

The Effect of Temperature Increases on Brain Tissue Oxygen Tension in Patients with Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Substudy

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Fever may aggravate secondary brain injury after traumatic brain injury (TBI). The aim of this study was to identify episodes of temperature increases through visual plot analysis and algorithm supported detection, and to describe associated patterns of changes in on brain tissue oxygen tension ($P_{bt}O_2$). Data derive from the high-resolution cohort of the multicenter prospective Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study. Temperature increases ($\geq 0.5^\circ C$) were visually identified in 33 patients within the first 11 days of monitoring. Generalized estimating equations were used to detect significant changes of systemic and neuromonitoring parameters from baseline to the highest temperature. Patients were median 50 (interquartile range [IQR], 35–62) years old, and presented with a Glasgow Coma Scale (GCS) of 8 (IQR, 4–10). In 202 episodes of temperature increases, mean temperature rose by $1.0^\circ C \pm 0.5^\circ C$ within 4 hours. Overall, $P_{bt}O_2$ slightly increased ($\Delta P_{bt}O_2 = 0.9 \pm 6.1$ mmHg, $p = 0.022$) during temperature increases. $P_{bt}O_2$ increased in 35% ($p < 0.001$), was stable in 49% ($p = 0.852$), and decreased in 16% ($p < 0.001$) of episodes. During episodes of temperature increases and simultaneous drops in $P_{bt}O_2$, cerebral perfusion pressure (CPP) decreased ($\Delta CPP -6.3 \pm 11.5$ mmHg; $p < 0.001$). Brain tissue hypoxia ($P_{bt}O_2 < 20$ mmHg) developed during 27/164 (17%) episodes of effervescences, in the remaining 38/202 episodes baseline $P_{bt}O_2$ was already < 20 mmHg. Comparable results were found when using algorithm-supported detection of temperature increases. In conclusion, during effervescences, $P_{bt}O_2$ was mostly stable or slightly increased. A decrease of $P_{bt}O_2$ was observed in every sixth episode, where it was associated with a decrease in CPP. Our data highlight the need for special attention to CPP monitoring and maintenance during episodes of fever.

Keywords: traumatic brain injury, temperature increases, brain tissue oxygen tension, critical care, CENTER-TBI

Introduction

SEVERE TRAUMATIC BRAIN injury (TBI) is a devastating disease that is still associated with a considerable rate of morbidity and mortality despite tremendous improvements in the critical care management (Steyerberg *et al.*, 2019). Sys-

temic complications, including fever frequently occur in the early phase after trauma and likely exacerbate secondary brain injury (Walter *et al.*, 2016). Up to 50% of patients following acute brain injury develop fever within the hospitalization time (Kilpatrick *et al.*, 2000). While deleterious effects of fever and their association with unfavorable outcomes

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This multicenter study was performed at 21 European sites.

are well described (Greer *et al.*, 2008), underlying pathophysiologic mechanisms are still not fully elucidated. Fever is associated with multiple systemic and cerebral changes, such as an increased metabolic demand (Busija *et al.*, 1988; Holtzclaw, 1992), increased endogenous stress levels, alterations in blood pressure levels (Walter *et al.*, 2016), increases in cardiac output and heart rate (HR) (Bain *et al.*, 2014), hyperventilation, the synaptic release of excitatory amino acids (Stocchetti *et al.*, 2005), elevated intracerebral pressure (ICP) levels (Rossi *et al.*, 2001; Stocchetti *et al.*, 2005; Nyholm *et al.*, 2017), ischemic cortical depolarizations, and blood–brain barrier breakdown (Wang *et al.*, 2014).

Assessing brain tissue oxygen tension ($P_{bt}O_2$) along with other hemodynamically relevant factors during episodes of temperature increases may provide insight into changes in oxygen supply and consumption (Le Roux *et al.*, 2014). Most data investigating the influence of different temperature levels on cerebral oxygenation are derived from animal studies or from human studies in which mostly patients with hypothermia were studied (Tokutomi *et al.*, 2003; Zhi *et al.*, 2003; Flynn *et al.*, 2015). Some studies in humans (Stocchetti *et al.*, 2005; Spiotta *et al.*, 2008; Nyholm *et al.*, 2017) assessed the association between $P_{bt}O_2$ and fever and report no significant decrease of $P_{bt}O_2$ levels during fever. However, little is known how changes in body temperature (in particular increases) influence brain tissue oxygen tension, irrespective of the absolute temperature.

In this study, we aimed to quantify changes in $P_{bt}O_2$ during temperature increases in severe TBI patients and to explore simultaneous changes of hemodynamic parameters and the cerebral autoregulatory state (cerebral perfusion pressure, CPP; mean arterial pressure, MAP; HR; pressure reactivity index, PRx; oxygen reactivity index, ORx). Moreover, we intended to compare episodes of temperature increases identified through visual plot analysis and by algorithm-supported detection. Our primary hypothesis was that the rise in temperature carries the risk of brain tissue hypoxia, explained by hemodynamic changes.

Methods

Study population

In the intensive care unit (ICU) stratum of the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI, registered at clinicaltrials.gov NCT 02210221) core study, high-resolution data were collected in a subset of 277 patients admitted to 21 European centers. Of these, 102 patients were selected with reliable continuous temperature recordings. Thirty-three patients had additional monitoring of $P_{bt}O_2$ and were included in the final analysis. Patients were recruited from January 2015 until December 2017. These patients were admitted to the ICU following a moderate (initial Glasgow Coma Scale [GCS] 9–12) or severe (GCS ≤ 8) TBI. Few patients initially suffered from mild-to-moderate TBI but deteriorated early prompting ICU admission. Insertion of ICP probes confirmed to BTF (Brain Trauma Foundation) guidelines in all patients (Carney *et al.*, 2017). Therefore, a multimodal neuromonitoring bundle was only initiated in patients with severe TBI on admission or in those with neurologic deterioration. Data collection in the CENTER-TBI study adhered to ethical standards and the study was approved by the Medical Ethics Committees of all participating

centers. Informed consent was obtained in accordance with local regulations (Steyerberg *et al.*, 2019). The Austrian Ethics approval is given as an example (Medical University of Innsbruck, AN2014-0336 343/4.22). The list of ethics committee approvals of participating sites is online.*

Data collection and preprocessing

All demographic variables were prospectively collected and entered in an electronic case report form (Quesgen, Inc., Burlingame, CA) after interpretation by physicians and/or research assistants. Clinical data were collected on a daily basis: at ICU admission, during ICU stay (days 1–7, 10, 14, 21, 28), and at ICU discharge. Demographic variables were derived from the Core Registry (V2.0).

