Microcirculatory Biomarkers of Secondary Cerebral Ischemia in Traumatic Brain Injury

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Introduction

Secondary cerebral ischemia (SCI) is still one of the leading causes of mortality and disability in patients who have experienced a traumatic brain injury (TBI) [1]; however, changes in microcirculation parameters that occur with posttraumatic SCI still remain underinvestigated [2]. The purpose of this work was to study changes in cerebral microcirculation parameters in the development of SCI.

Materials and Methods

This retrospective, observational, nonrandomized, single-center study was conducted as an analysis of a prospectively maintained database cohort (2013–2018) and included patients with a head injury and unilateral foci of posttraumatic ischemia. The protocol of the study was reviewed and approved by the institutional ethics committee, and conformed to the standards of the Declaration of Helsinki. Neuromonitoring parameters were measured as part of standard patient care, and the data were archived in a physiological monitoring database. Age, sex, injury severity, and clinical condition data were recorded in this database at the time of monitoring. The study inclusion criteria were as follows: moderate or severe TBI within 6 h after head injury, with a Glasgow Coma Scale (GCS) score $\leq$ 12, and unilateral foci of posttraumatic ischemia on perfusion computed tomography (PCT). We excluded patients who were younger than 16 years or had an Injury Severity Score (ISS) greater than 60. All patients were subjected to multiphase PCT using a 64-slice Philips Ingenuity CT tomograph (Philips Medical Systems, Cleveland, OH, USA). PCT was performed 1–4 days after TBI (mean 3.3 ± 0.5 days). The perfusion examination report included initial contrast-free CT of the brain. Further extended scanning with a contrast agent was performed within 60 s, focusing on 16 areas of interest, 160 mm in thickness. The scanning parameters were 160 kVp, 160 mA, 70 mAs, 512 × 512. The contrast agent Ultravist 370 (Schering, Berlin, Germany) was administered, using a syringe injector (Medrad Stellant, Bayer HealthCare, Whippany, NJ, USA), into a peripheral vein through a standard 20 G catheter at a rate of 4–5 mL/s in a dose of 30–50 mL per examination. After the scanning, the data were transferred to a KIR picture-archiving and communication system (PACS) (JSC, Kazan, Russia) and a Philips Extended Brilliance Workspace workstation (Philips HealthCare, Amsterdam, the Netherlands) with MATLAB 2013b (The MathWorks, Natick, MA, USA). Artery and vein marks were automatically recorded, followed by manual control of indices in the time–concentration diagram. The region of interest was established on the basis of subcortical areas of the middle cerebral artery (MCA). Errors introduced by delay and dispersion of the contrast bolus before arrival in the cerebral circulation were corrected by use of a block-circulant deconvolution algorithm. Quantitative perfusion indices, including cerebral blood flow (CBF), were calculated on a voxel-wise basis and were used to generate color-coded maps. Voxels with CBF >100 mL/100 g/min or cerebral blood volume (CBV) >8 mL/100 g were assumed to contain vessels and removed from the perfusion map [3]. Core infarction on PCT was defined as CBV <2.0 mL/100 g or a relative decrease in CBF >38% in comparison with the contralateral hemisphere [4]. Immediately after PCT, Doppler ultrasound of the MCA was recorded bilaterally with 2 MHz probes (Sonomed 300 M, Spektromed, Moscow, Russia). A Centaurus 2.0 neuromonitor (Privolzhsky State Medical University, Nizhny Novgorod, Russia) was used to monitor the cerebral complex during the

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study. Arterial blood pressure and its amplitude (MAP_{amp}) were measured noninvasively using a Cardex MAP-03 monitor (Cardex, Nizhny Novgorod, Russia). The cerebrovascular resistance (CVR), cerebral arterial compliance (CAC), cerebrovascular time constant (CTC), and critical closing pressure (CCP) were measured using a complex neuromonitoring, as described previously [5, 6].

Statistical Analysis

To determine whether the data were normally distributed, a Shapiro–Wilk test was used. The data were expressed as mean ± standard deviation. A statistical analysis of all results was performed using a paired Student's *t* test. To specify the structure of the relationship of the variables, factor analysis was performed. We used a two-factor model with a raw varimax rotation. *P* values <0.05 were considered statistically significant.

