Change in Cerebrovascular Resistance as Diagnostic Index of Cerebral Hemodynamics in Patients with Severe Combined Traumatic Brain Injury

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The aim of the investigation was to evaluate changes in cerebrovascular resistance (CVR) in severe combined traumatic brain injury (CTBI) against the background of intracranial hematoma development and its role in diagnosing the state of cerebral hemodynamics.

Materials and Methods. Treatment outcomes in 70 patients with severe CTBI (42 males and 28 females) were studied. Mean age was 35.5±14.8 years (from 15 to 73 years). Depending on the presence of intracranial hemorrhage, the patients were divided into two groups: group 1 — without hematomas, group 2 — with hematomas. The severity of condition according to the Glasgow Coma Scale in group 1 averaged 10.4±2.6 scores, in group 2 it was 10.6±2.8. The severity of injuries according to ISS scale was 32±8 and 31±11 scores, respectively. Epidural hematomas in group 2 were revealed in 6 persons, subdural ones were found in 26, there were multiple hematomas in 4 patients. All the sufferers underwent surgery within the first three days, 30 patients (83.3%) were operated on for hematomas during the first day.

All the patients underwent perfusion CT examination of the brain, transcranial Doppler of both middle cerebral arteries, their mean arterial pressure was measured. Relying on these data, cerebral perfusion pressure and CVR (cerebrovascular resistance) were calculated.

Results. The mean CVR values in each group (both with and without hematomas) appeared to be statistically significantly higher than the mean normal value of this parameter. Intergroup comparison of CVR values showed statistically significant increase in the CVR level in group 2 on the side of removed hematoma (p=0.037). Cerebrovascular resistance in the perifocal zone of removed hematoma remained significantly higher compared to the symmetrical zone in the contralateral hemisphere (p=0.0009).

Conclusion. Cerebrovascular resistance in patients with combined traumatic brain injury is significantly increased compared to the normal value and remains significantly elevated after evacuation of hematoma in the perifocal zone compared to the symmetrical zone in the contralateral hemisphere. This is indicative of certain correlation between the mechanisms of cerebral blood flow autoregulation and maintaining CVR.

Key words: combined traumatic brain injury; intracranial hematomas; cerebrovascular resistance.

Maintenance of optimal cerebral perfusion and oxygenation is one of the key aspects in management of sufferers with traumatic brain injury [1, 2]. This optimum can be determined using simultaneously several methods of evaluating cerebral macro- and microcirculation with subsequent calculation of derived indices and values [3–5]. Such approach is widely used in studying cerebral blood flow [6, 7].

The use of complex approach provides the opportunity to assess the immediate state of cerebral microcirculatory bed noninvasively [8–10], to calculate the indices of cerebral hemodynamics with high accuracy and also to determine "surrogate" secondary parameters reflecting the state of cerebral microcirculatory bed [11, 12]. One of these values is cerebrovascular resistance (CVR) [13–15].

It has been established that CVR provides constant brain perfusion in conditions of changing hydrostatic and systemic arterial pressure (AP), which prevents vasogenic edema development [16, 17]. Such CVR effect occurs within the same AP interval where the mechanisms of cerebral blood flow autoregulation operate. It speaks of definite correlation between the mechanisms of cerebral blood flow autoregulation and maintaining CVR [18].

Change in CVR occurs mainly due to changing smooth muscle tonus of the whole microcirculatory bed, namely, precapillary arterioles and true capillaries, which account for 50% of total vascular resistance [19, 20].

Thus, CVR reflects the status of all vascular bed components (mainly, pial bed) and is of great importance for understanding the genesis of vascular impairment in brain injuries [21, 22].

There is information that CVR growth is a premonitory sign of cerebral vasospasm and ischemia development [7, 18, 23, 24]. Therefore, understanding microcirculatory bed reaction, particularly in conditions of combined traumatic brain injury (CTBI) against the background of intracranial hematoma formation, allows predicting the development of cerebral blood flow impairment.

The aim of the investigation was to evaluate changes in cerebrovascular resistance in severe combined traumatic brain injury against the background of intracranial hematoma development and its role in diagnosing the status of cerebral hemodynamics.

