Brain Temperature Influences Intracranial Pressure and Cerebral Perfusion Pressure After Traumatic Brain Injury: A CENTER TBI Study

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Research

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Abstract

Background

After Traumatic Brain Injury (TBI) fever is frequent. Brain temperature, which is directly linked to body temperature, may influence brain physiology. Increased body and/or brain temperature may cause secondary brain damage, with deleterious effects on intracranial pressure (ICP), cerebral perfusion pressure (CPP) and outcome.

Methods

CENTER-TBI, a prospective, multicenter, longitudinal study on TBI in Europe and Israel, includes a high resolution (HR) cohort of patients with data sampled at high-frequency (from 100 Hz to 500 Hz). In this study, simultaneous BT, ICP and CPP recordings were investigated. A mixed effects linear model was used to examine the association between different BT levels and ICP. We additionally focused on changes of ICP and CPP during the episodes of BT changes (delta BT ≥ 0.5 °C, lasting from 15 minutes to 3 hours) up or down-wards. The significance of ICP and CPP variations was estimated with the paired samples Wilcoxon test.

Results

Twenty-one patients with 2435 hours of simultaneous BT and ICP monitoring were studied. All patients reached a BT of 38° and experienced at least one episode of ICP above 20 mmHg.

The linear mixed effects model revealed an association between BT above 37.5°C and higher ICP levels that was not confirmed for lower BT.

We identified 149 episodes of BT changes. During BT elevations (n=79) ICP increased while CPP was reduced; opposite ICP and CPP variations occurred during episodes of BT reduction (n=70). All these changes were of moderate clinical relevance, even if statistically significant (p<0.0001). It has to be noted, however, that a number of therapeutic interventions against intracranial hypertension was documented during those episodes.

Conclusion

Patients after TBI usually develop BT> 38° soon after the injury. Brain temperature may influence brain physiology, as reflected by ICP and CPP. An association between BT exceeding 37.5°C and a higher ICP was identified. The relationship between BT, ICP and CPP become clearer during rapid temperature changes.

Trial registration: The core study was registered with ClinicalTrials.gov, number NCT02210221, registered on July 29, 2014

Introduction
The injured brain is extremely sensitive and vulnerable to body temperature changes [1, 2]. An increase in temperature leads to an increase in cerebral metabolism, with augmented cerebral blood flow (CBF), and a concurrent increase in cerebral blood volume (CBV). If the compensatory mechanisms are exhausted, this high CBV [3] may raise intracranial pressure (ICP) [4]. In an experimental model of brain contusion, hyperthermia (39 °C for 3 hours) caused enlargement of the contusion volume and had a negative effect on outcome [5].

High body temperature can also worsen the cerebral ischemia. In experimental models of brain ischemia hyperthermia increased the release of glutamate [6] and the extent of tissue damage [7]. Even though traumatic brain injury (TBI) is a different pathology from acute ischemic stroke, there is evidence [8] that abnormalities in flow-metabolism coupling and areas of true ischemia are fairly common in TBI patients. Most moderate and severe TBI patients experience hyperthermia during their ICU stay [9, 10, 11] and are therefore exposed to the deleterious effects of increased temperature on ICP, brain metabolism and the risk of ischemia.

A substantial proportion of experimental and clinical evidence on the interplay between hyperthermia and the brain is based on temperature measured outside the brain, either with sensors measuring temperature in the bladder [12, 13, 14], rectum [12, 13, 15, 16, 17], esophagus [12], pulmonary artery [13, 18] and jugular vein [15] - which are collectively indicated as core temperature (CT), or placed externally (axillary [13], and tympanic [12] temperatures).

Unfortunately, temperatures measured outside the brain may markedly underestimate the brain temperature (BT), especially when it rises [18]. The mean difference between brain and core temperature is 0.3–0.4 °C, but it may be significantly higher during the development of pyrexia - up to 2.6 °C, depending on several factors [15, 18, 19, 20, 21]. Nevertheless direct BT monitoring in patients with brain injuries is rarely used [22].

We consulted a centralized data collection covering several centers in Europe [23] to obtain information on simultaneously monitored BT and ICP. The aims of this study were:

- To provide a general description of BT, ICP and cerebral perfusion pressure (CPP) in a limited sample of TBI patients;
- To clarify the relationships between BT, ICP and CPP during acute BT changes.

