETCO_2$ values (mean difference was 12.8 mmHg) concluded that even lower $ETCO_2$ targets than currently recommended may be safe and appropriate. Notably, however, neither this nor other studies provide clinical outcome data to support any specific $ETCO_2$ target range.

Table 3 Survival analyses for the association between hypo- and hypercapnia on mortality

	Hypocapnia (< 35 mmHg)		Hypercapnia (≥ 45 mmHg)		Number of $ETCO_2$ measurements/patients/mortality events
Complete case analysis	**HR**	**95% CI**	**HR**	**95% CI**	
Overall	1.65	1.42–1.92	0.82	0.65–1.04	2505/1342/506
Confirmed TBI	1.64	1.40–1.92	0.89	0.70–1.13	2051/1094/462
Isolated TBI	1.77	1.43–2.19	0.93	0.67–1.28	1069/567/246
Patients with symptoms of cerebral herniation					
Absence of PEARL$^{\pm}$	1.44	1.21–1.73	0.82	0.62–1.09	1113/598/317
Signs of elevated ICP on CT$^{\$}$	1.44	1.22–1.71	0.99	0.76–1.29	871/461/319
Only considering a single CO_2 value per patient					
First $ETCO_2$	1.71	1.42–2.07	0.81	0.63–1.04	1224/1224/460
Second $ETCO_2$	1.60	1.35–1.91	0.89	0.58–1.37	1281/1281/481
Nadir $ETCO_2$	1.68	1.42–2.00	0.96	0.62–1.49	1342/1342/506
Peak $ETCO_2$	1.58	1.32–1.89	0.83	0.66–1.06	1342/1342/506
After multiple imputation	**HR**	**95% CI**	**HR**	**95% CI**	**NA**
Overall	1.63	1.42–1.88	0.78	0.62–0.97	
Confirmed TBI	1.58	1.37–1.82	0.85	0.67–1.06	
Isolated TBI	1.68	1.38–2.06	0.88	0.64–1.21	
Patients with symptoms of cerebral herniation					
Absence of PEARL$^{\pm}$	1.43	1.22–1.67	0.81	0.63–1.04	
Signs of elevated ICP on CT$^{\$}$	1.40	1.21–1.63	0.95	0.75–1.19	
Only considering a single CO_2 value per patient					
First $ETCO_2$	1.68	1.41–2.01	0.77	0.60–0.98	
Second $ETCO_2$	1.59	1.34–1.89	0.84	0.55–1.30	
Nadir $ETCO_2$	1.72	1.44–2.06	0.65	0.36–1.17	
Peak $ETCO_2$	1.69	1.41–2.02	0.77	0.61–0.96	
Confounder adjusted	**HR**	**95% CI**	**HR**	**95% CI**	**NA**
Overall	1.28	1.12–1.46	0.90	0.74–1.10	
Confirmed TBI	1.27	1.11–1.45	0.92	0.75–1.13	
Isolated TBI	1.23	1.01–1.51	0.88	0.67–1.16	
Patients with symptoms of cerebral herniation					
Absence of PEARL$^{\pm}$	1.28	1.10–1.49	0.93	0.73–1.17	
Signs of elevated ICP on CT$^{\$}$	1.19	1.03–1.37	0.94	0.77–1.14	
Only considering a single CO_2 value per patient					
First $ETCO_2$	1.21	1.01–1.47	0.87	0.69–1.09	
Second $ETCO_2$	1.34	1.13–1.58	0.94	0.64–1.38	
Nadir $ETCO_2$	1.31	1.11–1.56	0.86	0.51–1.46	
Peak $ETCO_2$	1.33	1.10–1.61	0.88	0.71–1.09	

