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Targeted temperature management and $P_{bt}O_2$ in traumatic brain injury

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ABSTRACT

Introduction: Targeted Temperature Management (TTM) to normothermia is widely used in traumatic brain injury (TBI). We investigated the effects to of TTM to normothermia patients with TBI (GCS≤12) monitored with multimodality monitoring, to better understand the physiological consequences of this intervention.
Research question: In TBI patients cooled to normothermia and in which brain oxygenation deteriorates, are there changes in physiological parameters which are pertinent to brain oxygenation?
Material and method: 102 TBI patients with continuous recordings of intracranial pressure (ICP) and brain oxygen tension ($P_{bt}O_2$) were studied retrospectively. Non-continuous arterial carbon dioxide (P_aCO_2) and oxygen (P_aO_2) tensions, and core body temperature (T_c) were added. P_aO_2 and P_aCO_2 were also corrected for T_c. Transitions from elevated T_c to normothermia were identified in 39 patients. The 8 h pre and post the transition to normothermia were compared. Data is given as median [IQR] or mean (SD).
Results: Overall, normothermia reduced ICP (12 [9–18] −11 [8–17] mmHg, $p < 0.009$) and T_{core} (38.3 [0.3]-36.9 [0.4] °C, $p < 0.001$), but not $P_{bt}O_2$ (23.3 [16.6]-24.4 [17.2–28.7] mmHg, NS). Normothermia was associated with a fall in $P_{bt}O_2$ in 18 patients (24.5 [9.3] −20.8 [7.6] mmHg). Only in those with a fall in $P_{bt}O_2$ with cooling did ICP (15 [10.8–18.5] −12 [7.8–17.3] mmHg, $p = 0.002$), and temperature corrected P_aCO_2 (5.3 [0.5]- 4.9 [0.8] kPa, $p = 0.001$) decrease.
Discussion and conclusion: A reduction in $P_{bt}O_2$ was only present in the subgroup of patients with a fall in temperature corrected P_aCO_2 with cooling. This suggests that even modest temperature changes could result in occult hyperventilation in some patients. pH stat correction of ventilation may be an important factor to consider in future TTM protocols.

1. Introduction

1.1. General

Traumatic brain injury (TBI) is one of the leading causes of death and disability in the world, with an estimated 69 million cases each year (Hyder et al., 2007; Blennow et al., 2016; Dewan et al., 2018). The injured brain is at an increased risk of secondary injuries which can occur later (Kinoshita, 2016; Mckee and Daneshvar, 2015). These include hypotension, hypoxia, raised intracranial pressure and fever. Management of TBI is principally directed at prevention and treatment of secondary injury (Whitaker-Lea and Valadka, 2017).

Elevated body temperature or fever, (≥38.3 °C) is common in TBI patients and can occur due to both infection and/or dysfunction of the hypothalamus caused by injury (Thompson et al., 2007; Badjatia, 2009). Research suggests that elevated body temperature is associated with excess mortality and morbidity of TBI patients, however it is unclear whether this is an independent risk factor or a marker of the severity of injury (Badjatia, 2009; Young et al., 2018).

None the less treating fever in brain injured patients is widely practiced (Rincon, 2018; Picetti et al., 2019; Lavinio et al., 2023; Cariou et al., 2017) and often referred to as targeted temperature management (TTM). However, there is significant variation as to what this treatment is and there is a lack of high-quality evidence to support its use (Picetti et al., 2019; Golding et al., 2016). The use of more aggressive cooling to moderate hypothermia was not supported by large, high quality randomised controlled trials (Clifton et al., 2011; Cooper et al., 2018; Maekawa et al., 2015; Miller et al., 2001; Andrews et al., 2015a). Moreover,

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the Eurotherm 3235 trial found that cooling was associated with harm (Andrews et al., 2015a). Addressing the uncertainties over the correct use and consequences of fever control could therefore be important.

To optimize TTM, a more complete appreciation of any adverse effects of this practice and how best these might be resolved is important. We have previously reported the reduction in brain oxygen tension ($PbtO_2$) in some patients undergoing hypothermia as part of the Eurotherm 32–25 trial (Flynn et al., 2015). In our clinical practice we also notice that this can happen as some patients are cooled to normothermia, treating fever.

Low $PbtO_2$ has been repeatedly found to be associated with poor outcome in TBI patients (van Santbrink et al., 1996; Stiefel et al., 2005; Eriksson et al., 2012; Robba et al., 2020), making this an important potential target TBI management. $PbtO_2$ is highly influenced by cerebral blood flow (CBF) and the arterial oxygen tension (PaO_2) (Rosenthal et al., 2008). Falling $PbtO_2$ with the onset of hypothermia, or TTM to normothermia, could indicate an important reduction in cerebral blood flow, offsetting any potential benefits of the therapy on outcomes.

This study sought to study the physiological consequences of cooling to normothermia in a cohort of patients with moderate or severe traumatic brain injury undergoing continuous invasive monitoring of intracranial pressure (ICP) and $PbtO_2$. We hypothesised that in patients in which $PbtO_2$ fell with cooling there could be changes in physiological parameters that are known to be important in the control of $PbtO_2$. Specifically, ICP, CPP and $PaCO_2$ regulating cerebral blood flow along with PaO_2 for is contribution to oxygen content of the blood being delivered to the brain. Since temperature affects the tension of gases in solution, we also corrected the tensions of arterial oxygen and carbon dioxide for the actual temperature of the patient at the time.

