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Intracranial dynamics biomarkers at traumatic cerebral vasospasm

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ABSTRACT

Introduction: Patients who suffer severe traumatic brain injury (sTBI) and cerebral vasospasm (CVS) frequently have posttraumatic cerebral ischemia (PCI).
The research question: was to study changes in cerebral microcirculatory bed parameters in sTBI patients with CVS and with or without PCI.
Material and methods: A total of 136 severe TBI patients were recruited in the study. All patients underwent perfusion computed tomography, intracranial pressure monitoring, and transcranial Doppler. The levels of cerebrovascular resistance (CVR), cerebral arterial compliance (CAC), cerebrovascular time constant (CTC), and critical closing pressure (CCP) were measured using the neuromonitoring complex. Statistical analysis was performed using parametric and nonparametric methods and factor analysis. The patients were dichotomized into PCI-positive (n = 114) and PCI-negative (n = 22) groups. Data are presented as mean values (standard deviations).
Results: CVR was significantly increased, whereas CAC, CTC, and CCP were significantly decreased in sTBI patients with CVS and PCI development ($p < 0.05$). Factor analyses revealed that all studied microcirculatory bed parameters were significantly associated with the development of PCI ($p < 0.05$).
Discussion and conclusion: The changes in all studied microcirculatory bed parameters in TBI patients with CVS were significantly associated with PCI development, which enables us to regard them as the biomarkers of CVS and PCI development. The causes of the described microcirculatory bed parameters changes might include complex (cytotoxic and vasogenic) brain edema development, regional microvascular spasm, and dysfunction of pericytes. A further prospective study is warranted.

1. Introduction

Posttraumatic cerebral vasospasm (CVS) is one of the leading causes of ischemic complications in traumatic brain injury (TBI) (Dicpinigaitis et al., 2022). However, despite improving diagnosis and management after traumatic subarachnoid hemorrhage (SAH), posttraumatic cerebral ischemia (PCI) still negatively impacts TBI outcomes (Murakami et al., 2019). The frequency of CVS development varies in different epidemiological studies due to different diagnostics approaches (Shah et al., 2022). According to transcranial ultrasound Doppler (TCD), the frequency of CVS in severe TBI is 48%, while angiographic methods show a frequency of 63% (Kramer et al., 2013). A large body of data demonstrated that angiography is a more accurate CVS diagnosis method than TCD (Mastantuono et al., 2018; Darsaut et al., 2022).

Given that a dramatic deterioration in TBI outcomes accompanies the development of symptomatic CVS, the issue of early PCI diagnosis is of paramount importance. In this light, multiphase perfusion computer tomography (PCT) seems the most preferable, as it enables a simultaneous assessment of cerebral microcirculation and volumetric hemodynamic studies of large cerebral vessels (Neulen et al., 2019; Bergin

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et al., 2023a). As previously shown, this technique is well suitable for assessing changes in microcirculatory bed by multiple parameters, including cerebrovascular resistance (CVR), cerebral arterial compliance (CAC), cerebrovascular time constant (CTC), and critical closing pressure (CCP) – all are of significant interest for evaluation microcirculatory bed remodeling in various brain diseases and injuries (Trofimov et al., 2021). The aim was to study cerebral microcirculatory bed parameters changes in severe TBI patients with CVS and with or without PCI.

2. Methods and methods

2.1. Study design and population

This observational retrospective non-randomized single-center study was conducted to analyze a maintained database cohort (2013–2022). The protocol of the study was approved by the University Ethical Committee. The informed consent was waived due to the retrospective study design.

The physiological data recording on mean arterial pressure (MAP) (mean duration - 27.3 ± 8.3 h), cerebral blood flow velocity (CBFV) (mean duration - 15.3 ± 7.3 h), intracranial pressure (ICP) (mean duration - 22.3 ± 7.8 h), brain saturation ($SctO_2$) (mean duration - 22.4 ± 12.4 h) were conducted at 10 Hz frequency as a part of routine intensive care and archived in a database.