In the high-resolution CENTER-TBI substudy, high-frequency digital signals of vital parameters were recorded during the ICU stay. Arterial blood pressure (ABP) was most often measured through either radial or femoral arterial lines. ICP was obtained using an intraparenchymal probe (Codman ICP MicroSensor; Codman & Shurtleff, Inc., Raynham, MA), parenchymal fiberoptic pressure sensor (Camino ICP Monitor; Integra Life Sciences, Plainsboro, NJ) or, rarely, external ventricular drain. Signal processing was done using the ICM+ software (Cambridge Enterprise Ltd., Cambridge, United Kingdom).

Signal artifacts were removed partially through visual inspection and also using automated algorithmic methods. For ABP (0–300 mmHg) and ICP (0–100 mmHg) a primary filter was used. ABP data were removed if the pulsatility of ABP ($ABP_{max} - ABP_{min}$) within 1.5 seconds was <20 or >200 mmHg. HR was calculated with use of the fundamental frequency function within 10 seconds on the ABP signal (using the Fourier fast transformation) with a lower and upper limit of 40/min and 180/min. $P_{bt}O_2$ levels >60 or <0 mmHg and temperature levels $>45^\circ C$ or $<30^\circ C$ were considered implausible and therefore deleted. CPP was calculated as follows: MAP – ICP. Autoregulatory indices were calculated as previously described: PRx was calculated as a moving Pearson correlation between 30 consecutive 10-second averages of ICP and MAP, resulting in a moving 5-minute time window, increasing in 10-second steps (Czosnyka *et al.*, 1997). Similarly, ORx was calculated as a moving Pearson correlation between 120 consecutive 30-second averages of $P_{bt}O_2$ and CPP, resulting in a 1-hour moving time window (Jaeger *et al.*, 2006).

High-frequency data (MAP; HR; fraction of inspired oxygen, FiO_2 ; temperature; ICP; CPP; $P_{bt}O_2$; ORx; PRx) were averaged over 10 minutes.

Brain tissue hypoxia was defined as $P_{bt}O_2 <20$ mmHg, since this is the threshold prompting interventions according to current practices (Le Roux *et al.*, 2014).

Fever definitions

Temperature was either measured intracranially ($N=16$, 49%), external-axillary ($N=2$, 6%), by a bladder ($N=11$, 33%), or tympanic temperature sensor ($N=2$, 6%). In two patients (6%), temperature was derived from a mixed source. Fever was defined as temperature levels above $38.3^\circ C$, irrespective of the measurement site. Temperature levels were

*CENTER-TBI. Ethical approval. <https://www.center-tbi.eu/project/ethical-approval>

TABLE 1. DEMOGRAPHICS OF 33 PATIENTS

	N (%) or median (IQR)
Clinical characteristics on admission	
Age	50 (34–66)
Female sex	6 (18)
Marshall Score	3 (2–5)
GCS	8 (4–10)
GCS motor	3 (1–5)
Pupil reactivity	
Both reactive	28 (85)
Both unreactive	2 (6)
One unreactive	3 (9)
Preinjury ASA score	2 (1–3)
Injury severity score	27 (25–41)
Hospital complications	
Cranial surgery	18 (55)
Meningitis	0 (0)
Ventilator-associated pneumonia	18 (55)
Bloodstream infection	4 (12)
Urinary tract infection	8 (24)
Neuroworsening during ICU-stay	18 (55)
Progression on CT-scan	12 (36)
Outcomes	
GOSE at 6 months	
1	10 (30)
2	2 (18)
3	2 (6)
4	5 (15)
5	6 (18)
6	2 (6)
7	2 (6)

ASA, American Society of Anesthesiologists; CT, computed tomography; GCS, Glasgow Coma Scale; GOSE, Extended Glasgow Outcome Scale; ICU, intensive care unit; IQR, interquartile range.

further categorized using the following definitions: subfebrile 37.5–38.3°C, normothermia 36.5–37.5°C, low body temperature 35–36.5°C, and hypothermia 32–35°C.

Data analysis

There was no significant difference in temperature in the subset of patients with $P_{bt}O_2$ probes compared with all patients with temperature data, both following similar distributions. To minimize bias from a few longer monitoring sessions, periods of duration greater than 11 days were cropped at 11 days for the purpose of analysis. A clinically relevant episode of temperature increase (effervescence) was defined as an increase by $\geq 0.5^\circ\text{C}$ irrespective of a time limit or measurement site. These episodes were manually identified by data visualization. Episodes with changes in FiO_2 during temperature increases were excluded ($N=9$). Changes in vital and neuromonitoring parameters were expressed by calculating the difference between the baseline (defined by the lowest temperature level of each episode) and the highest temperature within each episode of temperature increase and reported as mean \pm standard deviation of the difference. $P_{bt}O_2$ changes were further categorized into decreasing, increasing, or stable by visual $P_{bt}O_2$ curve inspection. Based on the characteristics of the temperature curves of manually detected temperature increases, an algorithm-supported detection of temperature increases was developed with two prerequisites: (1) baseline temperature $>35^\circ\text{C}$ and (2) velocity of temperature increase $>0.0167^\circ\text{C}/10$ minutes $= 0.1^\circ\text{C}/\text{h}$ based on the lower quartile of manual detection. Applying this algorithm, additional characteristics of the assisted episode algorithm have been evaluated with different parameters: (1) $\geq 0.5^\circ\text{C}$ increase, (2) temperature

