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

James Price ![ORCID] ,[1,2] Daniel D Sandbach,[1] Ari Ercole ![ORCID] ,[1,3] Alastair Wilson,[1,4] Ed Benjamin Graham Barnard ![ORCID] [1,2,5]

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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 ($ETCO_2$) of 4.0–4.5 kPa (30.0–33.8 mm Hg) to achieve a low-normal arterial partial pressure of CO_2 ($PaCO_2$), and reduce secondary brain injury. This recommendation assumes a 0.5 kPa (3.8 mm Hg) $ETCO_2$–$PaCO_2$ gradient. However, the gradient in the acute phase of TBI is unknown. The primary aim was to report the $ETCO_2$–$PaCO_2$ 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 (R^2). A Bland-Altman plot was used to test for paired $ETCO_2$ and $PaCO_2$ agreement and reported with 95% CI. $ETCO_2$–$PaCO_2$ 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 $PaCO_2$ 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 mean $ETCO_2$–$PaCO_2$ gradient was 1.7 (±1.0) kPa (12.8 mm Hg), with moderate correlation (R^2=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 (R^2=0.13, p=0.10), and this cohort had a larger $ETCO_2$–$PaCO_2$ gradient, 2.0 (±1.1) kPa (15.1 mm Hg), p=0.01. Patients who underwent prehospital arterial blood sampling had an arrival $PaCO_2$ of 4.7 (±0.2) kPa (35.1 mm Hg).

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). Lower $ETCO_2$ targets than previously recommended may be safe and appropriate, and there may be a role for prehospital $PaCO_2$ measurement.

Key messages

What is already known on this subject
► The optimal management of ventilation in patients with serious traumatic brain injury (TBI) reduces secondary brain insult.
► Current guidance recommends the use of end-tidal carbon dioxide ($ETCO_2$) as a surrogate for arterial carbon dioxide ($PaCO_2$) to guide ventilation strategy in the prehospital environment.
► The effect of the $ETCO_2$–$PaCO_2$ gradient on resultant $PaCO_2$ early in this disease process is unknown.

What this study adds
► This retrospective cohort study of 40 patients receiving prehospital emergency anaesthesia found only moderate correlation of $ETCO_2$ and $PaCO_2$ in patients with serious TBI, thus the use of $ETCO_2$ to guide ventilation is a blunt tool in this cohort.
► The $ETCO_2$–$PaCO_2$ gradient is larger than previously reported and is increased by the presence of coexisting thoracic injuries. Prehospital $PaCO_2$ measurement resulted in more accurate titration of ventilatory strategy.

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 ($ETCO_2$) as a surrogate for the arterial partial pressure of carbon dioxide ($PaCO_2$) to guide ventilation.[7 8] Under normal physiological

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conditions, alveolar dead space accounts for a 0.5 kPa (3.8 mm Hg) $ETCO_2$–$PaCO_2$ gradient in ventilated patients.[9] In-hospital data demonstrate good correlation in patients with TBI.[10–12] The Association of Anaesthetists recommend an $ETCO_2$ 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 $ETCO_2$ are limited, but are not consistent with in-hospital findings; leading to some criticism of the use of $ETCO_2$ 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 $ETCO_2$–$PaCO_2$ gradient on resultant $PaCO_2$ early in this disease process is unknown. The primary objective of this study was to report the $ETCO_2$–$PaCO_2$ 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 $ETCO_2$–$PaCO_2$ 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.[19]

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 $ETCO_2$ 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). $ETCO_2$ 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 $ETCO_2$–$PaCO_2$ 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 $ETCO_2$–$PaCO_2$ gradient at hospital arrival; to report the effect of a coexisting serious (AIS ≥3) thoracic injury on the $ETCO_2$–$PaCO_2$ 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. $ETCO_2$ 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 $ETCO_2$ 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