The inclusion criteria were as follows:

- severe TBI with a GCS less than 9, Marshall score II-IV;
- "angiographic" CVS on computed tomography angiography source image (CTASI);
- dynamic multiphase perfusion computed tomography (PCT during the first 5 days after trauma);
- monitoring of ICP, MAP, and cerebral perfusion pressure (CPP) for at least 12 h;
- Admission Glasgow Coma Score (GCS) and Glasgow Outcome Scale (GOS) data are available.

The exclusion criteria were as follows:

- blast and/or penetrate TBI;
- age younger than 16 years and older than 70 years;
- serum creatinine values of more than 120 mg/L
- GCS less than 4 and more than 8, Marshall scores I, V, VI

A total of 136 severe TBI patients with CVS were recruited in the study. For statistical analyses, the patients were dichotomized into PCI-positive (n = 114) and PCI-negative (n = 22) groups. The primary outcome measurement was the CVS development on CTASI, and the secondary outcome was PCI development on PCT when the cause was to be due to CVS.

3. Perfusion computed tomography

PCT was performed 1–5 days after TBI (mean 3.2 ± 0.7 days) on a Philips Ingenuity CT scanner (Philips Medical Systems, USA). The scan parameters were as follows: z-axis coverage - 160 mm, 80 kV, 150 mA, effective dose = 3.3 mSv, slice thickness = 5 mm, collimation = 64 × 0.625 mm. A total of 50 mL of Ultravist 370 (Schering AG, Germany) was injected intravenously through a 20-gauge catheter with an automatic injector (Stellant, Bayer HealthCare, USA) at a rate of 5 mL/s. After scanning, the data volume was transferred to the picture-archiving and communication system (KIR, RF) and a workstation Philips Extended Brilliance Workspace (Philips HealthCare, Amsterdam, the Netherlands) with MATLAB 2013b (The MathWorks Inc., Natick, USA). The arterial input function was detected automatically using a cluster-analysis algorithm and subsequently used by the Bayesian probabilistic method to generate the maps of perfusion parameters: cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT). The so-called "region of interest" (ROI) was established based on subcortical areas of the middle cerebral artery. Posttraumatic cerebral ischemia voxels were recognized using the thresholds: CBF>30% and CBF <2 mL/100 g of the opposite side values (Donahue and Wintermark, 2015). The voxels with CBF of >100 mL/100 g/min or CBV of >8 mL/100 g were assumed to contain vessels and removed from the ROI.

The CTASI analysis enabled us to visualize the brain's main vessels and assess the state of their lumen (Kerkeni et al., 2015). In all patients included in this study, the minimal intensive projection data analysis identified the local luminal narrowing middle cerebral artery of more than 30% of the diameter as compared to adjacent sections of the same vascular segment, based thereon an "angiographic" CVS was diagnosed (Danura et al., 2015). The vasospasm, according to its severity, is usually classified into three grades: mild – the vessel still has 70% of luminal flow; moderate – there is more than 50% reduction of the lumen; severe – the vessel has less than 30% of the luminal flow on angiography.

All CTASI and CTP maps were reviewed for CVS and PCI by two neuroradiologists (ST and KL-G), blinded to clinical conditions.

3.1. Multimodal neuromonitoring

Immediately after PCT, CBFVs in both middle cerebral arteries were recorded using ultrasound Doppler with 2-MHz probes attached with a headband (Sonomed 300 M, Spectromed, RF). MAP was measured non-invasively. ICP was monitored using the parenchymal probe (Codman MicroSensors ICP, Codman & Shurtleff, Raynham, MA, USA). The physiological variables and ICP were recorded continuously every 2 s during the PCT using a bedside monitor (IntelliView MP5, Philips Medizin Systeme, Germany).