Results

The patients' sex distribution had a male predominance (15 women, 187 men). The mean age was 54.7 ± 15.6 (range 17–87) years. The mean level of wakefulness, according to the GCS score, was 9.1 ± 0.5 (range 5–12). The distribution of TBI patients according to the Marshall Classification is shown in Table 1. Analysis of the studied parameters (Table 2) showed that in all patients with TBI, the mean CVR values were significantly higher than normal reference values ($P < 0.05$) and there was a significant difference in the CVR between the SCI zone and the opposite locus of the contralateral hemisphere (4.06 ± 2.16 vs. 2.7 ± 1.1 mmHg × 100 g × min/mL, $p = 0.0009$). In all patients with TBI, the mean CAC values were significantly lower than normal reference values ($P < 0.05$) and the CAC was significantly lower in the hemisphere with SCI than in the opposite hemisphere without SCI (0.026 ± 0.017 vs. 0.049 ± 0.035 mL/mmHg, $p = 0.017$). The mean CTC, as a product of the CAC and CVR in both hemispheres in patients with SCI, appeared to be significantly shorter than the mean normal value ($p < 0.05$). We also saw a small but significant decrease in the CTC between the hemispheres with and without SCI (0.10 ± 0.07 vs. 0.08 ± 0.08 s, $p = 0.015$). Analysis of the studied parameters showed that the mean CCP values appeared to be significantly higher than the mean normal value ($p < 0.01$). There was a significant difference in the CCP between the hemisphere with SCI development and the hemisphere without SCI (46.88 ± 14.05 vs. 45.44 ± 10.73 mmHg, $p = 0.65$). In factor analysis of potential risk factors for SCI development, the CVR and CCP were significant risk factors for SCI ($P < 0.05$).

Table 1 Distribution of patients with traumatic brain injury according to the Marshall Classification

Classification			
Class	Definition	Number	Percentage
I	No visible intracranial pathology	0	0
II	Midline shift of 0–5 mm, basal cisterns remain visible, no high- or mixed-density lesions >25 cm^3	24	11.9
III	Swelling	28	12.7
IV	Shift	37	16.8
V	Evacuated mass lesion	113	51.4
VI	Nonevacuated mass lesion	0	0

Discussion

Microcirculatory disturbances remain the cornerstone of development of cerebral hypoperfusion and SCI in patients with TBI [7]. Evaluation of the pial bed status is necessary since it can serve as a predictor of SCI development. This study showed that with development of SCI in the acute period (on days 2–3) after craniocerebral injury, the CAC and CTC significantly decrease while the CCP and CVR significantly increase in comparison with normal reference values. In our opinion, there may be a few reasons for these CAC and CTC reductions and CCP and CVR augmentations, but all of them seem to be associated with brain edema. First, development of combined (vasogenic and cytotoxic) edema due to blood–brain barrier disruption and SCI development may lead to compression of the pial vessels [8]. CT signs of brain edema found in all 202 patients in our study indirectly confirmed this assumption. The second reason may be

Table 2 Acquired and analyzed data

	CVR (mmHg × 100 g × min/mL)	CAC (cm^3/mmHg)	CTC (s)	CCP (mmHg)
Hemisphere with SCI[a]	4.06 ± 2.16	0.026 ± 0.017	0.10 ± 0.07	46.88 ± 14.05
Hemisphere without SCI[a]	2.7 ± 1.1	0.049 ± 0.035	0.08 ± 0.08	45.44 ± 10.73
P value (for comparison between hemispheres)	0.0009*	0.017*	0.015*	0.65

CAC cerebral arterial compliance, *CCP* critical closing pressure, *CTC* cerebrovascular time constant, *CVR* cerebrovascular resistance, *SCI* secondary cerebral ischemia

[a]The data are expressed as mean ± standard deviation

*P values <0.05 are statistically significant

regional microvascular vasospasm due to increases in the concentrations of blood degradation products trapped in the subarachnoid spaces. This effect results from auto-oxidation of oxyhemoglobin to methemoglobin with the release of ferric" [i.e., Fe(III)]. Furthermore, it is supposed that superoxides change the NO concentration [9], which leads to development of microvascular vasospasm [10]. In our study, Doppler ultrasound revealed no signs of MCA vasospasm in patients suffering from TBI. However, this ultrasound method does not provide the possibility to evaluate microvascular spasm. The third cause of pial bed compression may be swelling of astrocyte endfeet directly adjacent to the capillary wall [11]. Such swelling evolving in the first hours after TBI may persist for a week thereafter [12]. Finally, compression of pial vessels both in brain injury and in vasospasm is associated with dysfunction of pericytes located in the basal pericapillary membrane. It has been shown that narrowing of arterioles and capillaries occurs because of disturbance in the expression of endothelin-1 and pericytial receptor types A and B, as well as migration of over 40% of pericytes from the basal membrane [13].

Our study had the following limitations. First, it was impossible to carry out dynamic assessment of microcirculatory parameters without repeated PCT. Second, we have to admit that we failed to completely eliminate a mathematical error associated with measurement of the "area of interest" space. Third, the obtained data incorporated therapeutic and surgical influences, which could not be removed. Fourth, the data artifacts were removed manually by two experts (AT and DM), and we could not exclude the possibility that some artifacts went unnoticed. Lastly, no corrections for multiple testing were performed.

Clearly, this new approach to the concept of microcirculatory biomarkers in TBI still needs to undergo more thorough scrutiny. Further studies need to be performed to confirm these findings and provide better insight into how to interpret data derived from patients with TBI [14].

Conclusion

In this study, changes in cerebral microcirculation parameters (the CVR, CAC, CTC, and CCP indices) in patients with traumatic intracranial hemorrhage were associated with progression of secondary ischemia ($P < 0.05$), suggesting they have promising potential for use as early biological markers of SCI development. Further studies are needed to confirm these findings.

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

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