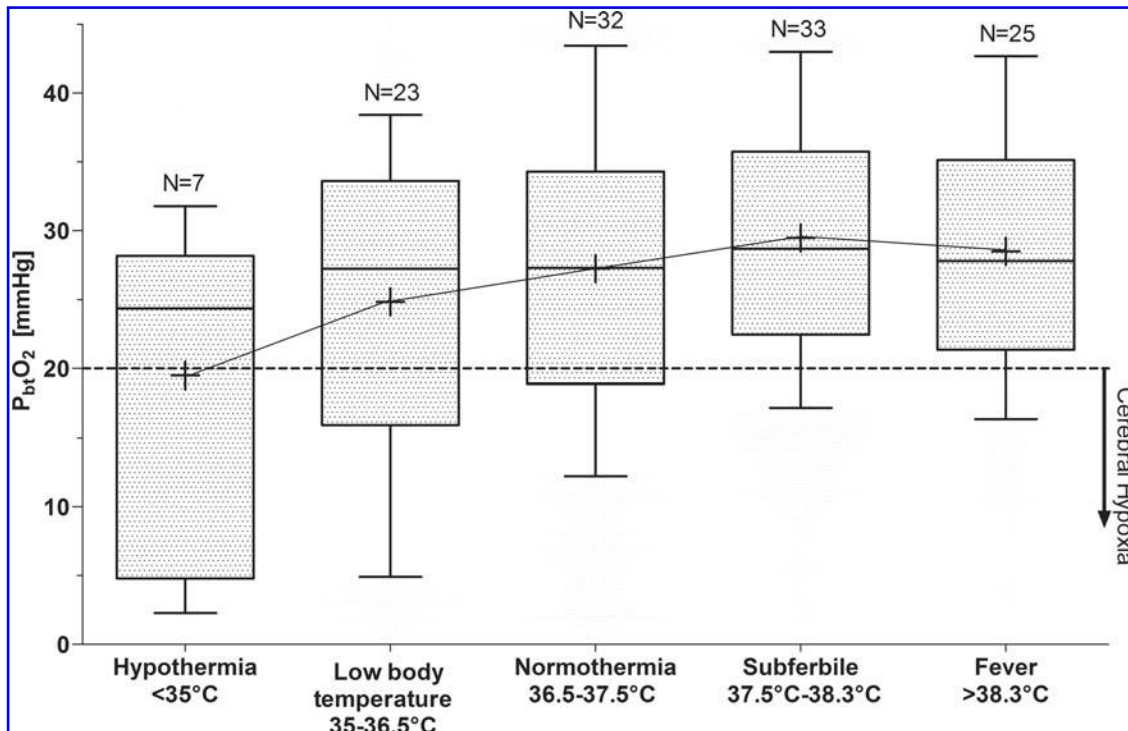


FIG. 1. Mean $P_{bt}O_2$ values were significantly higher at higher temperature levels ($p < 0.001$). $P_{bt}O_2$, brain tissue oxygen tension.

TABLE 2. CHANGES IN BRAIN TISSUE OXYGEN TENSION AND HEMODYNAMIC VARIABLES DURING TEMPERATURE INCREASES SPLITTING AT DIFFERENT PATTERNS OF BRAIN TISSUE OXYGEN TENSION CHANGES

	$P_{bt}O_2$ bl	$P_{bt}O_2$ peak	$\Delta P_{bt}O_2$	T bl	T peak	ΔT	CPP bl	CPP peak	Δ CPP	MAP bl	MAP peak	Δ MAP
$N=202$	27.7±10.1	28.6±10.2	0.9±6.1	36.9±0.8	37.9±0.7	1.0±0.5	80.1±16.8	76.1±14.9	-4.1±12.6	95.9±17.6	93.1±17.2	2.7±10.5
	OR=1.04; 95%-CI=1.01-1.07; $p=0.022$						OR=0.89; 95%-CI=0.83-0.95; $p=0.001$			OR=0.92; 95%-CI=0.87-0.97; $p=0.002$		
$P_{bt}O_2$ increase	26.6±9.8	32.3±8.8	5.7±4.4	36.9±0.8	37.9±0.8	1.0±0.4	79.7±16.8	77.4±16.1	-2.3±13.6	96.7±17.3	95.5±16.8	1.3±9.8
$N=71$	OR=1.22; 95%-CI=1.18-1.27; $p<0.001$						OR=0.88; 95%-CI=0.77-0.998 $p=0.046$			$p=0.106$		
$P_{bt}O_2$ stable	28.2±10.6	27.5±10.5	0.6±5.3	37.0±0.8	38.0±0.6	1.0±0.5	81.0±17.2	76.3±14.6	-4.7±12.2	96.4±17.8	93.7±16.9	-2.7±9.9
$N=98$	$p=0.852$						OR=0.91; 95%-CI=0.83-0.99; $p=0.028$			OR=0.92; 95%-CI=0.86-0.99; $p=0.022$		
$P_{bt}O_2$ decrease	28.7±9.4	23.6±9.7	-5.1±3.5	36.7±1.0	37.7±0.8	1.0±0.6	78.5±15.7	72.2±13.1	-6.3±11.5	92.2±17.8	86.1±17.4	-5.7±13.1
$N=33$	OR=0.78; 95%-CI=0.72-0.85; $p<0.001$						OR=0.72; 95%-CI=0.61-0.83; $p<0.001$			OR=0.72; 95%-CI=0.61-0.86; $p<0.001$		

Hemodynamic and neuromonitoring parameters are expressed as mean±standard deviation at baseline and highest temperature within each episode of temperature increase. Using generalized estimating equations, the significance of changes of each variable (Δ) within temperature increases was tested in univariate analysis. Significant changes ($p<0.05$) are bold.

bl, baseline; CI, confidence interval; CPP, cerebral perfusion pressure; HR, heart rate; ICP, intracerebral pressure; MAP, mean arterial pressure; OR, odds ratio; ORx, oxygen reactivity index; $P_{bt}O_2$, brain tissue oxygen tension; PRx, pressure reactivity index; T, temperature.

increases lasting >1 hour, and (3) temperature increases lasting >20 minutes.