Materials and Methods. Hemodynamics was studied in 70 patients with severe CTBI undergoing treatment in N.A. Semashko Nizhny Novgorod Regional Clinical Hospital in 2011–2014. The study involved 42 males and 28 females. The patients were aged 15 to 73 years, mean age being 35.5±14.8 years. All of them received therapy according to the international protocol, Advanced Trauma Life Support. The study complies with the Declaration of Helsinki (adopted in June 1964 (Helsinki, Finland) and revised in October 2000 (Edinburgh, Scotland)) and was approved by the Ethics Committee of N.A. Semashko Nizhny Novgorod Regional Clinical Hospital. All the patients gave informed consent to participate in the study.

Depending on the presence of intracranial hemorrhage, the patients were divided into two groups: group 1 included 34 CTBI patients without hematomas, group 2 comprised 36 sufferers with CTBI and cerebral compression due to intracranial hematomas (ICH). Intracranial brain injuries were evaluated according to classifications of Potapov et al. [25]. The groups were comparable in age and severity of traumatic brain injury and concomitant lesions (Table 1).

The severity of condition according to the Glasgow Coma Scale in group 1 averaged 10.4±2.6 scores, in group 2 it was 10.6±2.8 scores.

The severity of injuries according to ISS scale (Injury Severity Score) in group 1 averaged 32±8 and was 31±11 scores in group 2.

Among 36 patients of group 2 epidural hematomas were revealed in 6 persons, subdural ones were found in 26, multiple hematomas were revealed in 4 sufferers. All hematomas were located mainly in the fronto-temporal lobes.

All the sufferers underwent surgery within the first three days. Thirty patients (83.3%) were operated on for hematomas during the first day.

Treatment outcomes were assessed according to Glasgow Outcome Scale on discharge from hospital (Table 2).

All the patients underwent a single perfusion CT examination of the brain on 64-slice tomographic scanner, Toshiba Aquilion TSX-101A (Toshiba Medical systems, Netherlands).

In group 1 perfusion CT examination of the brain was performed within the first 14 days from the moment of getting injured (on day (4±3), on average), in group 2 it was done within 2–8 days after evacuation of hematomas (on day (4±2), on average). All the patients breathed spontaneously, required no sedation or vasopression support.

Table 1

Clinical profiles of patients under study

Injuries	Group 1 (CTBI without ICH)	Group 2 (CTBI with ICH)
Moderate brain contusion (II degree)	11	13
Severe brain contusion (III degree)	23	23
Long bone fracture	5	17
Pelvic fracture	6	4
Total	34	36

Table 2

Distribution of patients in studied groups according to the Glasgow Outcome Scale

Groups	Good recovery (I degree)	Moderate disability (II degree)	Severe disability (III degree)	Vegetative state (IV degree)	Death (V degree)	Total
Group 1 (CTBI without ICH)	15	10	6	2	1	34
Group 2 (CTBI + ICH)	16	9	7	2	2	36

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Perfusion CT examination of the brain was performed according to the following protocol. Initial unenhanced CT of the brain was carried out [4, 5], then 4 extended scans of 32 mm thick area were performed during 55 s against contrast medium infusion. The contrast medium (Ultravist 370; Shering AG, Germany) was infused by automatic injector (Stellant; MEDRAD Inc., USA) to the peripheral vein via a standard catheter at the rate of 5 ml/s in the dose of 50 ml per one examination or to the central vein at the rate of 3 ml/s in the dose of 35 ml per one examination.

After scanning the data were transferred and analyzed using standard computer program Vitrea 2 (Vital Imaging, Inc., USA, v. 4.1.8.0). "The regions of interest" were established symmetrically subcortically in the temporal lobes on the level of middle temporal gyrus, which corresponded to the vascular supply area of the middle cerebral artery. In patients of group 2 "the region of interest" located on the side of removed hematoma corresponded to the perifocal zone of microcirculatory changes.

