End-tidal and arterial carbon dioxide gradient in serious traumatic brain injury after prehospital emergency anaesthesia: a retrospective observational study

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ABSTRACT

Objectives In the UK, 20% of patients with severe traumatic brain injury (TBI) receive prehospital emergency anaesthesia (PHEA). Current guidance recommends an end-tidal carbon dioxide (ETCO₂) of 4.0–4.5 kPa (30.0–33.8 mm Hg) to achieve a low-normal arterial partial pressure of CO₂ (PaCO₂), and reduce secondary brain injury. This recommendation assumes a 0.5 kPa (3.8 mm Hg) ETCO₂–PaCO₂ gradient. However, the gradient in the acute phase of TBI is unknown. The primary aim was to report the ETCO₂–PaCO₂ gradient of TBI patients at hospital arrival.

Methods A retrospective cohort study of adult patients with serious TBI, who received a PHEA by a prehospital critical care team in the East of England between 1 April 2015 and 31 December 2017. Linear regression was performed to test for correlation and reported as R-squared (R²). A Bland-Altman plot was used to test for paired ETCO₂ and PaCO₂ agreement and reported with 95% CI. ETCO₂–PaCO₂ gradient data were compared with a two-tailed, unpaired, t-test.

Results 107 patients were eligible for inclusion. Sixty-seven patients did not receive a PaCO₂ sample within 30 min of hospital arrival and were therefore excluded. Forty patients had complete data and were included in the final analysis; per protocol. The mean ETCO₂–PaCO₂ gradient was 1.7 (±1.0) kPa (12.8 mm Hg), with moderate correlation (R²=0.23, p=0.002). The Bland-Altman bias was 1.7 (95% CI 1.4 to 2.0) kPa with upper and lower limits of agreement of 3.6 (95% CI 3.0 to 4.1) kPa and −0.2 (95% CI −0.8 to 0.3) kPa, respectively. There was no evidence of a larger gradient in more severe TBI (p=0.29). There was no significant gradient correlation in patients with a coexisting serious thoracic injury (R²=0.13, p=0.10), and this cohort had a larger ETCO₂–PaCO₂ gradient, 2.0 (±1.1) kPa (15.1 mm Hg), and −0.2 (95% CI −0.8 to 0.3) kPa, respectively. There was no evidence of a larger gradient in more severe TBI (p=0.29).

Conclusion There is only moderate correlation of ETCO₂ and PaCO₂ at hospital arrival in patients with serious TBI. The mean ETCO₂–PaCO₂ gradient was 1.7 (±1.0) kPa (12.8 mm Hg). Lower ETCO₂ targets than previously recommended may be safe and appropriate, and there may be a role for prehospital PaCO₂ measurement.

BACKGROUND

Traumatic brain injury (TBI) is the leading cause of death and disability following trauma, with 69 million estimated new cases each year worldwide.1 Optimising cerebral blood flow (CBF) is the mainstay of treatment to prevent secondary brain injury and reduce mortality.2 Early management of raised intracranial pressure (ICP) includes controlled ventilation via prehospital emergency anaesthesia (PHEA).3 A growing number of emergency medical services are providing this.4 At present, it is estimated that one in five patients with severe TBI undergo PHEA.5

The use of end-tidal capnography to confirm endotracheal tube position is widely accepted.6 Current guidance encourages the use of end-tidal carbon dioxide (ETCO₂) as a surrogate for the arterial partial pressure of carbon dioxide (PaCO₂) to guide ventilation.7,8 Under normal physiological
conditions, alveolar dead space accounts for a 0.5 kPa (3.8 mm Hg) \( \text{ETCO}_2 - \text{PaCO}_2 \) gradient in ventilated patients. \(^3\) In-hospital data demonstrate good correlation in patients with TBI. \(^{10-12}\) The Association of Anaesthetists recommend an \( \text{ETCO}_2 \) target of 4.0–4.5 kPa (30.0–33.8 mm Hg) to achieve normocapnia. \(^7\)

The mechanisms of autoregulation of CBF differ with changes in ICP. \(^{13}\) Respiratory dysfunction and loss of autoregulation is common in patients with TBI, \(^{14}\) and a 1% change in PaCO\(_2\) can lead to changes of up to 4% in CBF. \(^{15}\) Prehospital data evaluating the use of \( \text{ETCO}_2 \) are limited, but are not consistent with in-hospital findings; leading to some criticism of the use of \( \text{ETCO}_2 \) to guide ventilation. \(^{16-18}\) In most cases of TBI, an increase in ICP evolves over hours, and therefore moderate hypercapnia prehospital would be expected to increase CBF. However, the effect of the \( \text{ETCO}_2 - \text{PaCO}_2 \) gradient on resultant PaCO\(_2\) early in this disease process is unknown. The primary objective of this study was to report the \( \text{ETCO}_2 - \text{PaCO}_2 \) gradient at hospital arrival in a cohort of patients with serious TBI who underwent PHEA.