The values were automatically processed for sets of given parameters. For imputation, the function “last observation carry forward” was used from the zoo package. This function replaces each missing value with the most recent nonmissing value before it (Zeileis and Grothendieck, 2005). Imputations were made in (1) 9/71 episodes of $\geq 0.5^\circ\text{C}$ increase, (2) 54/183 episodes of temperature increases lasting >1 hour, and (3) 171/532 episodes of temperature increases lasting >20 minutes.

Statistics

Statistical analysis of anonymized patient data was performed by L.H. who was not involved in data collection and who was blinded to the clinical course of all patients. For creation of the summary tables of each episode, the summary tools package was used (Dominic Comtois, 2019; summarytools: Tools to Quickly and Neatly Summarize Data, R package version 0.9.4).

$P_{bt}O_2$ changes ($\Delta P_{bt}O_2$), as well as changes of other vital and neuromonitoring parameters within temperature increases were tested in univariate analysis using generalized estimated equations with an autoregressive matrix to account for repeated measurements. Vital or neuromonitoring parameters at baseline or highest temperature points were compared across different $P_{bt}O_2$ characteristics using the t -test or Mann-Whitney U Test, as appropriate.

The analysis and visualizations were conducted using R version 3.6.0 (2019-04-26) and SPSS (version 24.0; IBM SPSS Statistics, Armonk, NY). The analysis was conducted under the consolidation of RMarkdown notebooks, which allowed the analysis code and representation in one document. RMarkdown allows a notebook interface to the analysis, which was especially useful with regard to changes of the data, layout refinement, plots, and discussion of the authors. Statistical significance was attributed to a p -value <0.05.

Results

Of 102 patients prospectively included in the high-resolution ICU cohort, 33 patients met the inclusion criteria for the current analysis. Baseline characteristics were not different between the study population and excluded patients

(age $p=0.202$, sex $p=1.000$, GCS at baseline $p=0.114$, GCS motor at baseline $p=0.377$). Detailed information on baseline characteristics, hospital complications, and outcomes of 33 patients is given in Table 1. In total, 3587 neuromonitoring hours (median per patient 86; interquartile range [IQR] 61–159 hours) with simultaneous $P_{bt}O_2$ and temperature measurements during the first 11 days of ICU stay were analyzed. Episodes of fever within the study time occurred in most patients (26/33, 79%) and were observed during 13% of monitoring time (471 hours). During episodes of fever, brain tissue hypoxia ($P_{bt}O_2 < 20$ mmHg) was found in 20% of measurements, which was comparable to the overall incidence of brain tissue hypoxia (25%) over the whole study period. Mean $P_{bt}O_2$ values were significantly higher at higher temperature levels (Kruskal-Wallis: $p<0.001$) (Fig. 1). In this line, there was a weak-positive correlation between higher temperature and higher $P_{bt}O_2$ levels ($\rho=0.11$; $p<0.01$).

Changes in $P_{bt}O_2$ and hemodynamic variables during temperature increases

Two hundred two episodes of clinically significant temperature increases ($\geq 0.5^\circ\text{C}$) were visually identified (Supplementary Fig. S1). Mean temperature increase was $1.0^\circ\text{C} \pm 0.5^\circ\text{C}$ from $36.9^\circ\text{C} \pm 0.8^\circ\text{C}$ to $37.9^\circ\text{C} \pm 0.7^\circ\text{C}$ within 4 hours resulting in a mean slope of $0.33 \pm 0.34^\circ\text{C/h}$ (median 0.22°C/h , IQR 0.16–0.35). Overall, $P_{bt}O_2$ slightly increased by 0.9 ± 6.1 mmHg ($p=0.022$) from baseline to temperature peak. Neither a higher Δ temperature nor higher rate of the temperature increase influenced the change of $\Delta P_{bt}O_2$ (Generalized linear model: $p=0.179$; $p=0.160$). Importantly, mean $P_{bt}O_2$ values were within normal range (≥ 20 mmHg) both at baseline and at the highest temperature of each episode, as shown in Table 2. Manual classification revealed clinically important patterns of $P_{bt}O_2$ changes within periods of temperature increase. $P_{bt}O_2$ increased in 35% ($\Delta P_{bt}O_2 = +5.7 \pm 4.4$ mmHg, $p<0.001$), did not change in 49% ($\Delta P_{bt}O_2 = -0.6 \pm 5.3$ mmHg, $p=0.852$), and decreased in 16% ($\Delta P_{bt}O_2 = -5.1 \pm 3.5$ mmHg, $p<0.001$) (Fig. 2) of episodes. During episodes with drops in $P_{bt}O_2$, brain tissue hypoxia was either evident at baseline (3/33, 9%) or developed during effervescence (30%, 9/30). In the overall cohort, baseline brain tissue hypoxia was found in 38/202 (19%) episodes. Of the remaining 164 episodes of effervescence

TABLE 2. (CONTINUED)