CVR, CAC, CTC, and CCP values were calculated as described earlier (Trofimov et al., 2016, 2018).

3.2. Statistical analysis

Statistical analysis was done using Statistica 12 software (TIBCO Software Inc., Palo Alto, USA). Data were evaluated for normality using the Kolmogorov-Smirnov test. Statistical analysis was carried out using U-criterion Manna-Whitney as appropriate. Fisher's exact test was used for continuous variables. We used a weighted kappa statistic to measure the agreement between our raters. Factor analysis was performed to specify the structure of the relationship of the variables. We used a two-factor model with a Varimax raw. Data are presented as mean values (standard deviations) for continuous variables; the significance level was preset at $p < 0.05$.

4. Results

We identified 136 severe TBI patients (women 53; men 83) with CVS evidence secondary to trauma, all of whom received a dynamic multiphase PCT. The interrater reliability kappa for CVS and PCI was 0.689. The distribution of CVS patients according to the Marshall Classification is shown in Table 1, and the outcome according to the Glasgow Outcome

Table 1
The distribution of CVS patients according to the Marshall Classification.

Marshall type	N	%
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)	5	3.7
III (swelling)	94	69.1
IV (shift)	37	27.2
V (evacuated mass lesion)	0	0
VI (non-evacuated mass lesion)	0	0

Scale is shown in Table 2. Cerebral microcirculatory parameters in the enrolled patients are shown in Table 3.

One hundred fourteen patients (83,8 %, women 47, men 67) had cerebral vasospasm and PCI evidence, and twenty-two patients (16.2%, women 6, men 16) although had cerebral vasospasm on CTASI, but did not have proof of cerebral ischemia on PCT. The age and gender differences were not significant ($p > 0.05$).

All patients were stratified into 2 groups: group I (18–58 years old (yo), n = 114, GCS 7.2 ± 1.5) – microcirculatory bed parameters of the patients with CVS and PCI, and group II (19–56 yo, n = 22, GCS 7.8 ± 0.9) – microcirculatory bed parameters of the patients with CVS but without PCI (Table 2).

There were statistically significant differences in microcirculatory bed parameters between patients with CVS-associated PCI and those without. CVR was significantly higher ($p < 0.001$), and CAC, CTC, and CCP were significantly decreased in groups with CVS and PCI than without PCI ($p = 0.012$, $p = 0.023$, $p < 0.01$, respectively).

To specify the structure of the variable's relationship with regard to the above features, a factor analysis was performed. We used a two-factor model with the Varimax raw.

The eigenvalues of factors 1 and 2 were 3.106 and 2.203, and the total dispersion percentages of factors 1 and 2 reached 47.3% and 32.6%, respectively.

Thus, the changes in all studied microcirculatory bed parameters in TBI patients with CVS were reliably associated ($p < 0.05$) with post-traumatic cerebral ischemia development, and it enables us to suggest them as biological markers of CVS development.

Among 136 severe TBI patients with CVS based on CTASI data (angiographic vasospasm), PCI development was observed in 103 patients with TCD CVS (dopplerographic vasospasm) and 8 patients without TCD CVS (dopplerographic vasospasm). On the other hand, among 25 patients with CVS and without PCI development, eight of them had dopplerographic vasospasm, and seventeen had no dopplerographic vasospasm.

Thus, Fisher's exact test demonstrated that PCI development was frequently observed in simultaneous angiographic and dopplerographic CVS ($P < 0.0001$).

5. Discussion

The aim of our study was to evaluate changes in the cerebral microcirculatory bed parameters in severe TBI patients with CVS and with or without PCI. Although we performed TCD in all 136 patients, it has been shown that dopplerographic CVS were observed only in 103 patients with angiographic CVS and PCI development (75.7%) and in almost 6% without PCI (8 patients).