**Hypothesis**

Patients with serious TBI who undergo PHEA have an \( \text{ETCO}_2 - \text{PaCO}_2 \) gradient greater than 0.5 kPa (3.8 mm Hg).

**METHODS**

In this retrospective observational study, a convenience sample of patients who underwent PHEA by a single UK prehospital team (East Anglian Air Ambulance, EAAA) between 1 April 2015 and 31 December 2017 was extracted from the EAAA electronic medical record.

**Prehospital critical care team**

EAAA is a medical charity that provides prehospital critical care to the statutory ambulance service in the East of England (East of England Ambulance Service NHS Trust). EAAA operates from two bases (Cambridge and Norwich), dispatching a physician-paramedic prehospital critical care team in either an H145 helicopter or rapid response vehicle, depending on patient location, weather constraints and time of day (H145 available 07:00–23:59 in Cambridge, and 07:00–19:00 in Norwich). During the study period, the Cambridge EAAA base was operational from 07:00 to 01:30 daily, and the Norwich base was operational 24 hours per day 7 days per week with a paramedic-only service (without PHEA capability) from 19:00 through 07:00.

**Inclusion criteria**

In order to report outcomes, only patients who were primarily transported by EAAA to the regional neurosciences (and major trauma) centre (Cambridge University Hospitals NHS Foundation Trust, CUH) were included. This allowed cross-reference of injury patterns and outcomes collated by the CUH Trauma Office, and also for retrieval of PaCO\(_2\) data from the CUH electronic medical record. Patients were included if they were attended by EAAA, were ≥18 years old, underwent PHEA, were transported to CUH from scene, had a serious (or more severe) TBI and had complete data. Consistent with recent large data methodology, patients without a PaCO\(_2\) measurement within 30 min of hospital arrival were excluded. \(^9\)

**Definitions**

PHEA was defined as drug-assisted endotracheal intubation in the prehospital setting. Serious TBI was defined as a retrospectively applied Abbreviated Injury Scale (AIS) score for ‘head’ ≥3, and serious thoracic injury was defined as an AIS ≥3 for ‘thorax’.

**Data collection**

The side-stream \( \text{ETCO}_2 \), values and BP (reported as mean arterial pressure, MAP) at hospital handover were obtained from the EAAA electronic medical record that includes a time-stamped download from the prehospital monitor (ZOLL X Series Monitor/Defibrillator, ZOLL Medical Corporation of Asahi Kasei Corp., Tokyo). The in-hospital PaCO\(_2\) values were obtained from the CUH electronic medical record that includes a time-stamped download of data from an ABG analyzer (COBAS B 221 Blood Gas Analyzer, Roche Diagnostics, Indianapolis, IN, USA). \( \text{ETCO}_2 \) and PaCO\(_2\) data were recorded in kilopascal (kPa) units; a conversion of (kPa*7.50062=mm Hg) has been used to present units of millimetres of mercury alongside kPa.

Demographic, mechanism of injury, injury severity (AIS and Injury Severity Score (ISS)), 30 day mortality and functional outcome (Glasgow Outcome Scale (GOS) score) data were obtained from the CUH Trauma Office records.

**Primary outcome**

The primary outcome was to report the \( \text{ETCO}_2 - \text{PaCO}_2 \) gradient at hospital arrival.

**Secondary outcomes**

The secondary outcomes were to report the relationship between the severity of TBI (serious (AIS=3) and severe (AIS=4) versus critical (AIS=5)) and \( \text{ETCO}_2 - \text{PaCO}_2 \) gradient at hospital arrival; to report the effect of a coexisting serious (AIS ≥3) thoracic injury on the \( \text{ETCO}_2 - \text{PaCO}_2 \) gradient at hospital arrival; and to compare the PaCO\(_2\) at hospital arrival in patients that received prehospital arterial blood sampling.