ICP bl	ICP peak	Δ ICP	HR bl	HR peak	Δ HR	PRx bl	PRx peak	Δ PRx	ORx bl	ORx peak	Δ ORx
15.7 \pm 11.6	17.3 \pm 12.7	1.7 \pm 9.7	75.7 \pm 17.2	80.9 \pm 17.4	5.1 \pm 9.6	0.11 \pm 0.33	0.13 \pm 0.38	0.01 \pm 0.39	0.23 \pm 0.36	0.25 \pm 0.35	0.02 \pm 0.41
OR=1.05; 95%-CI=1.00-1.11; p=0.039			OR=1.13; 95%-CI=1.08-1.18; p<0.001				<i>p</i> =0.476			<i>p</i> =0.721	
17.0 \pm 14.4	18.0 \pm 15.0	1.1 \pm 10.4	75.3 \pm 17.2	81.1 \pm 17.7	5.8 \pm 9.2	0.10 \pm 0.36	0.09 \pm 0.37	0.02 \pm 0.39	0.21 \pm 0.36	0.23 \pm 0.35	0.00 \pm 0.36
15.3 \pm 9.6	<i>p</i> =0.311	2.5 \pm 10.2	OR=1.17; 95%-CI=1.09-1.26; p<0.001			0.11 \pm 0.31	0.16 \pm 0.38	0.05 \pm 0.38	0.27 \pm 0.35	0.24 \pm 0.37	0.03 \pm 0.43
17.9 \pm 10.6	<i>p</i> =0.134		75.0 \pm 16.3	79.9 \pm 17.1	4.9 \pm 9.9		<i>p</i> =0.610			<i>p</i> =0.099	
13.8 \pm 9.7	14.1 \pm 12.9	0.2 \pm 5.2	78.8 \pm 19.7	83.2 \pm 18.2	4.4 \pm 9.5	0.15 \pm 0.34	0.12 \pm 0.37	0.02 \pm 0.39	0.17 \pm 0.37	0.35 \pm 0.29	0.18 \pm 0.45
	<i>p</i> =0.565		OR=1.21; 95%-CI=1.03-1.42; p=0.023				<i>p</i> =0.350		OR=1.01; 95%-CI=1.00-1.01; p=0.048		

where $P_{bt}O_{2baseline}$ was ≥ 20 mmHg, brain tissue hypoxia developed in 27/164 (17%) episodes. Persistent brain tissue hypoxia (not resolving until the peak of temperature increase) was seen in 15/164 (9%) episodes of temperature increases. Importantly, different $P_{bt}O_2$ patterns were observed within individual patients.

Descriptive analysis of important covariates reflecting the hemodynamic situation and autoregulatory state during temperature increases demonstrated an increase in HR ($p<0.001$), irrespective of $P_{bt}O_2$ characteristics. During temperature increases with drops in $P_{bt}O_2$, a decrease in CPP was more pronounced as compared with episodes when $P_{bt}O_2$ increased. During CPP decreases, drops in MAP ($p<0.001$), but not increases in ICP ($p=0.565$), were observed. Details are given in Table 2.

The autoregulatory status as assessed with the PRx was not different at baseline ($p=0.564$) or peak temperature ($p=0.826$) comparing episodes when $P_{bt}O_2$ decreased or increased and PRx did not change during effervescences (Table 2). In this line, the percentage of impaired autoregulation (PRx ≥ 0.2) was equally distributed among changes in $P_{bt}O_2$ ($P_{bt}O_2$ drops: baseline 36%, peak 35%; $P_{bt}O_2$ increases: baseline 36%, peak 38%).

Brain tissue hypoxia at baseline of effervescence was evident in 19% of episodes (38/202). When analyzing only these episodes, overall $P_{bt}O_2$ improved ($\Delta P_{bt}O_2 +5.0\pm 7.2$ mmHg, $p<0.001$). $P_{bt}O_2$ increased in 47%, did not change in 45%, and decreased in 8% of these episodes. CPP_{baseline} ($p<0.001$) and CPP_{peak} ($p=0.001$) levels were lower as compared with temperature increases with normal $P_{bt}O_2$ levels at baseline (Table 3).

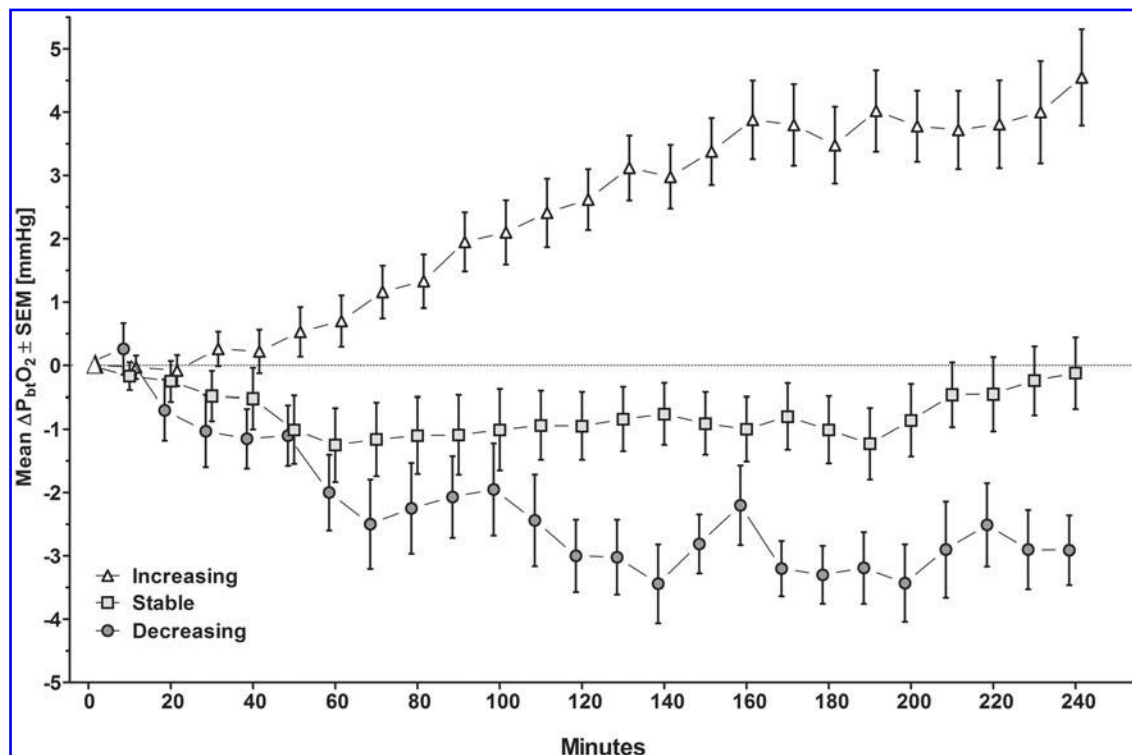


FIG. 2. Displays different mean $P_{bt}O_2$ changes during 202 episodes of temperature increases. $P_{bt}O_2$, brain tissue oxygen tension. SEM, standard error of the mean.

