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Effects of Hyperthermia on Intracranial Pressure and Cerebral Autoregulation in Patients with an Acute Brain Injury

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Introduction

Hyperthermia (an increased temperature of the "body core" above 38.30 °C) is considered a risk factor for secondary brain damage, regardless of the etiology of the primary damage (cerebral ischemia, traumatic brain injury, subarachnoid hemorrhage, etc.) [1–5]. The frequency of hyperthermia in neurointensive care units varies from 30% to 60% [3–8] and is associated with a prolonged duration of hospitalization, adverse outcomes, and high mortality [4, 5, 8–10].

The existing temperature gradient between the "core" of the body and the brain [11] explains the importance of direct measurement of cerebral temperature in patients with acute cerebral damage, and it is recommended to measure the temperature in the bladder or esophagus [4] for early diagnosis of hyperthermia [12].

The aim of this study was to estimate the effects of hyperthermia on intracranial pressure (ICP) dynamics and ICP dependence on cerebral autoregulation (CA), measured by the pressure reactivity index (PRx).

Materials and Methods

The study used data from multimodal monitoring of eight patients with acute brain injuries of various etiologies: three patients with a severe traumatic brain injury (TBI), three patients with a subarachnoid hemorrhage (SAH) due to rupture of a cerebral aneurysm (Hunt and Hess grade 3, Fisher grade 3), one patient with a gunshot wound to the head, and one patient who had undergone resection of a metastasis in the cerebral hemisphere. The average age of the patients was 53 (range 18–72) years. Six of the eight patients were female.

All patients were admitted to the neurointensive care unit 1 day (range 0–5 days) after the insult and had negative neurological status dynamics, cerebral edema, and signs of intracranial hypertension according to computed tomography (CT). The patients were treated with a standard local protocol, including mechanical ventilation and monitoring of ICP, cerebral perfusion pressure (CPP), and PRx.

ICP measurement was provided by a Neurovent-P-Temp sensor (Raumedic, Helmbrechts, Germany) combined with a temperature probe. The intraparenchymal sensor was installed at a depth of 2–2.5 cm at Kocher's point. Invasive arterial blood pressure monitoring was performed by a radial artery cannula. CPP was considered as the difference between the average blood pressure and the average ICP. All patients were monitored for partial expiratory CO_2 pressure ($EtCO_2$) by a mainstream CO_2 sensor (Philips Healthcare, Andover, MA, USA). The core body temperature was measured in the bladder by a Foley catheter combined with a thermistor (Smith Medical ASD, Dublin, OH, USA). Hyperthermia was defined as an increase in brain temperature above 38.3 °C.

All parameters were displayed on a Philips MP40 monitor. PRx was calculated by ICM+ software (Cambridge, UK). PRx is a linear correlation coefficient between 40 consecutive averaged measurements of mean arterial pressure and mean intracranial pressure with 5-s increments. PRx values <0 were considered to signify intact autoregulation, while PRx values ≥0 signified loss of autoregulation.

Statistica version 10.0 software (StatSoft, Tulsa, OK, USA) was used for statistical data analysis of parametric and nonparametric criteria. The median values and quartiles of each of the analyzed parameters were used because of the abnormal distribution of the variables.

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Results

Thirty-three episodes of an increase in cerebral temperature from 37.8 [quartiles 37.6–38] to 38.9 [quartiles 38.3–39.6] °C were detected. The cerebral temperature delta as a difference between median cerebral temperature before and during hyperthermia$_{(max - min)}$ was 1.2 [quartiles 0.5–2.6] °C.

Analysis of monitored parameters during development of cerebral hyperthermia (blood pressure, CPP, ICP, PRx, $EtCO_2$, and heart rate) revealed a significant change only in ICP, which increased by 6 [quartiles 3–11] mmHg ($p < 0.01$). The Spearman's rank correlation coefficient between brain temperature and ICP was 0.11 ($t(N - 2)$, $p < 0.01$).

The dependence of ICP dynamics on the initial value is shown in Table 1.