**Methods**

**Patient population**

Out of the 2138 ICU patients in the CENTER-TBI data collection, a sub-group of 277 patients had high-frequency digital signals from ICU monitoring (full waveform resolution at sampling frequencies at least 100 Hz, provided by the patient monitors) and was named “High Resolution CENTER TBI substudy” (HR CENTER-TBI). These patients were enrolled in 21 centers from January 2015 to December 2017, and treated in accordance with current evidence-based guidelines for TBI [24, 25]. In total 102 patients from this cohort
had simultaneous temperature and ICP monitoring; BT was monitored in 22 of them. Hypothermia was induced in one patient and continued throughout the whole HR-monitoring. Our analysis therefore includes 21 patients, in whom ICP was measured through parenchymal probes.

Data collection in the CENTER-TBI study adhered to ethical standards; medical ethical committees of all participating centers approved the study. Informed consent was obtained in accordance with local regulations [23].

Data collection and processing

Data was collected using ICM+ software (Cambridge Enterprise Ltd., Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk) or Moberg CNS Monitor (Moberg Research Inc, Ambler, PA, USA, https://www.moberg.com), or both. Arterial blood pressure (ABP) was obtained through arterial lines connected to pressure transducers. ICP was acquired from an intra-parenchymal strain gauge probe (Codman ICP MicroSensor; Codman & Shurtleff Inc., Raynham, MA) or parenchymal fiber optic pressure sensor (Camino ICP Monitor, Integra Life Sciences, Plainsboro, NJ, United States; https://www.integralife.com/). Brain temperature was measured through invasive parenchymal monitoring (Licox probe; Integra, Licox Brain Oxygen Monitoring System, Plainboro, NJ), usually placed in the frontal lobe. Signal processing was done with ICM+ software. Signal artefacts were removed partially automatically and partially manually. The whole process of HR CENTER-TBI signal acquisition and data processing is described in previous publications [26, 27]. Since none of the included patients had an induced hypothermia, BT lower than 36.0°C was excluded from the final analysis.

Parallel to the digital HR monitoring information on specific therapeutic interventions (such as osmotherapy, changes in sedation, suctioning, etc.) was recorded and synchronized to the corresponding monitored variables using ICM+. Interventions and their timing were subsequently extracted using HDFView Software (The HDF5 Group, https://www.hdfgroup.org) and analyzed. CT (with the probe located in rectum, bladder, esophagus, tympanum and nasopharynx) and epidemiological data were accessed using a bespoke data management tool, ‘Neurobot’ (http://neurobot.incf.org; RRID: SCR_01700), vs 2.1. Analysis was done using the files available in July 2019.

Statistical analysis

Data are summarized as mean and standard deviation (SD) or as median and interquartile range (IQR). For the general description of BT, ICP and CPP colored maps were plotted (with per-minute data presented on a color scale) for the first seven days of HR monitoring. Only simultaneous recordings of ICP and BT were analyzed, and missing values were excluded from the analysis.

CT was recorded daily by the investigators as the maximum and lowest temperature measured during a 24 hours interval. For this analysis the maximum CT was compared with the highest BT recorded during the corresponding monitoring day.

To examine the relations between absolute values of six BT ranges (<36.4; 36.5–36.9; 37–37.4; 37.5–37.9; 38–38.4; >38.5) and ICP we used a generalized mixed effects linear model, with a random intercept per
patient (that accounts for the repeated measurements in single patients). For the model the per minute values of BT and ICP were used. To correct for potential confounders, the mixed model was adjusted for TBI severity, using post-stabilization motor GCS ratings and pupil response [28]. For every BT group the previous BT level was used as a reference group. P-values were extracted to determine the significance of differences between ICP and BT groups. The figure was plotted using BT < 36.4 as the reference group.

To assess the effects on ICP and CPP of BT changes over time, episodes of BT elevation and reduction were manually selected according to the following criteria: elevations or reductions of at least 0.5 °C lasting from 15 minutes to 3 hours. A maximum of five episodes was identified in each patient. BT elevation and reduction episodes were analyzed separately.

To assess the significance of ICP and CPP changes in response to BT, the baseline and end-episode ICP and CPP within an episode were compared using the paired samples Wilcoxon test. A p-value < 0.05 was considered significant. ICP over 20 mmHg was defined as high ICP (hICP), and CPP below 60 mmHg was used as an indicator of low cerebral perfusion.