Table 1 Study population demographics

	N (%) or median (IQR)
Gender	
Male	24 (60.0)
Female	16 (40.0)
Age	
Total	45 (23–63)
Male	34 (22–62)
Female	50 (33–66)
Mechanism of injury	
Road traffic collision	22 (55.0)
Fall from height	17 (42.5)
Crush injury	1 (2.5)
Injury Severity Score	
ISS >15	39 (97.5)
ISS >25	33 (82.5)
'Head' Abbreviated Injury Severity	
Serious TBI (AIS 3)	8 (20.0)
Severe TBI (AIS 4)	8 (20.0)
Critical TBI (AIS 5)	24 (60.0)
Prehospital $PaCO_2$ measurement	
Yes	7 (17.5)
No	33 (82.5)
Patient outcome at 30 days	
Alive	28 (70.0)
Dead	12 (30.0)
Glasgow Outcome Score ≤3	24 (60.0)
Glasgow Outcome Score ≥4	16 (40.0)

AIS, Abbreviated Injury Scale score; ISS, Injury Severity Score; $PaCO_2$, partial pressure of arterial carbon dioxide; TBI, traumatic brain injury.

(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,
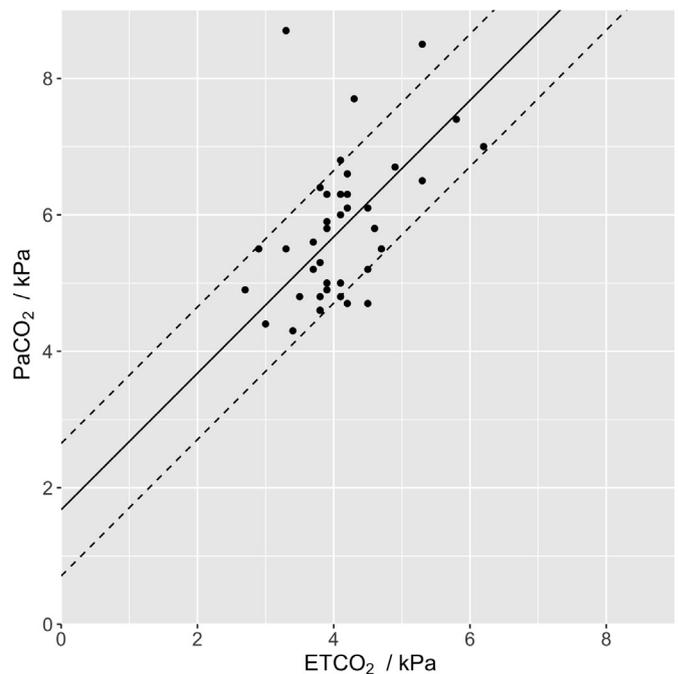

Figure 1 Scatter plot of the relationship between $ETCO_2$ and $PaCO_2$ at hospital arrival. 1.0 kPa=7.50062 mm Hg. The $ETCO_2$–$PaCO_2$ gradient was 1.7 (±1.0) kPa (12.8 mm Hg). The mean is plotted as a single line and SD as dashed lines. $ETCO_2$, end-tidal carbon dioxide; $PaCO_2$, arterial partial pressure of carbon dioxide.

