Cerebrovascular Resistance in Patients with Severe Combined Traumatic Stresspoints Brain Injury

A.O. TROFIMOV, G.V. KALENT’EV, D.I. AGARKOVA

The N.A. Semashko Nizhny Novgorod Regional Hospital

Cerebrovascular resistance is an important parameter of the microcirculation. The main objective of cerebrovascular resistance is to maintain the constancy of cerebral blood flow and protect downstream vessels when perfusion pressure changes. The purpose of the study was to assess cerebrovascular resistance (CVR) in patients with severe combined traumatic brain injury (CTBI) with and without intracranial hematomas (IHs). Material and methods. We analyzed treatment outcomes in 70 patients with severe CTBI (42 males and 28 females). The mean age was 35.5±14.8 years (min 15 years; max 73 years). All patients were divided into 2 groups, depending on the presence of intracranial hemorrhage. The first group included 34 patients without IH, and the second group included 36 patients with epidural (6), subdural (26), and multiple (4) hematomas. The GCS score was 10.4±2.6 in the first group and 10.6±2.8 in the second group. The ISS severity injury score was 32±8 in the first group and 31±11 in the second group. All patients were operated on within the first 3 days, with 30 (83.3%) patients being operated on during the first day. Perfusion computed tomography (PCT) of the brain was performed within 1—14 days after TBI in the first group and within 2—8 days after surgical evacuation of hematoma in the second group. After PCT, the mean arterial pressure was measured, and the blood flow rate in the middle cerebral artery was determined using transcranial dopplerography. Cerebrovascular resistance was calculated using the formula modified by P. Scheinberg. Comparisons between the groups were performed using the Student t-test and χ2 criterion. Results. The mean CVR values in each group (both with and without hematomas) were statistically significantly higher than the mean normal value of this parameter. Intergroup comparison of CVR values demonstrated a statistically significant increase in the CVR level in group 2 on the side of removed hematoma compared to group 1 (p=0.037). CVR in the perifocal zone of removed hematoma remained significantly higher compared to the symmetrical zone of the contralateral hemisphere (p=0.0009). Conclusions. Cerebrovascular resistance in patients with combined traumatic brain injury is significantly increased compared to the normal value. Cerebrovascular resistance in the perifocal zone after evacuation of hematoma in patients with multiple injury remains significantly increased compared to the symmetrical zone in the contralateral hemisphere.

Keywords: combined traumatic brain injury, intracranial hematoma, cerebrovascular resistance, critical closing pressure.

One of the key aspects of any effective brain injury treatment is to maintain the optimal levels of cerebral perfusion and oxygenation [1, 2]. There are different ways to define this optimum, including simultaneous use of modern techniques of assessment of cerebral macro- and microcirculation (for example, using Doppler sonography or laser studies simultaneously with perfusion X-ray or magnetic resonance tomography) with subsequent calculation of derivative indices and values [3—7]. This approach allows non-invasive assessment of the immediate state of cerebral microvasculature [8—10], high degree of accuracy in calculation of cerebral hemodynamics indicators, in particular cerebral perfusion pressure [11, 12], as well as determination of “secondary”, derivative, parameters reflecting the condition cerebral microvasculature. One of the parameters is cerebrovascular resistance (CVR) [13—15]. It has been demonstrated that cerebrovascular resistance (CVR) ensures constancy of the cerebral perfusion in case of spontaneous or induced changes in hydrostatic and systemic arterial blood pressure and prevents the development vasogenic edema [16, 17]. It has been noted that such effect of cerebrovascular resistance is achieved at an average arterial blood pressure of 40 to 140 mmHg, i.e. in the same interval in which the mechanisms of cerebral blood flow autoregulation operate. It demonstrates clear relationships between mechanisms of cerebral blood flow autoregulation and CVR maintenance [18]. CVR acts through changes in smooth muscle tone of the entire bloodstream. This process involves primarily precapillary arterioles and capillaries, which account for more than 50% of the total vascular resistance [19, 20]. Therefore, CVR reflects the status of all bloodstream components with emphasis on pial bed, which is essential for understanding the genesis of vascular disorders after brain injury [21, 22]. In addition, the increase in CVR is considered to be prognostic of development cerebral angiopasm and cerebral ischemia [7, 18, 23, 24]. It has been shown that cerebral microvasculature is particularly vulnerable in case of combined traumatic brain injury (CTBI), as well as in case of isolated traumatic cerebral compression [2]. However, relatively little is known about microvascular response in case of CTBI with intracranial hematomas [15, 16], which defines the relevance of our study. The purpose of this study is to evaluate cerebrovascular resistance in case of severe CTBI in groups with and without meningeal intracranial hematomas.