2. Materials and methods

2.1. Study sample

This was a retrospective cohort study using prospectively collected data. Data was extracted from a database that contained 122 patients with moderate to severe TBI (GCS $\leq$12) who were admitted to the regional intensive care unit (ICU) at the Western General Hospital, Edinburgh, UK, between 2010 and 2019. At that time, the Western General Hospital was the tertiary referral centre for neurosurgical cases in Southwest Scotland.

2.2. Patient management

Patients with moderate to severe TBI were managed according to the guidelines of the Brain Trauma Foundation (Carney et al., 2017). All patients were sedated, and invasively ventilated and appropriated mass lesions were removed via craniectomy. For patients requiring ICP monitoring, $P_{bt}O_2$, ICP and brain temperature were measured via sensors inserted into brain parenchyma via a dedicated triple lumen bolt, placing the sensors in the frontal white matter (Integra Licox system, Integra, Saint Priest, France). For diffuse injuries this was into the non-dominant hemisphere. When the injury was focal, the bolt was placed on the side of maximal injury, unless this would place the oxygen electrode into non-viable tissue.

ICP was controlled according to a step wise protocol. Initially all patients were sedated and nursed with 30-degree head elevation. Arterial carbon dioxide tension ($PaCO_2$) was controlled at 4.5–5.0 kPa by adjusting minute ventilation. Cerebral perfusion pressure was controlled (=>60 mmHg) by the regulation of mean arterial pressure with fluids and noradrenalin and the limitation of ICP ($\leq$ 20 mmHg). Thereafter $PaCO_2$ and CPP targets could be adjusted, guided by the response of $PbtO_2$, aiming for a $PbtO_2$ >20 mmHg.

Sustained elevations of ICP (>20 mmHg for >5 min, not secondary to inadequate sedation, high intra-thoracic pressures, poor positioning, cardiovascular instability, hypoxia or hypercapnia) would lead to an escalation of therapy. This included the use of hypertonic fluids (5% NaCl 125 ml or 20% mannitol 200 ml boluses), paralysis and further CT scanning. Lesions amenable to surgical intervention would be resected. CSF drainage was not performed. Barbiturate coma to burst suppression and/or decompressive craniotomy were options for refractory ICP elevation. Sustained fever, core temperature >38 °C (Oesophageal or Tympanic), was managed according to the treating clinical team's judgment. When fever control was sought, this involved treatment with paracetamol and the application of automated surface cooling (Arctic Sun, BD, Covington, Georgia, USA) to return core temperature to 37 °C.

PbtO2 was optimized according to a local algorithm, previously described (Rhodes et al., 2016b). This simple flow chart suggested adjustments to PaO_2, $PaCO_2$, CPP, ICP or haemoglobin (Hb) concentration if $PbtO_2$ was <20 mmHg.

Physiological parameters ($PbtO_2$, brain temperature (T_{brain}), CPP, MAP and ICP) were recorded continuously from the Licox and Drager bedside monitors systems using the ICU Pilot software (CMA, Sweden). Collection of data was stopped once ICP monitoring was no longer required or the patient has died. Data from the first 2 h of $P_{bt}O_2$ monitoring was excluded from the analysis to ensure the results were not influenced by the time required for the oxygen electrode to stabilise.

2.3. Study data

At the time of the study 122 patients had continuous per minute physiological data available as Excel spread sheets. In addition, data was available from body gas analysis for $PaCO_2$, PaO_2, FiO_2, and Hb as these samples were taken over the day, as required. In addition, hourly core body temperature data was also available. This additional data was manually added to the Excel sheets at the appropriate times. If patients had missing body temperature data or less than 24 h of data, they were excluded. From the original cohort of 122 patients, 20 patients were excluded. These remaining 102 data files were then scanned to identify regions of interest representing changes in core temperature from fever to normothermia.

2.4. Identifying regions of interest

The aim of the study was to quantify changes in physiology pertinent to cerebral oxygenation. Unfortunately, the records available in this retrospective study did not always make it clear when physical temperature management was commenced. Therefore, we developed an iterative approach to define what a transition from fever to normothermia looked like. For this phase only brain and body temperature data were inspected. T_{brain} and core body temperature (T_{core})verses time plots from 15 patients with clear drops in temperature from >38 °C to 37 °C were inspected and one author, JR, developed rules that defined this temperature drop in terms that could be written as Excel logic functions. These logic functions were than applied to another 30 files in the dataset by a second author, NCP, and the candidate regions of interest checked by JR. Adjustments were made to the rules until transitions in temperature from fever to stable normothermia could be reliably defined. Once the rules were agreed they were applied to the entire data set.

Using this approach a region of interest was defined as a temperature profile in which;

The last T_{core} prior to a temperature fall was $\geq$ 37.7 °C.

The average T_{core} in the 12 h prior to the drop was $\geq$ 37.5 °C.

T_{core} fell to between 35.5 °C and $\leq$ 37.5 °C within 10 h.

The average lower T_{core} was maintained for $\geq$ 12 h.