All statistical analysis was done using R (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

## Results

### Patients’ characteristics and monitoring

The study comprised 21 patients from four centers with simultaneous BT and ICP HR monitoring. Details of their baseline characteristics are given in Table 1. There were 18 males with median age 50 years (IQR 36–55). Monitoring was established within two days after ICU admission; a total of 3483 monitoring hours (median per patient 123; IQR 84–214 hours) were analysed. The final analysis included 2435 hours of monitoring (after excluding missing values) with simultaneous ICP and BT measurements.

Twenty out of 21 patients had daily maximum core temperatures recorded, for a total of 93 ICU days during which both BT and CT were measured.

### BT, ICP and CPP

The median BT for all the patients was 37.6 °C (IQR 37.3–37.9) with the lowest value of 36.0 °C reached in five patients, and the highest – 39.7 °C – in one. All patients reached a BT of 38 °C or higher during the monitoring. BT varied widely among the patients. Figure 1-A presents the BT color map during the first week of monitoring. BT maximum daily values of 38 °C or higher were observed during 65 days of matched (BT and CT) monitoring (70%). CT maximum daily temperatures exceeded that threshold only in 46 days of matched recording (49%).

Median ICP was 13 mmHg (IQR 11–20). During approximately a third of monitoring time (31%) ICP was > 20 mmHg. All patients experienced at least one episode of hICP (Fig. 1-B). Median mABP was 93 mmHg
IQR 87–104). Median CPP was 83 mmHg (IQR 79–86). All patients suffered episodes of CPP < 60 mmHg (Fig. 1-C); these episodes were short-lasting with only 5% of CPP recording time under the threshold.

The linear mixed effects model examined the interplay between six ranges of BT and ICP (Fig. 2). BT above 37.5 °C were associated with significantly higher ICP (p < 0.001). For lower BT (< 36.4 °C and 36.5–36.9 °C) this association was not confirmed.

**BT elevation/reduction analysis**

We identified 149 episodes of BT changes (at least 0.5 °C): 79 elevations and 70 reductions (Fig. 3). The total duration of all the selected episodes was 321 hours (13% of HR monitoring included in the current analysis).

Figure 4 describes ICP patterns during BT elevation (panel A) or reduction (panel B). The median BT elevation was 0.67 °C (IQR 0.57–0.9) and the median delta ICP 4.5 mmHg (IQR 0.7–7.1) (p < 0.0001). BT reached > 38 °C in 40 episodes (51%), and hICP was observed in 33 cases (42%). During these BT increases, mABP remained constant and consequently CPP decreased, with a median difference of 7.5 mmHg (IQR 0.9–13.6); this change was significant (p < 0.0001). During 44 episodes of BT elevation, 128 active therapeutic interventions were recorded (Table 2).

Starting from a median baseline BT of 38 °C (IQR 37.7–38.4), in the 70 episodes of BT reduction there was a median decrease of 0.67 °C (IQR 0.58–0.81). ICP decreased as well, with a median reduction of 1.7 mmHg (IQR 1.22; 6.03) (p < 0.001) (Fig. 4). Mean ABP remained constant and was accompanied by a significant (p < 0.005) but not clinically relevant increase of CPP (delta CPP 3.7 mmHg; IQR 1.96-9.8). During 41 episodes of BT reduction, 106 interventions were recorded (Table 2).

**Discussion**

Hyperthermia is a well-documented cause of secondary brain damage [4] after traumatic, ischemic and hemorrhagic injuries [10, 29, 30, 31]. Most studies have monitored body temperature, by either external or internal probes. However, to understand brain physiology better, direct information on BT would be of great interest, even if it requires an invasive approach [32]. To our knowledge this is the first study to use continuous high-frequency simultaneous monitoring of BT and ICP in TBI patients.

The first aim was to describe the behavior of BT, ICP and CPP and their interactions in a selected sample of patients during the first week after injury. BT showed a range of changes (Fig. 1A). All patients experienced BT higher than 38 °C, which is consistent with previous data [9, 18, 21].

Intermittent daily CT recording provided, as expected, less information on the occurrence of hyperthermia than the more granular documentation offered by High Resolution. While, according to CT maximal daily values, hyperthermia was disclosed during 46 days, a pathological BT was measured in 65 days. This finding indicate that CT may underestimate the severity of hyperthermia, as reported previously [18].
Concomitantly, ICP was generally well controlled, as reflected by a median of 13 mmHg (IQR 11–20). However, ICP fluctuated, so each patient suffered some hICP episodes and some low CPP (< 60 mmHg).