Material and methods

Over the course of the study we reviewed treatment outcomes of 70 patients with severe CTBI (42 men, 28 women, aged 15 to 73 years, with an average age of 35.5±14.8 years), who were treated in the N.A. Semashko Nizhny Novgorod Regional Hospital in 2011—2014. All patients received treatment according to the Advanced Trauma Life Support protocol.
The patients were divided into two groups based on the presence of intracranial hemorrhage. The first group included 34 patients with CTBI without hematomas; the second one included 36 CTBI patients with cerebral compression caused by intracranial hematomas. Intracranial brain damage was assessed according to classifications by A.N. Konovalov et al., A.A. Potapov et al. [25]. The study groups were comparable in age, gravity of the brain damage and the combined injuries.

Group 1 included 34 patients with focal hematomas and diffuse brain damage; 15 of them also had long bones fractures and 6 had skull fractures.

Group 2 included 36 patients with intracranial hematomas (6 epidural, 26 subdural, 4 multiple); 17 of them also had long bones fractures and 4 had pelvic fractures.

The vast majority of the patients with combined injuries also had internal organs hematomas of varying degrees. The gravity of the condition according to the Glasgow Outcome Scale (GCS) was 10.4±2.6 points in Group 1, 10.6±2.8 points in Group 2. All patients were operated on within the first 3 days. 30 (83.3 %) patients were operated for hematomas within the first day. Treatment outcomes were evaluated using Glasgow Outcome Scale at discharge. The outcomes for patients from Group 1 and Group 2 are shown in the Table 1.

**Instrumental methods**

All patients underwent a single perfusion CT examination of the brain on a 64-slice Toshiba Aquilion TSX-101A tomograph (“Toshiba medical systems”, Netherlands).

Perfusion computed tomography (PCT) of the brain was performed within 1—14 days (average of 4±3 days) after TBI in the first group and within 2—8 days (average of 4±2 days) after surgical evacuation of hematoma in the second group. All patients were on spontaneous breathing, did not require sedation or catecholamine support of the blood pressure.

PCT protocol included the initial un-enhanced CT examination of the brain on a 128-milimeter tomograph (“Toshiba medical systems”, Netherlands). After scanning, the data was transmitted to and analyzed by Vitrea 2 software (“Vital Imaging Inc.”, ver 4.1.8.0).

“Areas of interest” were defined symmetrically and subcortically in the temporal lobes at the level of the middle temporal gyrus, which corresponds to the area of the middle cerebral artery blood supply. In this study we calculated rate of cerebral blood flow rate in the MCA (cm/sec); Vm is systolic linear blood flow rate in the MCA (cm/sec).

Assessment of the mean arterial blood pressure (ABP) (Kardex, MAR-03, Russian Federation) was performed simultaneously with PCT and was immediately followed by transcranial dopplerography of both middle cerebral arteries (Sonomed 300M, “Spectromed”, Russian Federation) to provide consistent conditions for the study cerebral blood flow.

Based on the collected data, cerebral perfusion pressure was calculated using the formula by M. Czosnyka [26]:

\[
\text{Calculated CPP}=\frac{\text{aABP} \times \text{Vd}}{\text{Vm}} + 14,
\]

where CPP is cerebral perfusion pressure (mmHg); aABP is average arterial blood pressure (mmHg); Vd is diastolic linear blood flow rate in the MCA (cm/sec); Vm is systolic linear blood flow rate in the MCA (cm/sec).

We used the following formula to calculate CVR [27]:

\[
\text{CVR} = \frac{\text{CPP}}{\text{CBFR}},
\]

where CVR is cerebral vascular resistance (mmHg×100×min/mL); CPP is cerebral perfusion pressure (mmHg); CBFR is cerebral blood flow rate (ml/100 g×min).

Reference range for CVR (relative norm) was estimated according to [27] as 1.54 ±0.24 mmHg×100×min/mL.

**Statistical analysis**

The data were normally distributed; therefore, they are presented as the average±standard deviation. Comparisons between the groups were performed using the Student t-test and χ² criterion. The level of significance was set at p<0.05. Statistica 7.0 software package was used for data analysis.