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=0.7×10^{-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
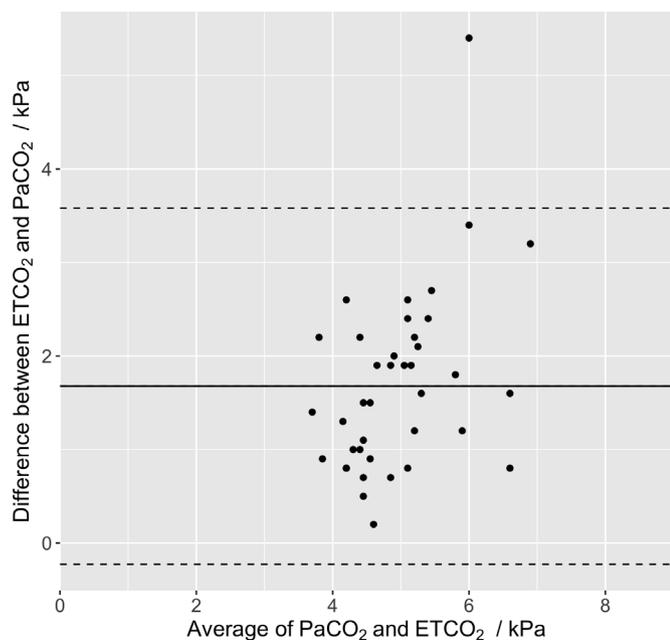
Figure 2 Bland-Altman plot of the agreement between $ETCO_2$ and $PaCO_2$ at hospital arrival. 1.0 kPa=7.50062 mm Hg. The bias is 1.7 (95% CI 1.4 to 2.0) kPa with upper and lower limits of agreement of 3.6 (95% CI 3.0 to 4.1) kPa and −0.2 (95% CI −0.8 to 0.3) kPa, respectively. The bias is plotted as a single line, and the upper and lower limits of agreement as dashed lines. $ETCO_2$, end-tidal carbon dioxide; $PaCO_2$, arterial partial pressure of carbon dioxide.

serious thoracic injury cohort, there was no evidence of correlation between $ETCO_2$ and $PaCO_2$. All patients who underwent prehospital $PaCO_2$ measurement had a low-normal $PaCO_2$ at hospital arrival.

$PaCO_2$ 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 $ETCO_2$ of 4.0–4.5 kPa (30.0–33.8 mm Hg) as a surrogate for a low-normal $PaCO_2$.[7] This guidance relies on the assumption that the $ETCO_2$–$PaCO_2$ gradient is approximately 0.5 kPa (3.8 mm Hg), and is predominantly extrapolated from healthy individuals. In this study, the mean hospital arrival $ETCO_2$ 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 $PaCO_2$ 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 $ETCO_2$–$PaCO_2$ gradient of 1.7 (±1.0) kPa (12.8 mm Hg). The result of this is that when relying on $ETCO_2$ as a surrogate, providers may not achieve an optimal prehospital $PaCO_2$.

The arterial-alveolar CO_2 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 $ETCO_2$–$PaCO_2$ gradient would be expected to be larger because the dead space is more appreciable, and it may be that the target $ETCO_2$ needs to be reconsidered. It is tempting to advocate a lower prehospital $ETCO_2$—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 ($PaCO_2$ <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 $ETCO_2$ and $PaCO_2$; statistically, only 23% of the variance (R^2, the coefficient of determination) observed in $ETCO_2$ can be explained by the $PaCO_2$. There was no $ETCO_2$–$PaCO_2$ 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 CO_2 gradient. Therefore, in those without an AIS ≥3 thoracic injury the $ETCO_2$–$PaCO_2$ gradient correlation was better; statistically 51% of the variance observed in $ETCO_2$ can be explained by $PaCO_2$. 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 $ETCO_2$,[11] 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 $ETCO_2$–$PaCO_2$ 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,[16] and has shown an increased mortality in 'abnormal' hospital-arrival $ETCO_2$.[27] In the subgroup of patients with a serious thoracic injury, the $ETCO_2$–$PaCO_2$ gradient was significantly higher than those without a serious thoracic injury, further compounding the inaccuracy in estimating $PaCO_2$ from $ETCO_2$ 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 $ETCO_2$–$PaCO_2$ gradient is minimal—without good evidence of strong correlation between $ETCO_2$ and $PaCO_2$, the provider cannot rely on $ETCO_2$ 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 significant 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.[28 29] 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.[30 31] 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 statistical 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.

ORCID iDs
James Price http://orcid.org/0000-0002-9643-692X
Ari Ercole http://orcid.org/0000-0001-8350-8093
Ed Benjamin Graham Barnard http://orcid.org/0000-0002-5187-1952

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