The generalized linear mixed model gave a biphasic pattern, tending toward higher ICP with BT above 37.5 °C and the opposite below BT of 37 °C (Fig. 2). One possible explanation is that BT below 37 °C depends on active manipulations, generally those used to control pathologically high ICP. Even though the physiological range of BT has not been established yet, current evidence suggests that it should be higher than 37 °C, the normal body temperature [33]. In fact, BT was generally higher than body temperature in all papers [16, 17, 18, 19, 20] but one [14]. BT below this level are not physiological, and may well depend on active treatment (i.e. intentional moderate cooling) or may be a side effect of other therapies (deep sedation, myorelaxants etc.) generally used to treat hICP. Bearing these considerations in mind, we separated Fig. 2 into two areas, showing in grey the part where we suspect the effect of treatment.

Focusing on the ICP increase with BT over 37 °C, our data partially contrast with some previous reports. Four studies [18, 19, 21, 34] found no consistent relationship between BT and ICP, when monitoring data were pooled and analyzed. However, the pattern we describe was found in one report of 87 patients, and in another series in which ICP was studied as a function of body rather than brain temperature [11].

The second aim of this study was to elucidate the impact of rapid BT changes (from 15 minutes to 3 hours) on ICP and CPP. We explored 149 episodes of significant BT changes (more than 0.5 °C), and found that both ICP and CPP deteriorated when BT rose. ICP and CPP changes were significant (p < 0.0001) but, more importantly, they were clinically relevant, with a median ICP increase of 4.5 mmHg, that crossed the threshold of 20 mmHg by the end of 40% of episodes. During these episodes active treatment for intracranial hypertension was provided, including osmotherapy and sedative and vasoactive drugs, documented by the total of 128 interventions during 44 BT elevation episodes (Table 2). It is therefore plausible to consider that therapy mitigated the actual ICP and CPP deteriorations caused by the rise in BT. In the absence of treatment more severe ICP and CPP alterations could well result from BT increases.

Reductions of BT were studied in 70 episodes. These events too affected ICP and CPP, reducing them both slightly but significantly.

Three previous studies looked into the relationship between ICP and rapid BT changes. Two studies from our group [9, 18] suggested an association, but this was not confirmed by Hushak et al. [21]. In clinical practice it is a common observation at the bedside that ICP can worsen during the development of fever and a recent consensus statement on TBI management suggested the correction of hyperthermia as one of the first steps for ICP control [35].

Our analysis has limitations: first, it involved a limited number of patients in few centers. Generalization of our results, therefore, would call for a larger cohort. Second, the physiopathological hypothesis linking BT to ICP and CPP is based on changes in cerebral metabolism, blood flow and content, as suggested in the Introduction. Since we did not measure these variables, our interpretation of the findings has to be considered speculative. Moreover, our study lacks the data on temperature treatments; that makes the conclusion about the natural physiological behavior of BT and ICP more complicated. Finally, our data set
did not include simultaneous and continuous recording of CT and BT, which could be extremely informative; consequently our comparison of CT and BT was restricted to a limited data set.

**Conclusion**

BT can be monitored in TBI patients during their ICU course and tends to vary widely, with frequent significant hyperthermia (BT > 38 °C). A general analysis indicates that BT exceeding 37 °C seems to involve a concomitant rise in ICP. The relationships between BT, ICP and CPP become clearer during rapid temperature changes. During episodes of hyperthermia, BT seems to have a significant impact on both ICP and CPP, despite active treatment to prevent intracranial hypertension. A similar impact, but less severe, is seen when temperature decreases.

**Abbreviations**

ICU: Intensive care unit; HR: High resolution; TBI: Traumatic brain injury; ABP: Arterial blood pressure; mABP: Mean arterial blood pressure; ICP: Intracranial pressure; CPP: Cerebral perfusion pressure; BT: Brain temperature; GSD: Standard deviation; IQR: interquartile range; hICP: High ICP; GCS: Glasgow coma scale; GOSe: Glasgow outcome scale extended; ER: emergency room

**Declarations**

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Authors’ contributions

FO, PS, MC and TZ collected the patient’s data. TB, FO, EW analyzed the data and drafted the tables and figures. TB and NS interpreted the data and drafted the manuscript. TB, FO and NS designed the study protocol, NS supervised the study. RH, SR, YS, MC, TZ and BI were involved in regular meetings on the manuscript and reviewed the manuscript multiple times. All authors were involved in the design of the CENTER-TBI study and reviewed and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available via https://www.center-tbi.eu/data on reasonable request.

