Cerebrovascular resistance in polytraumazed patients with cerebral vasospasm

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Abstract The aim is to determine the status of the cerebral vascular resistance (CVR) in a concomitant head injury (CHI) and cerebral vasospasm (CVS) with and without the development of intracranial hematomas (IH).

Material and Methods: The results of the treatment of 80 patients with CHI and CVS was studied. M : F–42 : 38. Depending on the presence of IH the patients were divided into 2 groups. Wakefulness according to GCS was 9.7 ± 2.5 in the 1st group and 10.1 ± 2.5 in the 2nd group. Epidural hematomas were revealed in the 2nd group in 6 patients, subdural hematomas in 29 persons and multiple hematomas in 4 sufferers. All the sufferers were operated within the first 3 days. All the patients were subjected to the brain perfusion computed tomography, transcranial Doppler of the both middle cerebral arteries and the evaluation of the mean arterial pressure. Based on the data obtained the cerebral perfusion pressure and the cerebral vascular resistance (CVR) were calculated. The comparisons between the groups were performed by using the Student's t-criterion and the criterion χ^2.

Results: The average CVR values in each of the groups (with or without IH) appeared to be statistically significantly higher than a mean specified value of this index. The CVR in the 2nd group was statistically significant higher than in the 1st group especially on the side of the former IH. There were significant difference in CVR between the perifocal zone of the former IH and the opposite locus of the contralateral hemisphere. The CVS development on the side of the removed IH enhanced even more the CVR.

Keywords cerebrovascular resistance, vasospasm, concomitant brain injury

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Introduction

Cerebral vasospasm (CVS) is a severe complication of a head injury that increases the mortality and affects the outcome [1, 2]. According to different reviews, the CVS frequency varies from 12 to 65%, but its true morbidity still remains unknown [3–5].

As shown, the posttraumatic vasospasm development does not always result in brain ischemia but in any case affects the cerebral microvasculature [6–8].

Thus, with increasing input blood flow rate, microthrombosis as well as brain edema and high intracranial pressure the ability of the pial bed to maintain the cerebral perfusion stability becomes of particular importance [9–14]. The value characterizing this ability is cerebrovascular resistivity (CVR) [15].

Any change in CVR mainly occurs due to remodeling (change) of the vascular bed tone, namely: of precapillary arterioles and capillaries with over 50% of the total vascular resistance [15–17].

However, the spasm expansion to the microcirculatory bed (the so-called 'microvascular VS') abruptly reduces the rate and increases the time of blood transit through the pial bed and as a result it reduces the capabilities of the pial bed to maintain the stability of the perfusion, thus constituting the basis for the development of oligemia and even ischemia of the brain [17–19].

Thus, it is assumed that the increasing CVR value in the acute period of a brain injury may precede the vasospasm development and the secondary ischemic brain damage. We have already studied the dynamics of the CVR with severe polytrauma and the brain compression previously [20, 21]. But peculiarities of the CVR in the development of the posttraumatic CVS and the brain compression still remain poorly explored [22]. So, it determines the relevancy of our research.

The purpose of our work was to determine the status of the cerebral vascular resistance (CVR) in a concomitant

Table 1 Clinical outcome (Glasgow Outcome Score) of polytraumatized patients with CVS.

	GOS 1 Good recovery	GOS 2 Moderate disability	GOS 3 Severe disability	GOS 4 Vegetative state	GOS 5 Death	Total
Group 1	15	12	8	3	3	41 (100%)
Group 2	16	9	8	3	3	39 (100%)

head injury and posttraumatic cerebral vasospasm with and without the development of intracranial hematomas.

Materials and methods

We examined 80 polytrauma patients with severe head injury and CVS who were treated at the Nizhny Novgorod Regional Trauma Center Level I in 2013–2015. The mean age of the patients with head injury was 35.5 ± 14.8 years (from 15 to 73 years). There were 38 women and 42 men.