2.5. Data analysis

For each of the identified regions of interest, average values of T_{brain}, T_{core}, $PbtO_2$, ICP, CPP, MAP, $PaCO_2$, PaO_2 were calculated for the 8 h pre and post cooling to normothermia.

2.6. pH stat correction

All blood gases were measured using the alpha stat hypothesis (where the blood gases sample is corrected to 37 °C). To correct $PaCO_2$ according to the body temperature of the patient (pH stat hypothesis), a method by Nunn et al. was used (Nunn et al., 1965):

$$\log(pco_2) = \log(pco_2) + 0.019(37 - t_m).$$

For correction of PaO_2 a method by Severinghaus et al. was used (Severinghaus, 1979):

$$\frac{\log(po_2)}{(37 - tm)} = \log(po_{2m}) + \frac{}{2.303}\left[\frac{0.058}{0.243(po2m/100)^{3.88}+1} + 0.013\right]$$

2.7. Data and ethics

This was an analysis of routinely collected data. Following review of the protocol, this was classified as service evaluation, by the Research Ethics Committee. Physiological data was kept in anonymous numbered excel files. These were linked to internal Ward Watcher (Scottish Intensive Care Society Audit Group) audit numbers. Via a hospital password protected computer, it was possible to access the audit number that could then be used to identify the patient. Using another password protected hospital information system (TRAK), clinical details could be verified where necessary. In this way all patient information was kept secure and no patient identifiable data was used in the analysis or is reported.

2.8. Statistical analysis

Statistical analysis was done using the software package SigmaPlot 11. (Systat Software, Inc; San Jose, California) and R (R Core Team (2022). R Foundation for Statistical Computing, Vienna, Austria.

URL https://www.R-project.org/). Normality was tested with the Shapiro -Wilk test. Parametric data was compared using paired Student *t*-tests for comparison of two groups and summarised using means and standard deviations. Non-parametric data was compared using the Wilcoxon Signed Rank test for paired data and summarised as medians and interquartile ranges. Correlations were calculated with Pearson's Correlation test. A general significance level was set as $p \leq 0.05$.

3. Results

3.1. Regions of interest

The use of the rule-set identified 39 patients with regions of interest constant with cooling to normothermia from the overall dataset of 102 patients. Surveying the available paper charts and discharge letters confirmed the use of fever control measures in 17 or the 39, 44%. In contrast documentary evidence of the use of TTM was available for 16 of 63, 25%, of the records in which a suitable region of interest was not identified.

The average peak T_{core} prior to TTM was 38.7 (38.3–39.0) °C, The last recorded T_{core} prior to cooling was 38.1 (27.8–38.3) °C and the average T_{core} in the 12 h prior to TTM was 38.3 (38.0–38.4) °C. The target temperature fall was achieved in 1.9 (1.0–3.0) hours with an average difference in T_{core} of 1.3 (1.1–1.6) °C. The average Tcore following cooling was 37.0 (36.6–37.2) °C. The peak T_{core} in the 63 patients in which a transition to TTM was not identified was 38.3 (38.0–38.7) °C, which was significantly lower than the peak T_{core} recorded in the 39 patients in which a transition to TTM from fever was defined, $p < 0.001$.

3.2. Patient characteristics

Patient demographics and outcomes are shown in Table 1. In the TTM group the average age was 43 (27.3–56.8) and most were male, 90%. The pre intubation GCS was high in the TTM group and the non TTM group, 9 (5.13–13.75) vs. 7 (Kinoshita, 2016; Mckee and Daneshvar, 2015; Whitaker-Lea and Valadka, 2017; Thompson et al., 2007; Badjatia, 2009), $p = 0.024$. In the TTM group a higher proportion of patients underwent surgery to remove space occupying lesions, 23 of 39 (59%) vs. 21 of 63 (33%), for TMM vs. No TTM respectively, $p = 0.02$. The predominant Marshall classifications were Diffuse II and Evacuated Mass Lesion. There were no differences between the TTM and non TTM groups for pupil reactivity, ICU survival or injury subtypes.

3.3. Changes in physiology with fever control

Both T_{brain} and T_{core} fell significantly with fever control, 39.4 (0.7) vs. 38.4 (0.8) °C $p < 0.001$ for T_{brain} pre vs. post and 38.3 (0.3) vs. 36.9 (0.4) °C $p < 0.001$ for T_{core} pre vs. post respectively. Overall, there was no change in average PbtO2 in the 8 h prior to cooling to normothermia compared to the 8 h post, Table 2. Significant changes in ICP 12 (9–18)

Table 1
Comparison of demographics and injury severity for the patients identified as having received TTM to normothermia and those who did not.