Ethics approval and consent to participate

In each recruiting site ethical approval was given; an overview is available online [36]
Consent for publication

Not applicable

Competing interests

None

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Tables
| Age | Sex | GCS (after stabilization in the ER) | Pupils                  | Marshall classification | Decompression | Duration of simultaneous BT and ICP monitoring (hours) | GOSE at SIX months |
|-----|-----|-----------------------------------|-------------------------|-------------------------|---------------|------------------------------------------------------|-------------------|
| 23  | M   | 8                                 | Both reactive           | III                     | Yes           | 159                                                  | 6                 |
| 70  | M   | 10                                | Both reactive           | VI                      | Yes           | 28                                                   | 1                 |
| 31  | M   | 9                                 | *                       | VI                      | No            | 110                                                  | *                 |
| 25  | M   | 4                                 | Both reactive           | II                      | No            | 104                                                  | *                 |
| 53  | M   | 8                                 | *                       | *                       | Yes           | 19                                                   | 1                 |
| 17  | M   | 7                                 | Both reactive           | II                      | No            | 112                                                  | 7                 |
| 55  | M   | 15                                | Both reactive           | VI                      | No            | 81                                                   | 5                 |
| 48  | F   | 14                                | Both reactive           | II                      | No            | 77                                                   | 5                 |
| 50  | M   | 12                                | Both reactive           | I                       | No            | 263                                                  | 1                 |
| 32  | M   | 4                                 | Both reactive           | III                     | No            | 36                                                   | *                 |
| 71  | M   | 11                                | Both reactive           | III                     | No            | 138                                                  | 1                 |
| 46  | M   | 7                                 | One reactive            | *                       | No            | 352                                                  | 5                 |
| 37  | M   | 6                                 | *                       | VI                      | No            | 168                                                  | 1                 |
| 51  | M   | 3                                 | Both reactive           | VI                      | Yes           | 92                                                   | 5                 |
| 44  | M   | 8                                 | Both reactive           | *                       | Yes           | 51                                                   | 3                 |
| 69  | M   | 10                                | *                       | VI                      | No            | 58                                                   | 1                 |
| 66  | F   | 8                                 | Both unreactive         | *                       | No            | 88                                                   | 1                 |
| 55  | F   | 8                                 | Both reactive           | II                      | No            | 218                                                  | *                 |
| Age | Sex | GCS (after stabilization in the ER) | Pupils | Marshall classification | Decompression | Duration of simultaneous BT and ICP monitoring (hours) | GOSE at SIX months |
|-----|-----|-----------------------------------|--------|------------------------|---------------|--------------------------------------------------|-------------------|
| 36  | M   | 7                                 | Both reactive | VI                      | No            | 35                                               | 5                 |
| 50  | M   | 3                                 | Both reactive | VI                      | No            | 211                                              | 1                 |
| 69  | M   | 8                                 | Both reactive | II                      | No            | 35                                               | 5                 |

This table shows the patients’ main baseline characteristics. *missing data. GCS – Glasgow coma scale. ER – emergency room. HR – high resolution. GOSE – Glasgow outcome scale extended

### Table 2

Interventions recorded during HR monitoring

| Intervention  | HR monitoring | High BT episodes | Low BT episodes |
|---------------|---------------|------------------|-----------------|
| Fluids        | 35            | 8                | 3               |
| Osmotherapy   | 122           | 4                | 5               |
| Suctioning    | 450           | 33               | 20              |
| Physiotherapy | 571           | 24               | 31              |
| Sedatives     | 609           | 27               | 22              |
| Vasopressors  | 678           | 32               | 25              |
| **Total**     | **2465**      | **128**          | **106**         |

### Figures
Figure 1

(A, B, C). Brain temperature, intracranial pressure, cerebral perfusion pressure during the first seven days of monitoring. These color maps show every per-minute average, employing a color scale, grey indicating missing values.
Figure 2

Generalized linear mixed model effects on ICP of six brain temperature ranges. Generalized linear mixed model including intracranial pressure (ICP) (mmHg) as dependent variable (median with 95% CI) in six ranges of brain temperature (°C) as independent variable. BT <36.4 was taken as the reference group. The grey area indicates the values below the physiological brain temperature range, which are likely to depend on active treatment.
Figure 3

Brain temperature elevation/reduction episodes

Figure 4
ICP response to BT changes. ICP at the beginning and end of BT episodes. A) ICP during all the BT elevation episodes. B) ICP during all the BT reduction episodes. Colored points represent different patients; all measurements in the same patient are the same color. P values for paired samples, Wilcoxon test.