**Results**

The parameters analyzed in the study groups are presented in the Table 2.

Average CVR values for each group of patients with severe CTBI (both with and without hematomas) were significantly higher than average norm for this parameter (p<0.05).

Intergroup comparison of CVR values showed statistically reliable increase in their levels in Group 2 on the side of the evacuated hematoma compared with Group 1 (p=0.037).

The largest differences have been identified in Group 2 patients: the average CVR in the perifocal area after evacuation of the hematoma remained significantly higher than in the symmetrical zone in the contralateral hemisphere (p=0.0009).

In addition, diastolic and average blood flow rates and cerebral perfusion pressure were also reliably different in these areas (p=0.005, p=0.001, and p=0.0000001, respectively).

No reliable differences (p>0.05) have been observed for CVR values for different types of intracranial hematomas.

**Table 1. Distribution of patients in the study groups according to Glasgow Outcome Scale (GCS)**

<table>
<thead>
<tr>
<th>Group</th>
<th>GCS 1 Low disability</th>
<th>GCS 2 Moderate disability</th>
<th>GCS 3 Severe disability</th>
<th>GCS 4 Persistent vegetative state</th>
<th>GCS 5 Death</th>
<th>Total</th>
</tr>
</thead>
</table>
Table 2. Distribution of study indicators in the groups

<table>
<thead>
<tr>
<th>№</th>
<th>Group</th>
<th>Average BP. mmHg</th>
<th>Vd. cm/sec</th>
<th>Vm. cm/sec</th>
<th>CBFR. mL/100 g × min</th>
<th>CPP. mmHg</th>
<th>CVR. mmHg × 100 × min/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>98.5±15.7</td>
<td>34±14.2</td>
<td>46.12±13.8</td>
<td>31.7±10</td>
<td>85.3±25.5</td>
<td>2.94±2.2</td>
</tr>
<tr>
<td>2</td>
<td>2 (on the side of the</td>
<td>99.9±14.7</td>
<td>32.5±11.5</td>
<td>36.8±12.8</td>
<td>32.3±17.7</td>
<td>109.4±36</td>
<td>4.06±2.16</td>
</tr>
<tr>
<td></td>
<td>evacuated hematoma)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2 (in the contralateral</td>
<td>99.9±14.7</td>
<td>25.5±9.9</td>
<td>48.7±17.7</td>
<td>28.4±11.1</td>
<td>67.5±17.2</td>
<td>2.7±1.1</td>
</tr>
<tr>
<td></td>
<td>hemisphere)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p&lt;0.05</td>
<td>0.701</td>
<td>0.631</td>
<td>0.005*</td>
<td>0.138</td>
<td>0.002*</td>
<td>0.037*</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>0.701</td>
<td>0.004*</td>
<td>0.5</td>
<td>0.194</td>
<td>0.001*</td>
<td>0.561</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.0000001*</td>
<td>1</td>
<td>0.005*</td>
<td>0.001*</td>
<td>0.247</td>
<td>0.0000001*</td>
<td>0.0009*</td>
</tr>
</tbody>
</table>

Note. * — Differences are statistically significant.

Discussion

It has been demonstrated that cerebral blood flow is directly related to the CPP and inversely related to the bloodstream resistance [22, 28, 29]. However, CVR dynamics in case of cerebral pathology and, in particular, in the event of severe combined injury has been insufficiently studied to date [2]. At the same time, assessment of CVR is essential since it can serve as a predictor for development of the post-traumatic angiospasm and ischemic brain damage [7].

Our research shows that CVR reliably increases in case of CTBI as compared to the norm.

We believe there are several possible explanations for CVR dynamics.

One of them may be associated with the development of mixed (cytotoxic and vasogenic) cerebral edema [30], which causes compression of the pial vessels and leads to an increase in vascular resistance. This is indirectly confirmed by the fact that in this study CT scans showed symptoms of cerebral edema in 100% of patients.

Another reason may be local microvascular vasoconstriction of blood vessels, constituting the microcirculatory bed, caused by the release of large number of vasoactive degradation products of the blood trapped in the subarachnoid perivascular spaces. It leads to oxidation of oxyhemoglobin into methemoglobin and release of iron ions, which, in their turn, cause formation of superoxide radicals. Superoxides are believed to cause changes in the concentration of nitric oxide [23] and peroxide damage to the endothelium of the pial vessels [31], which results in the development of microvascular vasospasm [32].