	TTM Group		No TTM Identified		p
	n = 39	% or (IQR)	n = 63	% or (IQR)	
Age	43	(27.3–56.8)	48	(24.2–61.5)	0.476
Male	35	0.90	51	0.81	0.365
GCS Pre Intubation	9	(5–13.75)	7	(4–8)	**0.024**
GCS Motor Score Pre-Intubation	5	(2.25–6.0)	4	(2–5)	0.138
Pupil Reactivity					
Both	34	0.87	49	0.78	0.452
One	3	0.08	10	0.16	
None	2	0.05	4	0.06	
Outcome					
ICU Survivors	33	0.85	47	0.75	0.344
ICU Non-Survivors	6	0.15	16	0.25	
Predominant Injury					
SDH	13	0.33	24	0.38	0.149
EDH	5	0.13	9	0.14	
Contusion/s	18	0.46	17	0.27	
Diffuse Injury	3	0.08	13	0.21	
Injury Type					
Focal	34	0.87	48	0.76	0.153
Mixed	4	0.10	6	0.10	
Diffuse Injury	1	0.03	9	0.14	
Marshal					
Diffuse Injury II	10	0.26	21	0.33	0.635
Diffuse Injury III	1	0.03	1	0.02	
Diffuse Injury IV	0	0.00	2	0.03	
Evacuated Mass Lesion	10	0.26	19	0.30	
Non-evacuated Mass Lesion	8	0.21	8	0.13	
Missing	10	0.26	12	0.19	
Craniotomy					
Surgery	23	0.59	21	0.33	**0.02**
No Surgery	16	0.41	42	0.67	

Table 2
Comparison of the 8 h average pre and post values for $PbtO_2$, ICP, CPP and arterial gas tensions, with and without temperature correction.

	Pre		Post		Difference		p
	Average	SD or (IQR)	Average	SD or (IQR)	Average	SD or (IQR)	
PbtO2 (mmHg)	23.3	(16.6–29.4)	24.4	(17.2–28.7)	0.2	(-3.5 to 3.4)	0.817
ICP (mmHg)	12.0	(9.0–18.0)	11.0	(8.0–17.0)	−1.0	(-3.0 to 0.8)	**0.009**
CPP (mmHg)	83.6	(6.3)	85.6	(8.7)	2.1	(7.3)	0.103
PaO2 (kPa)	14.2	(2.7)	14.9	(3.0)	0.8	(2.8)	0.11
PaCO2 (kPa)	5.2	(0.8)	5.1	(0.9)	0.0	(0.5)	0.705
Brain Temp (°C)	39.4	(0.7)	38.4	(0.8)	−1.0	(1.0)	<**0.001**
Body Temp (°C)	38.3	(0.3)	36.9	(0.4)	−1.4	(0.5)	<**0.001**
Corrected PaO2 (kPa)	15.1	(2.9)	14.9	(3.1)	−0.1	(2.8)	0.824
Corrected PaCO2 (kPa)	5.5	(0.9)	5.1	(0.9)	−0.3	(0.5)	**0.002**

vs. 11 (8–17) mmHg p = 0.009, and temperature corrected $PaCO_2$ 5.5 (0.9) vs 5.1 (0.9) kPa p = 0.02 were seen. CPP, PaO_2, $PaCO_2$ and temperature corrected PaO_2 did not change significantly with cooling to normothermia.

Plotting individual changes in $PbtO_2$ highlighted the considerable variation in the response of $PbtO_2$ to cooling, Fig. 1. The range of $\Delta PbtO_2$ pre vs. post TTM was −10.6 to 18.1 mmHg. $PbtO_2$ fell in 18 and rose in 21 episodes of TTM. Moderate correlations were found between $\Delta PbtO_2$ and ΔICP (r = 0.41, p = 0.045), $\Delta PaCO_2$ (r = 0.38, p = 0.0524) and temperature corrected $\Delta PaCO_2$ (r = 0.37, p = 0.0682). There were also moderate correlations between ΔICP and $\Delta PaCO_2$ (r = 0.29, p = 0.126) and ΔICP and temperature corrected $\Delta PaCO_2$ (r = 0.38, p = 0.0482), Fig. 2. Details of the univariate linear regression modelling with $\Delta PbtO_2$ as the dependant variable are given in Table 3. There was a significant relationship for $\Delta PbtO_2$ vs. ΔICP, coefficient 0.4496, p = 0.045, Fig. 2. There were strong trends between $\Delta PbtO_2$ vs $\Delta PaCO_2$ and $\Delta PbtO_2$ vs. temperature corrected $\Delta PaCO_2$, coefficient 4.2304, p = 0.0524 and coefficient 4.106, p = 0.0682 respectively.

3.3.1. *$PbtO_2$ sub-groups*

$PbtO_2$ fell in 18 and rose in 21 episodes of TTM. Comparison of the changes in average physiological parameters in the 8 h pre and post induction of TTM for the pre-defined subgroups of $PbtO_2$ falling and $PbtO_2$ not falling are shown in Fig. 3 and Table 4. In the $PbtO_2$ subgroup, the fall in $PbtO_2$ from 24.4 (9.3) to 20.8 (7.6) mmHg, was accompanied by significant reductions in ICP (15.0 (10.8–18.5) to 12.0 (7.8–17.3) mmHg, p = 0.002, and temperature corrected $PaCO_2$ (5.3 (0.5) to 4.9 (0.8) kPa, p = 0.001, but not uncorrected $PaCO_2$. In the $PbtO_2$ not falling group, $PbtO_2$ increased significantly with TMM, from 20.3 (16.3–228.2) to 25.0 (18.3–30.7) mmHg, p < 0.001. Apart from temperature, there were no other significant changes in this sub-group.