Before development of hyperthermia, ICP was within normal ranges in 25 observations (76%), with a median value of 11 [8–16] mmHg, while in eight observations (24%), ICP was moderately elevated, with a median value of 23 [22–25] mmHg (Table 1). During progression of hyperthermia, elevated ICP was found in 13 instances (52%) where it was initially normal, with a median value of 24 [22–28] mmHg, while further progression of intracranial hypertension occurred in all eight instances (100%) where ICP was initially elevated (Table 1), and the ICP value increased significantly to 31 [27–32] mmHg ($p < 0.01$).

According to the PRx, CA was intact in 17 observations (52%) and impaired in 16 (48%) (Table 2). CA became impaired in almost half (47%) of the instances where it was initially intact, whereas it recovered in half (50%) of the instances where it was initially impaired (Table 2). Thus, the total numbers of observations with intact and impaired CA remained the same (17 (52%) and 16 (48%), respectively, $p > 0.05$)).

Analysis of ICP dependence on the initial CA state during hyperthermia revealed that the number of episodes of elevated ICP increased by 41% in instances where CA was initially intact but ICP was above 20 mmHg and by 38% in instances where it was initially impaired and ICP was above 20 mmHg ($p > 0.05$) (Table 3). Thus, an increase in ICP during hyperthermia occurred both in instances with intact CA and in instances with impaired CA.

Table 1 Dynamics of intracranial pressure (ICP) during development of cerebral hyperthermia, depending on the initial ICP

$N = 33$ observations (100%) Median 14 [10–20] mmHg		
$ICP_1 \leq 20$ mmHg: $N = 25$ (76%) Median 11 [8–16] mmHg		$ICP_1 > 20$ mmHg: $N = 8$ (24%) Median 23 [22–25] mmHg
$ICP_2 \leq 20$ mmHg: $N = 12$ (48%) Median 13 [10–16] mmHg	$ICP_2 > 20$ mmHg: $N = 13$ (52%) Median 24 [22–28] mmHg	$ICP_2 > 20$ mmHg: $N = 8$ (100%) Median 31 [27–32] mmHg

The values shown in square brackets are quartiles ranges
ICP_1 intracranial pressure before hyperthermia, ICP_2 intracranial pressure during hyperthermia, N number of observations

Discussion

The existing literature data describing the effects of hyperthermia on ICP are controversial. Some researchers believe there is a direct linear relationship between the brain temperature and ICP, and that development of hyperthermia is thus accompanied by an increase in ICP and progression of brain edema [13–15]. Other researchers believe there is no correlation between the brain temperature and ICP [12].

In our study, we did not attempt to analyze the correlation between cerebral temperature and ICP for the entire monitoring period; however, their correlation during hyperthermia was analyzed. We compared the monitoring parameter values prior to hyperthermia with those during hyperthermia. According to our data, ICP parameters changed significantly only with development of cerebral hyperthermia above 38.3 °C. Changes in parameters such as the blood pressure, CPP, $EtCO_2$, heart rate, and PRx were bidirectional and non-significant, whereas the ICP value increased significantly during hyperthermia by 6 [quartiles 3–11] mmHg ($p < 0.05$).

Cerebral temperature measurement is considered a more accurate method for temperature monitoring in patients with

Table 2 Dynamics of autoregulation (as shown by the pressure reactivity index (PRx)) during development of cerebral hyperthermia

$N = 33$ observations (100%) Median − 0.01 [range quartiles −0.15 to 0.09]			
$PRx_1 < 0$: $N = 17$ (52%)		$PRx_1 \geq 0$: $N = 16$ (48%)	
$PRx_2 < 0$: $N = 9$ (53%)	$PRx_2 \geq 0$: $N = 8$ (47%)	$PRx_2 < 0$: $N = 8$ (50%)	$PRx_2 \geq 0$: $N = 8$ (50%)

N number of observations, $PRx < 0$ intact autoregulation, $PRx \geq 0$ impaired autoregulation, PRx_1 pressure reactivity index before hyperthermia, PRx_2 pressure reactivity index during hyperthermia. The values shown in square brackets are quartiles