**Statistical analysis**

Basic demographic, mechanism of injury and injury data have been reported as number (percentage) and mean (±SD) or median (IQR) as appropriate. \( \text{ETCO}_2 \) and PaCO\(_2\) data have been reported as percentage (95% CI) and mean (±SD). Comparisons of unpaired, normally distributed, continuous variables were undertaken with a two-tailed unpaired t-test (with Welch’s correction if samples had unequal deviations).

Fisher’s exact test has been used to compare proportions. Linear regressions have been performed to test for correlation and are reported as R-squared (\( R^2 \)) with gradient of the slope (m). A Bland-Altman plot has been used to test for agreement between paired \( \text{ETCO}_2 \) and PaCO\(_2\) data, and has been reported as bias (95% CI) with upper and lower limits of agreement.

Statistical analyses were performed using the R statistical programming language (R Core Team (2018); R: A language and environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria); significance was predefined at <0.05 and no corrections were made for multiple comparisons.

**Patient and public involvement**

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

**RESULTS**

**Demographics and injury**

107 patients were eligible for inclusion. Sixty-seven patients did not receive a PaCO\(_2\) sample within 30 min of hospital arrival and were therefore excluded. Forty patients had complete data and were included in the final analysis; per protocol. The median age was 45 (23–63) years, 24 (60.0%) were male. The most prevalent mechanism of injury was road traffic collision, n=22...
(55.0%). The median ISS was 31 (26–38), and 97.5% of the cohort had an ISS ≥15. The mean hospital arrival MAP was 93.7 (±24.4) mm Hg. Overall, 30 day mortality was 30.0% (95% CI 16.6 to 47.9), and all survivors had a GOS ≥3 (severe disability or better), table 1.

**ETCO$_2$–PaCO$_2$**

Overall, the mean ETCO$_2$ and PaCO$_2$ were 4.1 (±0.7) kPa (30.7 mm Hg) and 5.8 (±1.1) kPa (43.3 mm Hg), respectively. In 38/40 (95.0%, 95% CI 83.5 to 98.6) patients, the PaCO$_2$ was more than 0.5 kPa (3.8 mm Hg) higher than the ETCO$_2$. No patients were hypocapnic (PaCO$_2$ lower than 4.0 kPa (30.0 mm Hg)) and there was moderate correlation between ETCO$_2$ and PaCO$_2$ ($R^2=0.23$, $m=0.72$, $p=0.002$), figure 1.

**Primary outcome**

The mean ETCO$_2$–PaCO$_2$ gradient was 1.7 (±1.0) kPa (12.8 mm Hg), figure 1. The Bland-Altman analysis looking at the difference between PaCO$_2$ and ETCO$_2$ showed the bias to be 1.7 (95% CI 1.4 to 2.0) kPa with upper and lower limits of agreement of 3.6 (95% CI 3.0 to 4.1) kPa and −0.2 (95% CI −0.8 to 0.3) kPa, respectively, figure 2.

**Secondary outcomes**

**Severity of TBI**

Patients with a critical TBI (AIS of 5), n=24 (60.0%) had a comparable mean ETCO$_2$–PaCO$_2$ gradient compared with those with a serious or severe (AIS=3 or 4) injury—1.8 (±1.1) kPa (13.5 mm Hg) and 1.5 (±0.7) kPa (11.2 mm Hg), respectively.

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**Original research**


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**Table 1** Study population demographics