Mean AP (mAP) was measured (Cardex MAP-03; Cardex, Russia) alongside with perfusion CT examination, on CT completion there was performed transcranial Doppler of both middle cerebral arteries (Sonomed 300M; Spectromed, Russia), which provided similar conditions for cerebral blood flow examination.

Cerebral perfusion pressure (CPP) was calculated relying on the obtained data and using the formula modified by Czosnyka [26]:

$$CPP = mAP \cdot Vd/Vm + 14,$$

where Vd is diastolic cerebral blood flow velocity in the middle cerebral artery (cm/s); Vm is mean cerebral blood flow velocity in the middle cerebral artery (cm/s).

In this study we also calculated the values of regional cerebral blood flow (rCBF). To calculate CVR the following formula was used [27]:

$$CVR = CPP/rCBF,$$

where CVR was measured in mm Hg·100 g·min/ml; CPP and rCBF were measured in mm Hg and ml/100 g·min, respectively.

The mean normal CVR value (the conditional norm) was estimated according to [27] 1.54±0.24 mm Hg· 100 g·min/ml.

The obtained data had normal distribution, so they were presented as mean±SD. Comparison between the groups was carried out according to Student's t-test. The level of significance was taken at $p < 0.05$. The results were analyzed using Statistica 7.0 software.

Results. Analysis of the studied parameters in the groups (Table 3) showed that the mean CVR values in each group of sufferers with severe CTBI (both with and without hematomas) appeared to be statistically significantly higher than the mean normal value of this parameter. Intergroup comparison of CVR values showed statistically significant increase in the CVR level in group 2 on the side of removed hematoma as compared to group 1 (p=0.037).

The most significant differences were revealed in patients of group 2: the mean CVR index in the perifocal zone of removed hematoma remained significantly higher compared to that in the symmetrical zone of the contralateral hemisphere (p=0.0009).

Besides, diastolic and mean blood flow velocity as well as CPP differed significantly in the above zones (p=0.005; p=0.001 and p=0.0000001, respectively)

Analysis of CVR values in various types of intracranial hematomas showed no statistically significant differences (p>0.05).

Discussion. It has now been established that cerebral blood flow is in direct correlation with CPP and in negative relationship with cerebrovascular resistance [22, 28, 29].

At the same time, CVR dynamics in brain pathology and particularly in severe combined traumatic injury remains understudied [2]. However, evaluation of CVR status is necessary since it can serve as a predictor of posttraumatic vasospasm and secondary brain damage development [7].

T a b l e 3

Values of studied parameters in groups

Groups	Mean AP (mm Hg)	Vd (cm/s)	Vm (cm/s)	rCBF (ml/100 g·min)	CPP (mm Hg)	CVR (mm Hg·100 g·min/ml)
Group 1 (1)	98.5±15.7	34.0±14.2	46.1±13.8	31.7±10.0	85.3±25.5	2.94±2.20
Group 2: on the side of former hematoma (2)	99.9±14.7	32.5±11.5	36.8±12.8	32.3±17.7	109.4±36.0	4.06±2.16
Group 2: on the side opposite to former hematoma (3)	99.9±14.7	25.5±9.9	48.7±17.7	28.4±11.1	67.5±17.2	2.7±1.1
p_{1-2}	0.701	0.631	0.005	0.138	0.002	0.037
p_{1-3}	0.701	0.004	0.5	0.194	0.001	0.561
p_{2-3}	1	0.005	0.001	0.247	0.0000001	0.0009
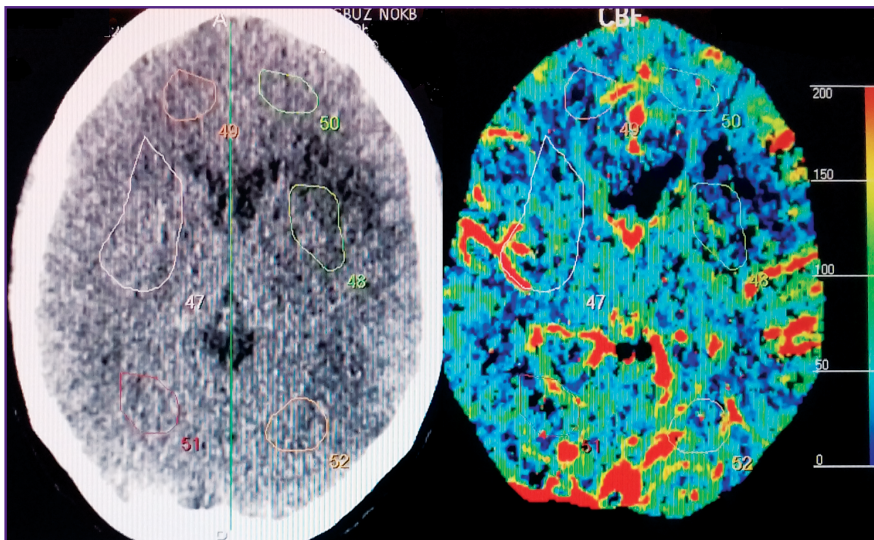
Revealing computed tomography signs of cerebral edema in a patient with combined traumatic brain injury