On the one hand, our data are somewhat different from previous studies, where CVS incidence did not exceed 60% (Al-Mufti et al., 2018). However, Crowley et al. showed that only 3% of PCI cases with SAH did not have CVS evidence (Crowley et al., 2011). On the other hand, it should be noted that we used one of the most advanced methods for CVS determining based on computed tomography angiography planimetric studies with high sensitivity and specificity (Bergin et al., 2023b; Greenberg et al., 2011; van der Harst Joep MD et al., 2019).

In this study, we have shown statistically significant differences in microcirculatory bed parameters between patients who developed CVS-associated PCI and those who did not.

Earlier, it has been shown that only CVR and CCP were significantly associated with PCI in moderate-to-severe TBI in the absence of CVS (Trofimov et al., 2021).

In our opinion, one of the leading causes of the observed microcirculatory bed parameters changes might be the complex (cytotoxic and vasogenic) brain edema development leading to pial vessel compression (Cernak et al., 2004), which was proved by CT signs of brain edema in all 136 patients.

However, although CVS can lead to vessels narrowing and intracranial compartment decrease, the development of ischemia and cytotoxic edema easily overcome this effect, leading to an increase in ICP, as described previously (Munakomi and M Das, 2023).

Also, among the reasons for microcirculatory bed parameter changes might be regional microvascular spasms due to the formation of a large amount of blood degradation product (methemoglobin) with iron ions and the release of superoxide radicals (Trofimov et al., 2018). The serum nitrogen oxide concentration change damages the pial vessels' endothelium, leading to microvascular spasm development (Rey et al., 2002).

The pial bed compression might also be associated with the dysfunction of pericytes – cells in the basal pericapillary membrane. It has been shown that the disturbance in the expression of endothelin-1 and types A and B pericytial receptors, as well as the migration of over 40% of pericytes from the basal membrane, might lead to arterioles and capillaries narrowing (Kreipke et al., 2010).

5.1. Study limitations

Some significant limitations of this study deserve mention.

First, despite a constantly renewed PCT database, this work was retrospective, non-randomized, and single-center.

Second, in this work, we could miss some PCI and CVS patients, especially those hemodynamically unstable, who had critical brain damage or uncontrolled intracranial hypertension due to canceled transportation to the CT suite or PCT performing. We will minimize this limitation in future studies using mobile CT or more optimized hemodynamic support methods.

Third, considering those above, the CVS-associated PCI incidence might be even greater than we showed. However, despite these limitations, a more accurate evaluation of microcirculatory bed parameters methods could better understand time-variant cerebral microcirculation remodeling processes at posttraumatic vasospasm underlying cerebral ischemia development.

6. Conclusion

The changes in all studied microcirculatory bed parameters in TBI patients with CVS were significantly associated with PCI development, and it enables us to suggest them as biological markers of posttraumatic cerebral ischemia development in sTBI patients with CVS. A further prospective study is warranted.

Table 2
The distribution of the outcome according to the Glasgow Outcome Scale.

Glasgow Outcome Scale	N	%
Death	21	15.4
Vegetative sate	9	6.6
Severe disability	73	53.7
Moderate disability	21	15.5
Low disability	12	8.8

Table 3
Cerebral microcirculatory parameters in the enrolled patients.

	CVR (mmHg x 100 g x min/mL)	CAC (cm3/ mmHg)	CTC (sec)	CCP (mmHg)
1. Hemisphere with CVS and PCI	4.21 ± 2.7	0.024 ± 0.017	0.07 ± 0.04	34.41 ± 12.23
2. Hemisphere with CVS without PCI	2.9 ± 1.2	0.049 ± 0.035	0.10 ± 0.05	46.88 ± 14.05
P (1–2)	<0.001*	0.012*	0.023*	<0.01*

*Significant difference ($p<0.05$). CVR - cerebrovascular resistance, CAC - cerebral arterial compliance, CTC cerebrovascular time constant, CCP - critical closing pressure.

Conflict of interest

The authors declare that they have no conflict of interest.

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