<table>
<thead>
<tr>
<th>Gender</th>
<th>N (%) or median (IQR)</th>
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<tr>
<td>Male</td>
<td>24 (60.0)</td>
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<tr>
<td>Female</td>
<td>16 (40.0)</td>
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<tr>
<td>Age</td>
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<tr>
<td>Total</td>
<td>45 (23–63)</td>
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<tr>
<td>Male</td>
<td>34 (22–62)</td>
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<tr>
<td>Female</td>
<td>50 (33–66)</td>
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<tr>
<th>Mechanism of injury</th>
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<tr>
<td>Road traffic collision</td>
<td>22 (55.0)</td>
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<tr>
<td>Fall from height</td>
<td>17 (42.5)</td>
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<tr>
<td>Crush injury</td>
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<th>Injury Severity Score</th>
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<tr>
<td>ISS &gt;15</td>
<td>39 (97.5)</td>
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<tr>
<td>ISS &gt;25</td>
<td>33 (82.5)</td>
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<tr>
<th>Head Abbreviated Injury Severity</th>
<th>N (%) or median (IQR)</th>
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<tr>
<td>Serious TBI (AIS 3)</td>
<td>8 (20.0)</td>
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<tr>
<td>Severe TBI (AIS 4)</td>
<td>8 (20.0)</td>
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<tr>
<td>Critical TBI (AIS 5)</td>
<td>24 (60.0)</td>
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<th>Prehospital PaCO$_2$ measurement</th>
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<td>Yes</td>
<td>7 (17.5)</td>
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<td>No</td>
<td>33 (82.5)</td>
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<td>Patient outcome at 30 days</td>
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<tr>
<td>Alive</td>
<td>28 (70.0)</td>
</tr>
<tr>
<td>Dead</td>
<td>12 (30.0)</td>
</tr>
<tr>
<td>Glasgow Outcome Score ≤3</td>
<td>24 (60.0)</td>
</tr>
<tr>
<td>Glasgow Outcome Score ≥4</td>
<td>16 (40.0)</td>
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| AIS, Abbreviated Injury Scale score; ISS, Injury Severity Score; PaCO$_2$, partial pressure of arterial carbon dioxide; TBI, traumatic brain injury.

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**Figure 1** Scatter plot of the relationship between ETCO$_2$ and PaCO$_2$ at hospital arrival. 1.0kPa=7.50062 mm Hg. The ETCO$_2$–PaCO$_2$ gradient was 1.7 (±1.0) kPa (12.8 mm Hg). The mean is plotted as a single line and SD as dashed lines. ETCO$_2$ end-tidal carbon dioxide; PaCO$_2$, arterial partial pressure of carbon dioxide.

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$p=0.29$. Both of these groups (AIS=5 and AIS=3 or 4) demonstrated a moderate correlation ($R^2=0.22$, $m=0.64$, $p=0.02$ and $R^2=0.31$, $m=1.31$, $p=0.03$, respectively).

**Thoracic injury**

22/40 (55.0%) patients had a serious thoracic injury. The mean ETCO$_2$–PaCO$_2$ gradient in this subgroup was 2.0 (±1.1) kPa (15.1 mm Hg), significantly higher than the 18/40 patients without a serious thoracic injury—1.3 (±0.5) kPa (9.5 mm Hg), $p=0.01$. There was no significant correlation in the thoracic injury subgroup ($R^2=0.13$, $m=0.54$, $p=0.10$), but there was a significant correlation in the group without serious thoracic injury ($R^2=0.51$, $m=0.78$, $p<0.001$). There was no significant difference in mean MAP at hospital arrival between patients with and without a serious thoracic injury—91.9 (±25.3) mm Hg and 95.9 (±23.7) mm Hg, respectively, $p=0.60$.

**Prehospital PaCO$_2$ measurement**

Seven (17.5%) patients underwent prehospital measurement of PaCO$_2$, using the iSTAT (Abbott Laboratories, Illinois, USA) point-of-care ABG (POC-ABG) analyzer. The POC-ABG group had a significantly lower, and more appropriate hospital arrival PaCO$_2$, compared with the no-ABG group—4.7 (±0.2) kPa (35.1 mm Hg) versus 6.0 (±1.1) kPa (45.0 mm Hg), respectively, $p=0.7 \times 10^{-7}$.

**DISCUSSION**

This study has demonstrated that patients with an AIS ≥3 TBI have a larger ETCO$_2$–PaCO$_2$ gradient at hospital arrival than previously reported. The severity of TBI was not significantly associated with the ETCO$_2$–PaCO$_2$ gradient. However, the presence of a coexisting serious thoracic injury was associated with a significantly larger ETCO$_2$–PaCO$_2$ gradient, which is manifest as an apparent bias in the Bland-Altman plot of figure 2. In the
Inadvertent hypocapnia is an important factor in avoidable neuronal injury following TBI via a reduction in CBF and an increase in cerebral oxygen consumption. However, the pragmatic clinical benefits of knowing PaCO2 is a major determinant of CBF through its effects on cerebral vascular tone. Ventilatory control is crucial to the management of TBI.20 Even modest hypercapnia may result in substantial increases in ICP when intracranial compliance is poor.21 Conversely, even modest hyperventilation has been shown to lead to dangerous cerebral ischaemia,22 and this may be of particular importance in the first hours after TBI when hypoperfusion is a dominant pathology.23