Cox regression analyses (complete-case analyses as well as after multiple imputation performed on all 1776 patients that had been selected from the BRAIN-PROTECT database) on hypo- and hypercapnia versus normocapnia for the overall population, as well as in subgroups of patients with confirmed and isolated TBI as well as in patients with signs of cerebral herniation. Additional sensitivity analyses consider only one measurement per patient, i.e., either the first or second measurement, as well as nadir and peak $ETCO_2$ values per patient. $^{\pm}$At arrival of HEMS; $^{\$}$midline shift > 5 mm or compressed/absent basal cisterns. All analyses including multiple $ETCO_2$ values per patient were adjusted for the measurement time point. Confounder adjusted analyses adjust for age (*spline variable*), sex, ASA score, systolic blood pressure (*spline variable)*, heart rate (*spline variable)*, oxygen saturation (*spline variable*), Injury Severity Score (*spline variable*), first Glasgow Coma Scale score, HEMS service involved in the treatment and distance between incident scene and trauma hospital (*spline variable)* after multiple imputation of missing variables. In all Cox regression models, mortality up to 1 year after the trauma was modeled

In the context of clinical outcome data, Howard et al. recently summarized the effects of CO_2 ($ETCO_2$ or PCO_2, depending on included studies) levels during the initial treatment of patients with TBI in a systematic review [7]. The authors identified six retrospective observational studies, of which five reported clinical outcomes [28–32].