Table 3 Dynamics of intracranial pressure (ICP) during development of cerebral hyperthermia, depending on the initial autoregulation status (as shown by the pressure reactivity index (PRx)) and the initial ICP

$N = 33$ observations (100%)			
Intact autoregulation, PRx < 0: $N = 17$		Impaired autoregulation, PRx ≥ 0: $N = 16$	
$ICP_1 < 20$ mmHg: $N = 14$ (82%)	$ICP_1 \geq 20$ mmHg: $N = 3$ (18%)	$ICP_1 < 20$ mmHg: $N = 11$ (69%)	$ICP_1 \geq 20$ mmHg: $N = 5$ (31%)
$ICP_2 < 20$ mmHg: $N = 7$ (41%)	$ICP_2 \geq 20$ mmHg: $N = 10$ (59%)	$ICP_2 < 20$ mmHg: $N = 5$ (31%)	$ICP_2 \geq 20$ mmHg: $N = 11$ (69%)

ICP_1 intracranial pressure before hyperthermia, ICP_2 intracranial pressure during hyperthermia, N number of observations

acute cerebral pathology, since cerebral hyperthermia is associated with secondary brain damage [16, 17].

The detrimental effects of hyperthermia could be explained by increases in the release of glutamate (excitotoxicity) [18], free radicals, and products of lipid peroxidation [19]; blood–brain barrier permeability; the severity of brain edema [20]; and protein degradation [21].

Development of secondary brain damage during hyperthermia can be assessed using the dynamics of the neurological status, changes in neuromonitoring parameters (such as ICP), and cerebral temperature monitoring, which directly indicates the probability of secondary brain damage [11, 12, 14–17].

In our study, we decided to diagnose hyperthermia by measuring the cerebral temperature, thus minimizing any controversy that could arise from the temperature gradient between the brain and the "core" [11, 12, 15]. In this chapter, we do not discuss the difference between hyperthermia and fever, because that was not the purpose of our study. It should be noted that we defined hyperthermia as an increase in cerebral temperature above 38.3 °C.

All patients included in the analysis had signs of cerebral edema on CT scanning, and in 24% of instances, ICP was already increased ICP (Table 1). These two facts may explain the increase in ICP due to the development of hyperthermia. In addition, in almost half of all instances (48%), CA was impaired according to the PRx (Table 2).

We excluded the increase in blood carbon dioxide (CO_2) stress because we did not observe a significant increase in $EtCO_2$ in the presence of hyperthermia. In our work, we did not evaluate brain metabolism, but it is known from the literature that hyperthermia leads to increases in brain metabolism and brain tissue oxygen consumption, which, through perfusion–metabolic coupling, cause a rise in the cerebral blood volume and, as a consequence, ICP elevation [13, 22].

Thus, analysis of the monitored parameters revealed that development of cerebral hyperthermia was accompanied by significant changes only in ICP. CA impairment during hyperthermia was observed in 47% of instances where it was initially intact and in 50% of those where it was initially impaired. A possible explanation for the autoregulatory response recovery phenomenon is increases in arterial blood pressure and CPP.

Conclusion

In this study, cerebral hyperthermia was associated with development of intracranial hypertension in 52% of instances where ICP was initially normal and further progression of intracranial hypertension in all instances where ICP was initially elevated. The cerebral hyperthermia–associated increase in ICP was not associated with impaired cerebral autoregulation.