TABLE 3. CHANGES IN BRAIN TISSUE OXYGEN TENSION AND HEMODYNAMIC VARIABLES DURING TEMPERATURE INCREASES SPLITTING AT BRAIN TISSUE OXYGEN TENSION <20 mmHg AND BRAIN TISSUE OXYGEN TENSION ≥ 20 mmHg AT BASELINE

	$P_{bt}O_2$ bl	$P_{bt}O_2$ peak	$\Delta P_{bt}O_2$	T bl	T peak	ΔT	CPP bl	CPP peak	Δ CPP	MAP bl	MAP peak	Δ MAP
$P_{bt}O_2$ baseline <20 mmHg N=38	12.3±5.2	17.3±7.8	5.0±7.2	36.7±0.8	37.8±0.7	1.1±0.6	69.4±13.9	69.1±13.8	0.3±11.0	86.1±12.1	87.2±13.7	1.0±10.3
$P_{bt}O_2$ baseline ≥20 mmHg N=164	31.3±7.2	31.2±8.9	-0.1±5.5	37.0±0.8	37.9±0.7	1.0±0.5	82.7±16.5	77.7±14.8	-5.0±12.8	98.1±17.9	94.5±17.6	-3.6±10.3
	OR=1.13; 95%-CI=1.08-1.19; p<0.001							<i>p</i> =0.995			<i>p</i> =0.909	
	OR=0.86; 95%-CI=0.80-0.94; p=0.001							OR=0.90; 95%-CI=0.85-0.96; p=0.001				

Hemodynamic and neuromonitoring parameters are expressed as mean±standard deviation at baseline and highest temperature within each episode of temperature increase. Using generalized estimating equations, the significance of changes of each variables (Δ) within temperature increases was tested in univariate analysis. Significant changes ($p<0.05$) are bold.

bl, baseline; CI, confidence interval; CPP, cerebral perfusion pressure; HR, heart rate; ICP, intracerebral pressure; MAP, mean arterial pressure; OR, odds ratio; ORx, oxygen reactivity index; $P_{bt}O_2$, brain tissue oxygen tension; PRx, pressure reactivity index; T, temperature.

Splitting temperature increases by baseline temperature (<37.5°C; 75% and ≥37.5°C; 25%), analysis revealed significant increases in $P_{bt}O_2$ only when baseline temperature was normothermic ($p=0.014$). Further details are given in Table 4.

Manually versus parametric detection of temperature increases

Assisted episode detection of temperature increases revealed (1) 71 (total increase of ≥0.5°C), (2) 183 (increase lasting ≥1 h), and (3) 532 (increase lasting ≥20 minutes) episodes when applying the algorithm as described in the Methods section. Again, $P_{bt}O_2$ more often increased (method 1: 51%, 2: 58%, 3:53%). Analysis of hemodynamic variables during algorithm-supported detection of temperature increases yielded similar results as compared with visually identified temperature increases (Supplementary Table S1 and Supplementary Fig. S2).

Discussion

The main finding of the current study is that variable changes in $P_{bt}O_2$ can be observed when temperature increases in severe TBI patients. $P_{bt}O_2$ increased on average in every third episode and decreased in every sixth episode. Importantly, a drop in $P_{bt}O_2$ occurred simultaneously to a decrease in CPP in the context of a decrease in MAP. Although more episodes of temperature increases were identified by visual curve inspection, algorithm-supported detection was feasible and revealed similar hemodynamic changes.

In the overall cohort, we found a weak-positive correlation between absolute temperature and $P_{bt}O_2$ levels, which is consistent with previous reports (Spiotta *et al.*, 2008; Nyholm *et al.*, 2017). To the best of our knowledge, this is the first study analyzing time-coded dynamic systemic changes and brain oxygenation during episodes of temperature increases at different baseline temperature levels. Our study suggests that alterations of temperature may negatively affect brain hemodynamics only in a minority of analyzed episodes. In a recent prospective observational study in TBI patients, brain temperature variations (>1°C) were associated with poor functional outcome (Weng *et al.*, 2019). Similarly, a higher temperature variability within the first 48 hours was associated with poor functional outcome in the control group treated with normothermia in a *post hoc* analysis of the EURO THERM trial (Abu-Arafeh *et al.*, 2018). It is important to mention that a higher temperature variation may simply reflect a higher treatment intensity of fever, which is more common in patients with more severe brain injury. In the current study, we aimed to study pathophysiological changes associated with temperature increases. Temperature decreases reflecting treatment episodes of fever were excluded because of the potential side effects of pharmacological interventions on systemic and cerebral hemodynamics (Ianos *et al.*, 2019). Based on the observed temperature increase per hour, the etiology of fever episodes in our study most likely represents either infectious or neurogenic fever and not physiologic circadian changes in body temperature.