Transcranial dopplerography used in this study revealed no evidence of vasospasm in the CTBI patients. However, it should be noted that, unlike laser Doppler flowmetry, transcranial dopplerography does not allow estimation of vasospasm of vessels, which constitute microvascularity, and it was one of the limitations of our study.

In addition, the compression of the microvascular bed can develop as a result of swelling of astrocyte processes, immediately adjacent to the capillary wall (astrocytic endfeet swelling). It can develop within the first hours after the injury and may persist for a week [17, 33].

Finally, the compression of the pial vessels in case of brain injury is associated with dysfunction of pericytes: cells that are located in the basal pericapillary membrane. It has been shown that mass constriction of arterioles and capillaries in case of TBI is due to impaired expression of endothelin-1 and its pericyctal type A and B receptors, as well as by the migration of more than 40% of pericytes from the basal membrane [34—38].

As has been shown above, all these reasons can lead to reduced total lumen of the capillary bed and, accordingly, to increased in CVR [6].

It should be noted that the development of brain compression due to meningeal hematomas alter CVR values even more [39]. For example, we have shown that even after the evacuation of meningeal hematoma, CVR value in its perifocal zone remained significantly higher than in the contralateral hemisphere.

Moreover, some researchers [21] noted that the compression of capillary network in the perifocal hematoma zone can reach values at which the blood flow in the arterioles stops. This value varies in different individuals and is called ‘critical closing pressure’.

It leads to drastic reduction in the number of functioning capillaries and thus to an increase in CVR on the side of the compression [39].

In such circumstances, temporary microvascular shunts are opened and phenomena of supracapillary and intracapillary shunts develop in order to maintain perfusion in the perifocal area [40].

Perhaps, the development of capillary shunt syndrome can explain the paradoxical result we obtained when the calculated value of the CPP at the side of the evacuated hematoma was higher than SBP.

Thus, our results suggest that in the early period of severe CTBI there are marked changes in cerebrovascular resistance and cerebral microcirculation, which are exacerbated by the development of meningeal hematomas.

Conclusions

Cerebrovascular resistance in patients with combined traumatic brain injury is significantly increased compared to the normal value. Cerebrovascular resistance in the perifocal zone after evacuation of hematoma in patients with multiple injury remains significantly increased compared to the symmetrical zone in the contralateral hemisphere.
The study conducted at the Nizhny Novgorod regional clinical hospital, discusses one of the important aspects of cerebral blood flow regulation: cerebrovascular resistance (CVR). The study included patients with combined traumatic brain injury (CTBI). According to the authors, little is known about CVR disruption in this category of patients, and non-invasive methods for assessing cerebral blood flow make it possible to use original study design. Based on a single measurement of cerebral blood flow by CT-perfusion and dopplerography, they compared parameters of central and cerebral hemodynamics in the groups of CTBI patients. The patients were classified into groups based on the presence or absence of meningeal hematomas.

In our opinion, the study covers sufficiently heterogeneous groups of patients. According to the presented data, the gravity of the condition in the study groups varied from grievous to light. The study methodology appears to be quite original, relying on the use of modern methods of research (CT-perfusion and dopplerography). However, the use of indirect calculated parameters, such as cerebral perfusion pressure and CVR, in the discrete variant of the study limits the interpretation of the results.

The results of the study showed that CVR was increased in both groups of patients, but more expressed disruptions of CVR were observed for the group with meningeal hematomas. According to the authors, the identified CVR disruptions can be attributed to many causes, from endothelial dysfunction, neuroinflammation and cytotoxic edema to development of vasospasm in the microcirculation. However, other mechanisms, such as a disruption of the venous outflow and intracranial hypertension, are not discussed. The study, apparently, did not have any patients with intracranial hypertension.

This work clearly demonstrates the disruption of cerebral microcirculation and CVR in acute traumatic brain injury. We hope that the team of authors will continue their studies of CVR in TBI and will, in their subsequent works, devote attention to the patients with traumatic brain edema and intracranial hypertension. It seems that particular attention should be given to clinical and prognostic aspects of CVR assessment.

The work will be of interest to wide range of professionals, who are involved in treating this category of patients: resuscitationist, neurosurgeons, neurologists, traumatologists.

A.V. Oshorov (Moscow, Russia)