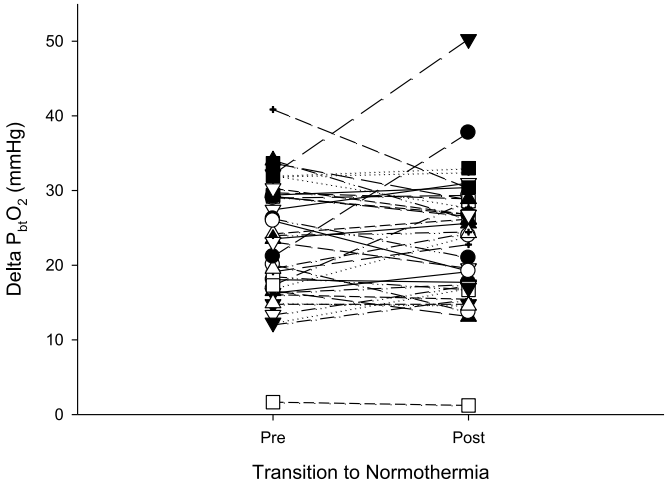

Fig. 1. Individual plots of 8 h average $PbtO_2$ pre and post transition to TTM.

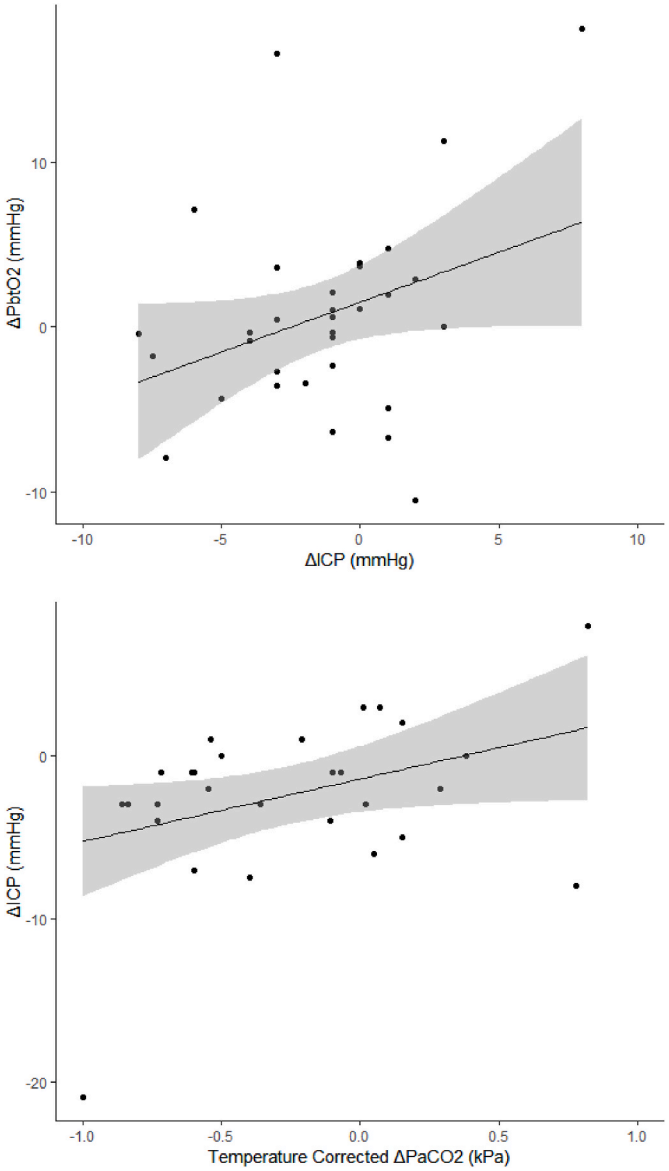

Fig. 2. Scatter plots of ΔICP vs. $\Delta PbtO_2$ (Upper), r = 0.45 p = 0,045 and temperature corrected $\Delta PaCO_2$ vs. ΔICP (Lower), r = 0.38, p = 0.048.

4. Discussion

Fever is a common occurrence in TBI patients (Thompson et al., 2007), and it may have detrimental effects on patient outcomes (Badjatia, 2009). There is limited research on TTM to normothermia. This

Table 3
Result of univariate logistic regression for $\Delta PbtO_2$ verses ΔICP, ΔCPP, ΔT_{brain}, ΔT_{core} and Δ arterial gas tensions, with and without temperature correction.

	Estimate	Std. Error	t value	p
Delta ICP	0.4496	0.2155	2.086	**0.045**
Delta CPP	0.21204	0.14101	1.504	0.142
Delta PaO2	0.04581	0.39627	0.116	0.909
Delta PaCO2	4.2304	2.0917	2.023	0.0524
Delta Brain Temp	−0.06295	1.02232	−0.062	0.951
Delta Body Temp	0.4775	1.8636	0.256	0.799
Temperature Corrected Delta PaO2	0.06753	0.41247	0.164	0.871
Temperature Corrected Delta PaCO2	4.106	2.164	1.897	0.0682