Conflict of Interest **The authors declare that they have no conflict of interest.**

References

1. Badjatia N (2011) Fever control in the NICU: is there still a simpler and cheaper solution? Neurocrit Care 15(3):373–374
2. Fernandez A, Schmidt JM, Claassen J, Pavlicova M, Huddleston D, Kreiter KT, Ostapkovich ND, Kowalski RG, Parra A, Connolly ES, Mayer SA (2007) Fever after subarachnoid hemorrhage: risk factors and impact on outcome. Neurology 68(13):1013–1019
3. Hajat C, Hajat S, Sharma P (2000) Effects of poststroke pyrexia on stroke outcome: a meta-analysis of studies in patients. Stroke 31(2):410–414
4. Madden LK, Hill M, May TL, Human T, Guanci MM, Jacobi J, Moreda MV, Badjatia N (2017) The implementation of targeted temperature management: an evidence-based guideline from the Neurocritical Care Society. Neurocrit Care 27(3):468–487
5. Scaravilli V, Tinchero G, Citerio G, Participants in the International Multi-Disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage (2011) Fever management in SAH. Neurocrit Care 15(2):287–294
6. Andrews PJD, Verma V, Healy M, Lavinio A, Curtis C, Reddy U, Andrzejowski J, Foulkes A, Canestrini S (2018) Targeted temperature management in patients with intracerebral haemorrhage, subarachnoid haemorrhage, or acute ischaemic stroke: consensus recommendations. Br J Anaesth 121(4):768–775
7. Niven DJ, Laupland KB (2016) Pyrexia: aetiology in the ICU. Crit Care 20:247. https://doi.org/10.1186/s13054-016-1406-2
8. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC (2008) Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke 39(11):3029–3035
9. Prasad K, Krishnan PR (2010) Fever is associated with doubling of odds of short-term mortality in ischemic stroke: an updated meta-analysis. Acta Neurol Scand 122(6):404–408
10. Springer MV, Schmidt JM, Wartenberg KE, Frontera JA, Badjatia N, Mayer SA (2009) Predictors of global cognitive impairment 1 year after subarachnoid hemorrhage. Neurosurgery 65(6):1043–1050
11. Childs C, Lunn KW (2013) Clinical review: brain–body temperature differences in adults with severe traumatic brain injury. Crit Care 17(2):222
12. Huschak G, Hoell T, Wiegel M, Hohaus C, Stuttmann R, Meisel HJ, Mast H (2008) Does brain temperature correlate with intracranial pressure? J Neurosurg Anesthesiol 20(2):105–109
13. Nyholm L, Howells T, Lewén A, Hillered L, Enblad P (2017) The influence of hyperthermia on intracranial pressure, cerebral oximetry and cerebral metabolism in traumatic brain injury. Ups J Med Sci 122(3):177–184
14. Rossi S, Zanier ER, Mauri I, Columbo A, Stocchetti N (2001) Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. J Neurol Neurosurg Psychiatry 71(4):448–454
15. Stocchetti N, Rossi S, Zanier ER, Colombo A, Beretta L, Citerio G (2002) Pyrexia in head-injured patients admitted to intensive care. Intensive Care Med 28(11):1555–1562
16. Busto R, Dietrich WD, Globus MY, Ginsberg MD (1989) The importance of brain temperature in cerebral ischemic injury. Stroke 20(8):1113–1114

17. Mellergard P, Nordstrom CH (1991) Intracerebral temperature in neurosurgical patients. Neurosurgery 28:709–713
18. Takagi K, Ginsberg MD, Globus MY, Martinez E, Busto R (1994) Effect of hyperthermia on glutamate release in ischemic penumbra after middle cerebral artery occlusion in rats. Am J Phys 267:H1770–H1776
19. Globus MY, Busto R, Lin B, Schnippering H, Ginsberg MD (1995) Detection of free radical activity during transient global ischemia and recirculation: effects of intraischemic brain temperature modulation. J Neurochem 65:1250–1256
20. Clasen RA, Pandolfi S, Laing I, Casey D Jr (1974) Experimental study of relation of fever to cerebral edema. J Neurosurg 41:576–581
21. Morimoto T, Ginsberg MD, Dietrich WD, Zhao W (1997) Hyperthermia enhances spectrin breakdown in transient focal cerebral ischemia. Brain Res 746:43–51
22. Kiyatkin EA (2018) Brain temperature: from physiology and pharmacology to neuropathology. Handb Clin Neurol 157:483–504