It has been demonstrated in our study that CVR in CTBI statistically significantly increases compared to the norm. One of the reasons for this increase is development of cytotoxic and vasogenic brain edema [30] resulting in compression of pial vessels and growth of vascular resistance. Computed tomography signs of brain edema found in all 70 patients (See Figure) indirectly confirm this hypothesis.

Another reason can be local microvascular vasospasm due to a large number of blood degradation products formed when blood gets to subarachnoid perivascular spaces. This effect results from oxidation of oxy-hemoglobin to methemoglobin with release of ferrum ions, which in their turn cause formation of superoxide radicals. Superoxides are supposed to change nitrogen oxide concentration [23] and peroxide damage to pial epithelium [31], which leads to development of microvascular vasospasm [32].

In our study transcranial Doppler revealed no signs of vasospasm in those suffered from CTBI. However, in contrast to laser Doppler flowmetry, this method does not provide the possibility to evaluate microvascular spasm, which turned to be a limitation of our investigation.

Also compression of microvasculature can develop due to astrocytic endfeet swelling in the directly adjacent to the capillary wall. Developing in the first hours after traumatic injury, it can persist during the week that follows [17, 33].

Finally, compression of pial vessels in traumatic brain injury is associated with dysfunction of pericytes, the cells embedded in the basement membrane of capillaries. It has been reported that massive narrowing of arterioles and capillaries in traumatic brain injury occurs due to impaired expression of endotellin-1 and its pericytic receptors type A and B and it is caused

by migration of more than 40% of pericytes from basement membrane [34–38].

All mentioned reasons, as it was pointed out earlier, can lead to diminishing of total capillary lumen and, consequently, to CVR increase [6].

It should be noted that brain compression by intracranial hematomas changes CVR even more [39]. Thus, we have found that even after intracranial hematoma evacuation CVR in its perifocal zone remained significantly higher than in the symmetrical zone of the contralateral hemisphere.

Some researchers point out that compression of capillary system in the perifocal zone of hematoma can reach such values at which blood flow in arterioles stops. Compression value is individual and known as critical closing pressure [21]. Such situation leads to severe reduction in the number of functioning capillaries and CVR increase on the side of compression [39].

In these conditions temporary microvascular shunts open and there develop supracapillary and intracapillary shunting phenomena to maintain perfusion in the perifocal zone [40]. Probably, the development of capillary shunting syndrome explains the paradoxical result obtained in our study, when predicted CVR value on the side of removed hematoma appeared to be higher than MAP.

Thus, the obtained findings enable us to conclude that in the early stage of severe combined traumatic brain injury there occur marked changes in cerebrovascular resistance and cerebral microcirculation, which are exacerbated by development of intracranial hematomas.

Conclusion. Cerebrovascular resistance in patients with combined traumatic brain injury is significantly increased compared to the normal value. After evacuation of hematoma in the former perifocal zone cerebrovascular resistance remains significantly elevated compared to the symmetrical zone in the contralateral hemisphere. Analysis of CVR status offers the possibility to distinguish a group of patients with high risk of cerebral vasospasm and posttraumatic secondary insult development.

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