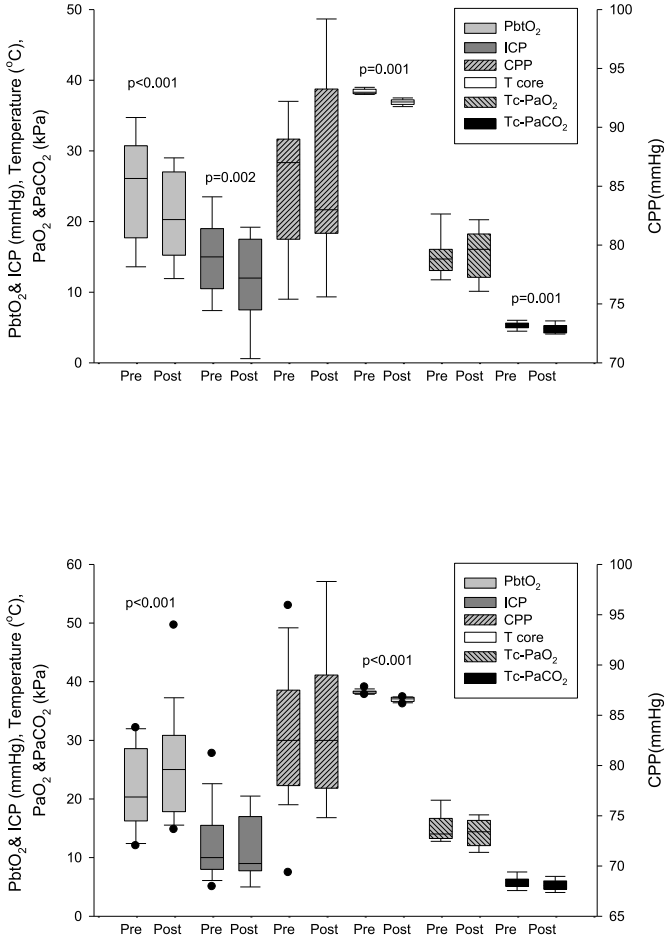

Fig. 3. Changes in pre and post cooling to normothermia for $PbtO_2$, ICP, CPP, core temperature (T core) and temperature corrected PaO_2 (Tc-PaO_2) and $PaCO_2$ (Tc-$PaCO_2$). Upper panel - the subgroup of patients in which there was a fall in $PbtO_2$. Lower panel - the subgroup of patients in which there was an increase in $PbtO_2$.

study aimed to describe the physiological changes that might affect cerebral perfusion on induction of TTM. We found that overall TTM was associated with a fall in ICP. However, the response of PbtO2 was variable and the reduction in ICP limited to the subgroup of patients in which PbtO2 fell. In this subgroup which uncorrected $PaCO_2$ was unchanged, there was a significant in temperature corrected $PaCO_2$ (pH Stat). Taken together this would suggest that cerebral vasoconstriction due to a reduction in true $PaCO_2$ could be reducing CBF, ICP and also $PbtO_2$.

4.1. TTM to normothermia analysis

Using a 4-point definition of the transition from fever to stable normothermia we were able to objectively identify 39 transitions from fever to normothermia. Patients identified as receiving TTM were broadly similar to the non TTM group. Pre-intubation GCS was higher in the TTM group and a significantly greater proportion of patients undergoing TTM had had a craniotomy. With the onset of cooling there were significant changes in both T_{brain} and T_{core}, along with a significant reduction in ICP. Temperature corrected $PaCO_2$ fell significantly but this was not seen for uncorrected PaO_2 and $PaCO_2$ or temperature corrected PaO_2.

The effect of hypothermia in reducing ICP is well recognised (Flynn et al., 2015; Shiozaki et al., 1993; Andrews et al., 2015b). That a small change in T_{core} of 1.4 (0.5) ^{o}C can lower ICP significantly, in a relatively small study sample, is interesting. This is likely to be one reason for continued interest in temperature-based therapies.

Historically much of the interest in the control of ICP is to maintain cerebral perfusion, and with that brain oxygenation. However, this is an indirect way of inferring that brain oxygenation is adequate when direct measurement of brain oxygen tension is available. It has been shown that significant hypoxia can be present despite attainment of guideline values of ICP and CPP (Stiefel et al., 2006; Rhodes et al., 2016a). The management of brain oxygen tension requires the optimisation of multiple parameters, including CPP, ICP, PaO_2 and $PaCO_2$. This is reflected in our own management algorithm for these patients (Rhodes et al., 2016b). The optimal brain oxygen tension and how best to achieve this have not been defined yet.

Unfortunately, the appreciation and management of patients based on $PbtO_2$ is rather more complex than that for ICP alone. $PbtO_2$ reflects both cerebral blood flow and diffusion of oxygen into the brain (Rosenthal et al., 2008). Diffusion limitation may result in significant and persistent cellular hypoxia despite optimisation of cerebral oxygenation at a macrovascular level (Sekhon et al., 2020, 2021; Veenith et al., 2016). Despite the potential challenges of diffusion limitation, this is not an argument for failing to optimize oxygen delivery, with persisting hypoxia/ischaemia at the large cerebral vessels. This would only exacerbate tissue hypoxia in the face of diffusion limitation.