In our cohort, the overall impact of temperature changes on brain tissue oxygen tension was minute. During most efferescence episodes, $P_{bt}O_2$ increased or remained stable, which

TABLE 4. CHANGES IN BRAIN TISSUE OXYGEN TENSION AND HEMODYNAMIC VARIABLES DURING TEMPERATURE INCREASES SPLITTING AT TEMPERATURE <37.5°C AND TEMPERATURE ≥37.5°C AT BASELINE

	$P_{bt}O_2$ bl	$P_{bt}O_2$ peak	$\Delta P_{bt}O_2$	T bl	T peak	ΔT	CPP bl	CPP peak	Δ CPP	MAP bl	MAP peak	Δ MAP
T baseline <37.5°C N=152	27.5±10.9	28.8±11.0	1.2±6.7	36.6±0.7	37.7±0.6	1.1±0.6	79.5±17.2	74.2±15.3	-5.3±12.6	94.5±18.6	90.7±17.1	-3.7±10.5
T ≥ 37.5°C N=50	28.2±7.5	28.0±7.5	-0.2±3.6	37.8±0.3	38.6±0.3	0.7±0.2	82.0±15.7	81.6±12.3	-0.4±12.2	100.0±13.3	100.4±15.5	0.4±9.8
	OR=1.04; 95%-CI=1.01-1.08; p=0.014							OR=0.89; 95%-CI=0.82-0.96; p=0.003		OR=0.93; 95%-CI=0.87-0.99; p=0.013		
	<i>p</i> =0.730							<i>p</i> =0.366		<i>p</i> =0.404		

Hemodynamic and neuromonitoring parameters are expressed as mean±standard deviation at baseline and highest temperature within each episode of temperature increase. Using generalized estimating equations, the significance of changes of each variables (Δ) within temperature increases was tested in univariate analysis. Significant changes ($p<0.05$) are bold.

bl, baseline; CI, confidence interval; CPP, cerebral perfusion pressure; HR, heart rate; ICP, intracerebral pressure; MAP, mean arterial pressure; OR, odds ratio; ORx, oxygen reactivity index; $P_{bt}O_2$, brain tissue oxygen tension; PRx, pressure reactivity index; T, temperature.

TABLE 3. (CONTINUED)

ICP bl	ICP peak	Δ ICP	HR bl	HR peak	Δ HR	PRx bl	PRx peak	Δ PRx	ORx bl	ORx peak	Δ ORx
16.7 \pm 10.7	18.1 \pm 13.2	1.3 \pm 6.6	72.2 \pm 16.5	75.6 \pm 19.5	3.4 \pm 10.7	0.23 \pm 0.34	0.07 \pm 0.38	-0.16 \pm 0.37	0.34 \pm 0.36	0.26 \pm 0.38	-0.15 \pm 0.48
15.4 \pm 11.8	$p=0.767$ 17.1 \pm 12.6	1.8 \pm 10.3	76.5 \pm 17.2	$p=0.161$ 82.1 \pm 16.7	5.6 \pm 9.3	0.09 \pm 0.33	$p=0.589$ 0.14 \pm 0.37	0.06 \pm 0.38	OR=0.997; 95%-CI=0.995-1.00; $p=0.031$ 0.21 \pm 0.36	0.25 \pm 0.35	0.05 \pm 0.40
OR=1.07; 95%-CI=1.00-1.13; $p=0.044$						OR=1.15; 95%-CI=1.09-1.21; $p<0.001$			$p=0.357$		
										$p=0.717$	

is in line with previous data (Stocchetti *et al.*, 2005). This observation was independent of baseline temperature and baseline $P_{bt}O_2$. It is important to keep in mind that the measured $P_{bt}O_2$ levels reflect the balance between oxygen delivery, consumption, tissue diffusion, and extraction (Rosenthal *et al.*, 2008). Therefore, the shift of the oxygen dissociation curve in hyperthermic conditions with a higher oxygen extraction may serve as one explanation for the observed overall increase of $P_{bt}O_2$ during effervescence (Siggaard-Andersen *et al.*, 1984). Moreover, normal or even increasing $P_{bt}O_2$ levels during temperature increases in our study suggest that the extended metabolic demand was met by upregulated energy supply (Rossi *et al.*, 2001; Stocchetti *et al.*, 2005). This is important and may separate pathophysiological changes observed during effervescences in TBI patients from other stroke patients, where fever exacerbates ischemic injury (Busto *et al.*, 1987). In case of metabolic coupling, regional cerebral blood flow (CBF) increases in parallel to $P_{bt}O_2$ through vasodilation (Jaeger *et al.*, 2005), which bears the risk of raised ICP (Stocchetti *et al.*, 2005). In our patients, ICP was well controlled and changes in ICP (Δ ICP 0.6 mmHg) were negligible, irrespective of the baseline autoregulatory status as expressed by PRx (data not shown). Other cardiovascular effects of temperature increases include a higher cardiac output, which may augment oxygen delivery (Bain *et al.*, 2014; Walter *et al.*, 2016). Another explanation, why $P_{bt}O_2$ increased in most of episodes is that cerebral autoregulation was preserved during the majority of episodes.

In a smaller proportion of episodes, we observed drops in $P_{bt}O_2$ levels. This is of interest as previous studies report on the overall effect of temperature increases on $P_{bt}O_2$ and did not

include the longitudinal information of $P_{bt}O_2$ patterns (Stocchetti *et al.*, 2005). The most likely explanation for $P_{bt}O_2$ drops is the observed decrease in CPP secondary to a decrease in MAP. It is well known that hypotension may occur during fever as a consequence of vasodilation and redistribution of blood (Bain *et al.*, 2014; Walter *et al.*, 2016). It is important to mention that most of the centers applied a $P_{bt}O_2$ -guided treatment concept aiming at the prevention of brain tissue hypoxia. Although, mean baseline $P_{bt}O_2$ was mostly above 20 mmHg, new brain tissue hypoxia was commonly observed during episodes when $P_{bt}O_2$ decreased (30%). In the overall cohort, brain tissue hypoxia developed on average in every sixth episode and persisted in every tenth episode reflecting a considerable risk of secondary brain injury during effervescences. We may have underestimated the incidence of brain tissue hypoxia in our cohort, based on the assumption that low $P_{bt}O_2$ was treated in most centers. In the current understanding, continuous monitoring of $P_{bt}O_2$, CPP, and blood pressure may help to minimize the risk of brain tissue hypoxia. Although a hyperventilatory response to pyrexia is common and may lead to a reduction in CBF and $P_{bt}O_2$ by respiratory alkalosis (Bain *et al.*, 2014), this well-established effect may be negligible in this patient population, where a controlled mechanical ventilation was applied.