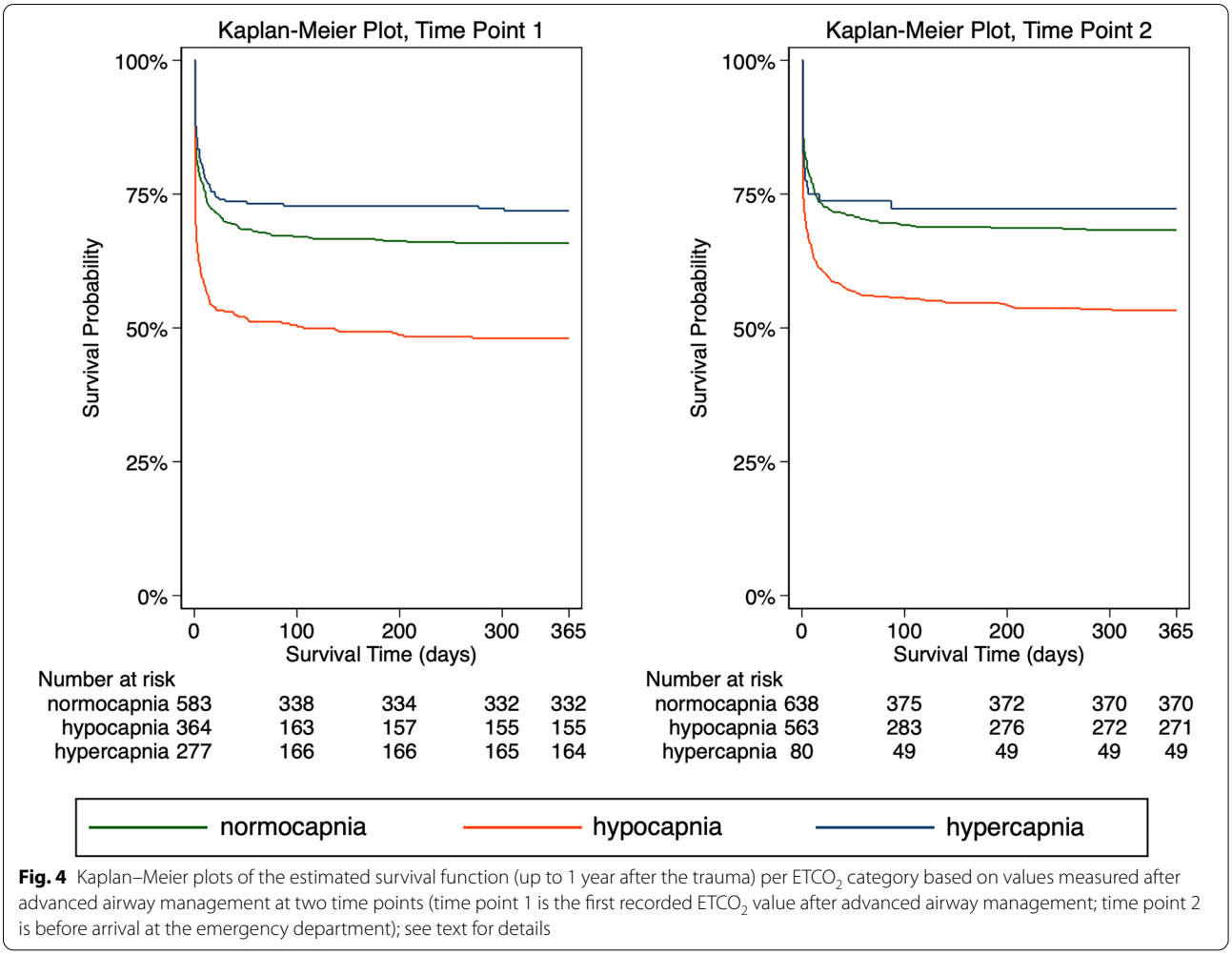

Fig. 4 Kaplan–Meier plots of the estimated survival function (up to 1 year after the trauma) per $ETCO_2$ category based on values measured after advanced airway management at two time points (time point 1 is the first recorded $ETCO_2$ value after advanced airway management; time point 2 is before arrival at the emergency department); see text for details

None of these studies considered CO_2 on its continuous scale, but rather used inconsistent and arbitrary thresholds to categorize CO_2 values. Moreover, most had a rather small sample size [28, 30, 31], poorly controlled for confounding [28, 30, 31], assessed a bundle of care rather than (hyper-)ventilation in isolation [32], or did not actually consider prehospital $ETCO_2$ values but rather used first documented in-hospital $PaCO_2$ values as a surrogate for prehospital ventilation [29–31]. While these studies consistently suggest worse outcomes with hypocapnia, potential detrimental effects of hypercapnia as well as the range of reasonable $ETCO_2$ values still remain unclear.

In contrast to previous studies, we considered $ETCO_2$ on the continuous scale and allowed for a non-linear association between $ETCO_2$ and the (logit of) mortality. The association between $ETCO_2$ levels and mortality was L-shaped, with a profound increase in mortality in $ETCO_2$ values < 35 mmHg, i.e., in hypocapnia. We did not observe an association between high $ETCO_2$ values and increased mortality, but the precision of the estimated association declined above 45 mmHg. Our data therefore do not allow the conclusion that $ETCO_2$ values > 45 mmHg are safe, and therefore, a "safe zone" of 35—45 mmHg $ETCO_2$ seems a reasonable target to guide prehospital ventilation in patients with severe TBI. Notably, this $ETCO_2$ range is higher than that currently recommended by many EMS protocols in the United States [11]. The increase in mortality with $ETCO_2$ values below 35 mmHg was observed across all subgroup analyses, including patients with isolated TBI and patients with signs of cerebral herniation. While these subgroup analyses must be interpreted with care, the data also do not support the unproven paradigm of temporary hyperventilation in patients with signs of cerebral herniation. [33]

Limitations

BRAIN-PROTECT is a prospective observational study project, and the inherent limitations of observational research such as risk of selection bias and information bias have to be considered. The steps taken to minimize

such bias have been described previously [12]. Importantly, observational data are subject to confounding, and we therefore emphasize that we observed an association but not necessarily a causal relationship between $ETCO_2$ values and 30-day mortality. Decreases in $ETCO_2$ levels are often due to hyperventilation, but may also have other causes, such as low cardiac output during circulatory shock, excessive blood loss, or tension pneumothorax. However, we thoroughly adjusted for potential confounders in the multivariable regression model. In plain language, for patients with everything else being held constant (i.e., same age, same injury severity score, same GCS score, same blood pressure, same heart rate, etc.), an $ETCO_2$ value < 35 mmHg is independently associated with a markedly increased mortality. Moreover, in our subgroup analysis of patients with isolated TBI—i.e., patients without other significant injuries that could bias the association—we also found a profound association between hypocapnia and mortality. Nonetheless, residual confounding cannot be excluded, and clinical recommendations are not directly supported by the data. However, accumulating evidence suggests detrimental effects of hyperventilation, and our data provide the best available evidence for a specific ventilation target.