Current guidance recommends an ETCO2 of 4.0–4.5 kPa (30.0–33.8 mm Hg) as a surrogate for a low-normal PaCO2.7 This guidance relies on the assumption that the ETCO2–PaCO2 gradient is approximately 0.5 kPa (3.8 mm Hg), and is predominately extrapolated from healthy individuals. In this study, the mean hospital arrival ETCO2 was 4.1 (±0.7) kPa (30.7 mm Hg), which suggests that the prehospital providers adhered closely to the extant guidelines. Despite this, the mean PaCO2 was 5.8 (±1.1) kPa (43.3 mm Hg)—far in excess of the target of 4.5–5.0 kPa,24 owing to a mean ETCO2–PaCO2 gradient of 1.7 (±1.0) kPa (12.8 mm Hg). The result of this is that when relying on ETCO2 as a surrogate, providers may not achieve an optimal prehospital PaCO2.

The arterial-alveolar CO2 gradient is determined by the ratio of physiological dead space and tidal volume. Since 2000 and the publication of the ARDSNet study, ventilatory practice has shifted towards the use of lower tidal volumes.25 Therefore, in contemporary practice the ETCO2–PaCO2 gradient would be expected to be larger because the dead space is more appreciable, and it may be that the target ETCO2 needs to be reconsidered. It is tempting to advocate a lower prehospital ETCO2—perhaps 2.8–3.3 kPa (21.0–24.8 mm Hg) in patients suspected of having an AIS ≥3 TBI (assuming a gradient of 1.7 kPa (12.8 mm Hg)), particularly in the setting of coexisting thoracic injury. However, this strategy may risk hypocapnia (PaCO2 <4.0 kPa (30.0 mm Hg)), which in the setting of a very high ICP may be of benefit via hypocapnic arterial vasoconstriction,21 but in the more likely prehospital clinical scenario (<24 hours after TBI) of normal ICP, may lead to severe cerebral ischaemia and worse outcomes.26

There was only moderate correlation between ETCO2 and PaCO2; statistically, only 23% of the variance (R2, the coefficient of determination) observed in ETCO2 can be explained by the PaCO2. There was no ETCO2–PaCO2 gradient correlation in the subgroup with an AIS ≥3 thoracic injury. We presume that this is owing to the effect of heterogeneous physiological dead space (caused by the thoracic injury) on the arterial-alveolar carbon dioxide gradient. Therefore, in those without an AIS ≥3 thoracic injury the ETCO2–PaCO2 gradient correlation was better; statistically 51% of the variance observed in ETCO2 can be explained by PaCO2. In order to ensure that the increased gradient observed in the AIS ≥3 thoracic injury group was not simply due to a lower systemic perfusion compared with the group without serious thoracic injury, MAP at hospital arrival was reported between the two groups. Although there is a known relationship between tissue perfusion and ETCO2, there was no difference between the MAP (used as a surrogate for perfusion) at hospital arrival between those with and without an AIS ≥3 thoracic injury. We think that this strengthens the theory that thoracic injury increases the physiological dead space. It is unclear from these data what variable(s) make up the remaining 49% of variance observed. We acknowledge the transfer from a prehospital to an in-hospital ventilator may be one factor in this. However, EAAA and CUH use identical ventilators (Dräger Oxylog 3000, Drägerwerk AG & Co., Lübeck, Germany), and it is standard practice to commence in-hospital ventilation using the prehospital settings.