That said, our study use $PbtO_2$ as a surrogate marker of cerebral blood flow (Rosenthal et al., 2008). Our clinical experience and formal study have shown that cooling can be associated, in some patients, with a reduction in $PbtO_2$ (Flynn et al., 2015). In this study the response of $PbtO_2$ to TTM was highly variable, falling in 18 and increasing in 21. One potential contributor to a fall in $PbtO_2$ with TTM is the effect of cooling on the solubility of gases in solution, which reduces the tension of both PaO_2 and $PaCO_2$ in vivo (Bacher, 2005). This is not obvious in practice as clinical blood gas analysis is conducted at 37 °C. In our data a significant reduction in $PaCO_2$ was only seen with temperature correction. Such a reduction in temperature corrected true $PaCO_2$ could be thought of as "hyperventilation by stealth", leading to hypocapnia-induced vasoconstriction (Yoon et al., 2012; Marín-Caballos et al., 2005). This, together with a left shift in the oxygen haemoglobin dissociation curve caused by the reduction in temperature, might reduce the tissue availability of oxygen in the brain, which may be reflected in the reduction of $PbtO_2$ (Flynn et al., 2015). The importance of temperature corrected $PaCO_2$ on cerebral haemodynamics is supported by our observation that a fall in $PaCO_2$ was only seen after temperature correction and the strength of the relationship between $\Delta PaCO_2$ and ΔICP was greater for temperature corrected $PaCO_2$ than for uncorrected $PaCO_2$, and only significant for the former. However, overall, only moderate correlations between $\Delta PbtO_2$ vs. $PaCO_2$ and $\Delta PbtO_2$ vs. temperature corrected $PaCO_2$ were seen, and whilst univariate logistic regression suggested clinically important effect coefficients, these did not quite reach significance.

The hypothesis that consideration of temperature corrected $PaCO_2$ values revels important reductions in $PaCO_2$ with cooling, sufficient to

Table 4
Sensitivity analysis for the subgroup in which $PbtO_2$ fell with cooling (Upper panel) and this in those in which $PbtO_2$ increased (Lower panel). Comparison of the 8 h average pre and post values for $PbtO_2$, ICP, CPP and arterial gas tensions, with and without temperature correction. *p < 0.001, confirmatory analysis only.

PbtO2 Falls	Pre		Post		Difference		p
	Average	SD or (IQR)	Average	SD or (IQR)	Average	SD or (IQR)	
PbtO2 (mmHg)	24.4	9.3	20.8	7.6	−3.7	2.9	*
ICP (mmHg)	15.0	(10.8–18.5)	12.0	(7.8–17.3)	−5.0	(-5.0 to −1.0)	**0.002**
CPP (mmHg)	84.8	5.8	87.0	9.3	2.3	7.9	0.254
PaO2 (kPa)	14.2	2.9	15.7	3.5	1.4	3.1	0.091
PaCO2 (kPa)	5.1	(4.7–5.3)	4.8	(4.3–5.2)	−0.2	(-0.5 to 0.1)	0.211
Brain Temp (°C)	39.4	0.9	38.3	0.7	−1.1	1.1	**0.001**
Body Temp (°C)	38.4	0.3	36.9	0.4	−1.6	0.6	**0.001**
Corrected PaO2 (kPa)	15.1	3.1	15.6	3.6	0.4	3.1	0.632
Corrected PaCO2 (kPa)	5.3	0.5	4.9	0.8	−0.5	0.5	**0.001**
PbtO2 Rose	Pre		Post		Difference		p
	Average	SD or (IQR)	Average	SD or (IQR)	Average	SD or (IQR)	
PbtO2 (mmHg)	20.3	(16.3–28.2)	25.0	(18.3–30.7)	3.1	(1.0–4.5)	*
ICP (mmHg)	12.0	6	12.1	5.9	−0.2	3.1	0.82
CPP (mmHg)	82.6	6.7	84.2	8.2	1.9	6.9	0.264
PaO2 (kPa)	14.3	2.5	14.3	2.5	0.2	2.3	0.732
PaCO2 (kPa)	5.4	1	5.4	0.9	0.2	0.5	0.22
Brain Temp (°C)	39.3	0.4	38.5	0.9	−0.8	0.8	<**0.001**
Body Temp (°C)	38.3	0.3	37.0	0.4	−1.3	0.5	<**0.001**
Corrected PaO2 (kPa)	15.2	2.8	14.3	2.4	−0.6	2.3	0.3
Corrected PaCO2 (kPa)	5.8	1.1	5.4	1	−0.2	0.5	0.269

reduced CBF, ICP and explain the drop in $PbtO_2$, is supported by our pre specified analysis. In this, the data for the TTM regions of interest was split by those in which $PbtO_2$ fell and those in which it rose. In the $PbtO_2$ falls subgroup there was a significant reduction in both ICP and temperature corrected $PaCO_2$ but not uncorrected $PaCO_2$. However, in the other group, in which $PbtO_2$ actually increased significantly, there was no change in ICP, or arterial gas tensions, even after temperature correction. The increase in $PbtO_2$ might be explained by a reduction in cerebral metabolic rate with cooling.