Missing data are also a limitation of our study. However, analyses produced consistent results after multiple imputation, [34] suggesting that missing data did not bias our results to a relevant degree. Moreover, data were collected in the Netherlands, a country with a high population density and highly developed emergency care infrastructure with short distances to trauma centers. The results may not necessarily generalize to other healthcare systems.

Our analysis focuses on 30-day mortality, which is clearly a clinically relevant endpoint. Nonetheless, neurologic recovery, e.g. as measured by the extended Glasgow Outcome Scale [15], is also of great importance and should be addressed in future studies. We had initially planned to analyze and show such data in the current study but refrained from doing so, because these data were incomplete and could not validly be imputed given the assumed mechanism of missingness.

Conclusions

We found an L-shaped association between $ETCO_2$ levels and 30-day mortality in patients with severe TBI. The range between 35 and 45 mmHg seems a reasonable target as lower $ETCO_2$ levels were significantly associated with increased 30-day mortality. These results suggest that the use of hyperventilation in prehospital treatment of severe TBI should be discouraged.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-023-07012-z.

Abbreviations

AIS: Abbreviated Injury Score; CI: Confidence Interval; EMS: Emergency Medical Services; GCS: Glasgow Coma Scale; HAIS: Head Abbreviated Injury Score; HEMS: Helicopter Emergency Medical Service; ISS: Injury Severity Score; LTR: Dutch National Trauma Registry ("Landelijke Trauma Registratie"); TBI: Traumatic Brain Injury; CBF: Cerebral Blood Flow; ICP: Intracranial Pressure; LMA: Laryngeal Mask Airway; PEARL: Pupils Equal And Reacting to Light.

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Author contributions
SMB and PS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis and take responsibility for this article as a whole. Concept and design: SMB, FM, SAL, AB, FWB, EMMVL, DDH, NH, JvdN, ARA, LAS, JWRT and PS. Acquisition, analysis, or interpretation of data: SMB, FM, SAL, AB, FWB, EMMVL, DDH, NH, JvdN, ARA, LAS, JWRT and PS. Drafting of the manuscript: SMB, FM, SAL and PS. Critical revision of the manuscript for important intellectual content: CB, FWB, EMMVL, DDH, NH, JvdN, ARA, LAS and JWRT. Statistical analysis: SMB, SAL, JWRT and PS. Obtained funding: SMB and PS. Administrative, technical, or material support: SMB, FM, SAL, LAS and PS. Supervision: SAL, CB, FWB, EMMVL, DDH, NH, JvdN, ARA, LAS, JWRT and PS.

Funding
This work was supported by the Dutch Brain Foundation ("Hersenstichting") under Grant F2010(1)-14, and Achmea Healthcare Foundation ("Stichting Achmea Gezondheidszorg") under Grant Z644. The funding sources did not have a role in the design or execution of this study and did not have any role during analysis and interpretation of the data, or in the decision to submit results.

Data sharing statement
Completely de-identified participant data as well as the data dictionary will be shared upon reasonable request, after approval by the scientific steering committee of the BRAIN-PROTECT study group. The study protocol has been published and is publicly available. Data will be available from 12 months following article publication and proposals may be submitted to the corresponding author (s.bossers@amsterdamumc.nl) up to 36 months following article publication.

Declarations

Conflicts of interest
SMB reported receiving grants from Achmea Healthcare Foundation during the conduct of the study. ARA reported receiving grants and personal fees from Becton Dickson and The Medicines Company; grants from Draeger; sponsor-initiated and funded phase 1 research from Rigel; and personal fees from PAION, Janssen Pharma, Ever Pharma, and Philips outside the submitted work. PS reported receiving grants from Dutch Brain Foundation and Achmea Healthcare Foundation during the conduct of the study. No other disclosures were reported.

Publisher's Note

Received: 26 October 2022 Accepted: 19 February 2023
Published: 19 April 2023

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