It is not necessarily surprising that in this small sample with significant variance we were not able to demonstrate a significant difference between the severity of TBI (as measured by AIS) and the ETCO2–PaCO2 gradient, and it is possible that this represents a type-2 error. Previous work has demonstrated an increased gradient in more severe injury (higher ISS), but has not examined head or thoracic injury specifically, and has shown an increased mortality in ‘abnormal’ hospital-arrival ETCO2.27 In the subgroup of patients with a serious thoracic injury, the ETCO2–PaCO2 gradient was significantly higher than those without a serious thoracic injury, further compounding the inaccuracy in estimating PaCO2 from ETCO2 in the severely injured trauma patient. The patients in our study were all primarily transported to the regional neurosciences (and major trauma) centre by a prehospital critical care team. Therefore, it is possible that we are missing data from both ends of the severity spectrum: patients with a lesser injury and those with a more immediate requirement for in-hospital resuscitation may have been initially transported to a local trauma unit hospital. Our limited analysis of the effect of severity of TBI on gradient demonstrated a non-significant trend of increasing gradient with increasing TBI severity. However, the pragmatic clinical benefits of knowing if severity of TBI affects the ETCO2–PaCO2 gradient is minimal—without good evidence of strong correlation between ETCO2 and PaCO2, the provider cannot rely on ETCO2 as a surrogate.

Inadvertent hypocapnia is an important factor in avoidable neuronal injury following TBI via a reduction in CBF and an increase in cerebral oxygen consumption.22 While we have...
concentrated on hypercapnia in this study, it is encouraging to 
see that even in the presence of significant heterogeneity in
ETCO$_2$–PaCO$_2$ gradient in this population, no patients were
hypocapnic on arrival to hospital using the extant guidelines.

Even from this small sample of patients it is evident that using
the ETCO$_2$ as a surrogate for PaCO$_2$ following TBI is a blunt
tool. There is a larger than previously reported mean ETCO$_2$–
PaCO$_2$ gradient and only moderate correlation. The practice of
low tidal volume ventilation may necessitate a reconsideration of
the expected ETCO$_2$–PaCO$_2$ gradient, but the lack of correlation
in those with a concomitant thoracic injury means that signifi-
cantly inaccuracy in using ETCO$_2$ as a surrogate for PaCO$_2$
would likely continue. Numerous other surrogates have been used for
PaCO$_2$, including transcutaneous CO$_2$ monitoring and capillary
blood gas analysis. However, at present, an ABG sample is
the only reliable way to obtain an accurate PaCO$_2$ with which
to guide ventilation in TBI. The advancement in technology and
production of smaller, portable analyzers allow providers to
accurately determine PaCO$_2$ prehospital and in other resource-
limited settings. A small number of patients in our study
underwent prehospital measurement of PaCO$_2$ using a POC
analyzer. There was evidence during chart review of these seven
patients that the providers made alterations to the ventilation
strategy after PaCO$_2$ analysis; they all demonstrated a favourable
hospital arrival PaCO$_2$.

This study used data from a single prehospital critical care
service and a single regional neurosciences centre, and as
such the results may not be widely applicable. In order to increase
the number of patients in this study, we included patients who
had an ABG up to 30 min after hospital arrival. It is therefore
possible that a proportion of the gradient variance observed
was due to changes in ventilation strategy during this period,
but standard clinical practice means this should be clinically
negligible. The availability of these data very early in this disease
process is extremely limited, resulting in a small sample size. It is
possible that non-significant findings are due to a lack of statis-
tical power.

CONCLUSION
There is only moderate correlation of ETCO$_2$ and PaCO$_2$
at hospital arrival in patients with serious TBI. The mean ETCO$_2$–
PaCO$_2$ gradient was 1.7 (±1.0) kPa (12.8 mm Hg)—greater
than previously reported. Lower ETCO$_2$ targets than previously
recommended may be safe and appropriate, particularly in the
presence of thoracic injury. There may be a role for prehospital
PaCO$_2$ measurement.

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Acknowledgements We acknowledge the assistance of Assiah Mahmood
and Jacques Bowman of the CUH Trauma Office in compiling the original data.

Contributors The study was conceived by JP, DDS and EBGB. The study permissions
were obtained by EBGB and AW. Data acquisition was undertaken by JP and DDS.
DDS, AE and EBGB interpreted the data. The manuscript was prepared by JP and
EBGB. Critical revisions were done by AE, AW and EBGB. All authors reviewed
and approved the final draft.

Funding The authors have not declared a specific grant for this research from
any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in
the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This service evaluation was registered with both EAAA and CUH.
Local agreement for the use of anonymised data from the EAAA electronic medical
record was granted through extant data use protocols. Anonymised, linked data
were obtained from the CUH Trauma Office, and PaCO$_2$ values obtained from the
CUH electronic medical record. Ethical review was undertaken by the Cambridge
University Hospitals NHS Foundation Trust Quality and Safety Support Department
(reference: PRN7866).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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Original research