Notably, different patterns of $P_{bt}O_2$ changes were observed in the same patient, suggesting that the association between temperature increases and $P_{bt}O_2$ may depend on many factors, including the phase of disease, baseline vasopressor need, and the status of cerebral autoregulation.

In the current study, we aimed to identify increases in temperature by manual and algorithm-supported detection.

TABLE 4. (CONTINUED)

ICP bl	ICP peak	Δ ICP	HR bl	HR peak	Δ HR	PRx ble	PRx peak	Δ PRx	ORx bl	ORx peak	Δ ORx
14.9 \pm 10.1	16.8 \pm 12.7	2.0 \pm 9.1	73.8 \pm 17.0	78.9 \pm 17.5	5.2 \pm 10.0	0.10 \pm 0.34	0.11 \pm 0.38	0.01 \pm 0.38	0.21 \pm 0.36	0.26 \pm 0.36	0.04 \pm 0.44
OR=1.07; 95%-CI=1.01-1.12; $p=0.012$ 18.0 \pm 14.9	18.8 \pm 12.6 $p=0.943$	0.8 \pm 11.3	OR=1.11; 95%-CI=1.06-1.17; $p<0.001$ 81.7 \pm 16.4	86.7 \pm 15.9	5.0 \pm 8.1	0.15 \pm 0.31	$p=0.332$ 0.19 \pm 0.37	0.04 \pm 0.41	0.29 \pm 0.34	$p=0.828$ 0.24 \pm 0.34	-0.06 \pm 0.33 $p=0.107$
OR=1.21; 95%-CI=1.09-1.34; $p<0.001$											

Interestingly, we could identify more episodes through visual plot analysis because of the basic and strict regulations of the parametric method. To align the method to the “softer” human detection, a better preprocessing and methods with a less rigid rule set may help in the identification. Still, a software-based detection of effervescence is feasible, and the results of associated brain and systemic hemodynamic changes were similar. Moreover, advanced multivariable time-series methods could allow better identification of episodes. Future studies are needed to investigate whether a software-based method could be used at the patients’ bedside to alarm the clinician even before a substantial temperature increase is reached. Such predictive models were feasible for predicting changes in ICP and $P_{bt}O_2$ (Myers *et al.*, 2016).

Limitations

Several limitations deserve consideration. We did not assess CBF and brain metabolic changes associated with effervescence, which leaves some interpretation of our results speculative. Second, time-coded vasopressor use was not recorded in our patients, which may have influenced the observed hemodynamic changes. Third, a $P_{bt}O_2$ -guided therapy targeting at normal $P_{bt}O_2$ levels was applied in several centers, which makes our results not transferrable to centers without oxygen monitoring and without a comparable treatment approach. Still, the risk of brain tissue hypoxia may be likely higher without monitoring. Fourth, to avoid a bias of hemodynamic side effects of pharmacologic fever treatment, we did not include episodes of temperature decreases in our study. Moreover, fever management varies between European centers (Picetti *et al.*, 2019) and may have made the interpretation of decreases in temperature challenging. Fifth, probe location of $P_{bt}O_2$ catheters was not integrated in the current analysis. Since we investigated relative changes, probe location might not be of high importance. Moreover, the observation that different $P_{bt}O_2$ patterns during temperature increase occurred within the same patients might further justify our approach. Sixth, the site to measure temperature differed among patients. It is well known that intracranial temperature may exceed body temperature by several degree Celsius in acute brain injury highlighting the difficulty of fever definition (McIlvoy, 2004). Since our analysis focused on temperature increases irrespective of fever, this definition was of minor importance. Next, a considerable number of patients with neuromonitoring had no simultaneous recordings of temperature and $P_{bt}O_2$ and had to be excluded, which constitutes the risk of a selection bias. However, baseline characteristics and temperature levels did not differ among the groups. Last, following the Gay-Lussac’s Law, the pressure of oxygen rises in parallel with the temperature increases. This phenomenon could have influenced our results, as we are not aware in which patients combined $P_{bt}O_2$ /temperature probes with automatic correction of $P_{bt}O_2$ for patients’ temperatures were used or whether temperature levels were manually entered in the remaining patients.

Conclusion

In summary, our study indicates that adequate brain tissue oxygen tension was preserved during most episodes of effervescences in patients with severe TBI. However, there was a considerable risk of brain tissue hypoxia during efferves-

cences. On average in every sixth episode a decrease of brain tissue oxygen tension was observed simultaneous to a decrease in CPP, which supports the idea of continuous (neuro)monitoring in severe TBI patients.

Animal or Human Experimentation

The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws of the country, where the recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the “Privacy Law”), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonized Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95; “ICH GCP”) and the World Medical Association Declaration of Helsinki entitled “Ethical Principles for Medical Research Involving Human Subjects.” Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF. Ethics approval was obtained for each recruiting site. The list of sites, Ethics Committees, approval numbers, and approval dates can be found on the website.

Acknowledgments

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Author Disclosure Statement

No competing financial interests exist.

Funding Information

Data used in preparation of this article were obtained in the context of CENTER-TBI, a large collaborative project with the support of the European Union 7th Framework program (EC grant 602150). Additional funding was obtained from the Hannelore Kohl Stiftung (Germany), from OneMind (United States), and from Integra LifeSciences Corporation (United States).

Supplementary Material

Supplementary Table S1
Supplementary Figure S1
Supplementary Figure S2

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