Taken together this work suggests two important ideas that warrant further investigation. Firstly, that the effects of even moderate cooling on cerebral physiology are not the same for all patients. The application of most therapeutic options in medicine are a balance of benefits and risks. The benefits we hope for with cooling are many and animal models suggest these include the reduction in cerebral metabolic demand, the inhibition of the inflammatory process, reduction in excitatory amino acids and reactive oxygen species, with reduced oedema, tissue injury and evidence of better outcomes on neuropsychological testing (Sinclair and Andrews, 2010). However, a reduction of cerebral blood flow sufficient to compromise cerebral oxygenation could represent a significant harm, offsetting any potential benefit. It is therefore possible that cooling therapies are not suited to all patients. In a secondary analysis of the Eurotherm 3235 trial of early hypothermia to control ICP, the greatest harm of cooling was seen in those patients with the least severe injuries (Andrews et al., 2017). One explanation is that in the least severely injured the benefits of cooling were outweighed by the risks. Secondly, it may be important to recognise that current cooling protocols are overly simplistic. Simply cooling to a predefined target temperature for a certain period of time, is not precise enough. Rather cooling measures might deliver better results if patients are better monitored to detect any harmful physiological consequences. Furthermore, greater consideration for the effect of cooling on $PaCO_2$ and correction of ventilation to avoid unintended “hyperventilation” could be important (Higgins, 2016).

4.2. Strengths and weaknesses

A major strength of this study was the use of continuously collected multimodality data. The 4 point definition of the transition from fever to controlled normothermia allowed the unbiased identification of regions of interest. However, as a retrospective study, there were issues with loss of data, particular the identification of exactly in whom and when TTM was started. This in fact mandated the 4 point definition. It is possible that this definition was overly sensitive and yielded some regions of interest in which TTM had not be applied. We feel that this is unlikely. Review of the records of the 63 patients in whom temperature transition to normothermia was not identified revealed documentary evidence of the use of TTM in 16. It is also possible that some of the regions of interest we identified occurred spontaneously, rather than as the result of TTM. Nevertheless, if this were the case, the changes in T_{core} were still real. Therefore, the physiological insights are still relevant. However, the choice of an 8-h period of fever and stable normothermia, in the definition of a region of interest, was made to reduce the chance of regions of interest occurring spontaneously. Therefore, we feel this is also unlikely.

The quality of data collected was also variable. A major weakness we faced was that arterial blood gas data was not available in some cases. There was also a lack of control over the timing of blood gas samples around the transition to TTM. Taken together these might explain weakness of the logistic regression results for $PbtO_2$ vs. temperature corrected $PaCO_2$. Details of respiratory parameters data such as changes in minute ventilation or PaO_2: Fraction inspired oxygen ratio pre and post colling were also missing from our analysis. These might have reviled some changes suggesting a different cause for the changes in $PbtO_2$ and temperature corrected $PaCO_2$ described. However, as neither PaO_2 nor $PaCO_2$ changed over all or in the subgroup analysis, we feel this is less likely.

Another limitation was that T_{core} was measured, recorded and transcribed manually and therefore was susceptible to transcriptional error. However, brain temperature was recorded continuously and automatically. Although an offset between brain and body temperature was seen the pattern of the brain temperature data with time served to reinforce the validity of the regions of interest identified.

Finally, this study essentially measured subgroups and therefore is subject to the risk of false positive reporting inherent in this design. None the less the changes in the variables reported are those that could be expected to contribute to $PbtO_2$ control, rather than random associations of unrelated factors. In other words, our results are consistent with our current understanding or cerebrovascular physiology and indeed clinical practice. Furthermore, as TTM to normothermia is a

widely practiced management strategy with no proof of efficacy we feel it is important to maintain awareness that refinement of the method and further research is essential to avoid harm hidden harm.

This is a hypothesis generating study, and as such a more robust prospective study would be required to confirm its results on the effects of TTM to normothermia on TBI patients' physiology. A prospective study with active data collection would address many of the issues faced. The effect of correction of pH-Stat $PaCO_2$ could be studied in a cross over design of adult patients with TBI. Similar small studies of the effect of pH-Stat vs. alpha-Stat in stroke and children with TBI, treated with hypothermia, have been published (Kollmar et al., 2009; Schibler and Humphreys, 2012). The safety and efficacy of TTM to normothermia to improve outcomes remains unproven. Mechanistic studies will ultimately support the development of high-quality clinical trials in this area.

5. Conclusions

Overall cooling to normothermia is associated with a reduction in ICP. However, in the prespecified subgroup analysis this was only seen in the patients in which temperature corrected $PaCO_2$ fell. Similarly, a reduction in $P_{bt}O_2$ with cooling was also only seen in patients in which temperature corrected $PaCO_2$ was reduced. This would suggest that even modest temperature changes, as practiced in TTM, could result in occult hyperventilation for some patients, the reduction in true $PaCO_2$ reducing cerebral blood flow and $PbtO_2$. pH-Stat correction of ventilation may be an important factor to consider in future TTM protocols.

Competing interests statement

JR is a member of the Integra Codman speakers bureaux and has received fees from BD for consultation and educational talks. JR is supported by an NHS Scotland Research Fellowship. TA, AR and NC-P have no competing interests to declare.

Authorship

Concept and design - JR, TA &NC-P, acquisition of data - JR NC-P, analysis and interpretation - JR, TA, AR &NC-P, drafting and revisions - NC-P & JR, final approval - JR, TA, AR &NC-P.

Declaration of competing interest

Jonathan Rhodes is a member of the Integra Codman speakers' bureaux and has received fees from BD for consultation and educational talks. He is also supported by an NHS Scotland Research Fellowship. Tom Anderson, Aryelly Rodriguez and Nika Cujkevic-Plecko have no competing interests to declare.

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