The criterion for the inclusion in the study was the CVS of the M_1 and M_2 segments of the middle cerebral artery revealed during the contrast-enhanced CT scanning of the brain. All patients were divided into 2 groups. The 1st group included 41 polytraumazed patients with the CVS in the acute period head injury without the development of intracranial hematomas (IH). The 2nd included 39 polytraumazed patients with the developed CVS and the brain compression by IH. The first group included 58 patients without IH and the second group included 58 patients with epidural (6), subdural (29,) and multiple (4) hematomas.

The wakefulness level according to GCS (Glasgow Coma Score) averaged 9.7 ± 2.5 in the 1st group and 10.1 ± 2.5 in the 2nd group. The severity of their state according to ISS (Injury Severity Score) was 34.3 ± 8.2 in the 1st group and 35.2 ± 9.3 in the second group. Clinical outcomes are summarized in Table 1.

Perfusion computed tomography

All patients were subjected to perfusion computed tomography (PCT) by 64-slice tomograph Philips Ingenuity CT (Philips Medical systems, Cleveland, USA). PCT was performed 1–12 days after TBI (mean 4 ± 3 days) in the 1st group and 2–8 days (mean 4 ± 2 days) after surgical evacuation of the hematoma in the 2nd group.

The perfusion examination report included an initial contrast-free CT of the brain [23]. Extended scanning was further performed of 16 "areas of interest," 160 mm in thickness, within 60 s with a contrast agent administered ("Perfusion JOG" mode). The scanning parameters were 160 kVp, 160 mA, 70 mAs, 512 × 512. The contrast agent (Ultravist 370, Schering AG, Germany) was administered with an automatic syringe injector (Stellant, Medrad, Indianola, PA, USA) into a peripheral vein through a standard catheter (20G) at a rate of 4–5 ml/sec in a dose of 30–50 ml per one examination. After scanning, the data volume was transferred to the PACS (JSC "KIR", Kazan, Russia) and a workstation Philips Extended Brilliance Workspace (Philips HealthCare Netherland B.V., Best, the Netherlands) and MATLAB 2013b (The MathWorks Inc., Natick, MA, USA). Artery and vein marks were automatically recorded, followed by the manual control of indices in the time-concentration diagram. The so-called "region of interest" (ROI) was established based on subcortical areas of middle cerebral artery.

The computed tomography angiography source image (CTASI) analysis enabled us to visualize the main vessels of the brain and to assess the state of their lumen [24]. In all patients included in this study the minimal intensive projection data analysis identified the local luminal narrowing MCA more than 30% of the diameter as compared to adjacent sections of the same vascular segment, based thereon an "angiographic" CVS was diagnosed [25]. 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% of reduction of the lumen, severe-the vessel has less than 30% of luminal flow on angiography.

Perfusion maps were derived from the tissue time-attenuation curve on the basis of the change in x-ray attenuation, which is linearly related to iodinated contrast concentration on aper-voxel basis with time. Errors introduced by delay and dispersion of the contrast bolus before arrival in the cerebral circulation were corrected for by using a block-circulant deconvolution algorithm. Quantitative perfusion indices, including CBF, were calculated on a voxelwise basis and used to generate color-coded maps. 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.

Cerebral blood flow velocity of the middle cerebral artery was recorded bilaterally using transcranial Doppler with 2-MHz probes attached with a headband (Sonomed 300 M, Spectromed, Moscow, Russia). Arterial blood pressure was measured noninvasively (MAP 03, Cardex, Moscow, Rus-

Table 2 Comparison of the analyzed parameters.

		MAP (mmHg)	Vd (sm/sec)	Vm (sm/sec)	CBF (ml/100 g × min)	eCPP (mmHg)	CVR (mmHg × 100 g × min/ml)
1	Group 1	98.3 ± 11.1	30 ± 9.3	44.4 ± 10.5	35.6 ± 18.1	87 ± 30.5	2.99 ± 1.4
2	Group 2 (ipsilateral sides)	91.5 ± 15.2	27.5 ± 9.4	48.6 ± 19.3	27.5 ± 17.7	100.4 ± 43.6	4.1 ± 2.7
3	Group 2 (contralateral sides)	91.5 ± 15.2	34 ± 14.4	41.7 ± 12.6	32.2 ± 16.4	71.4 ± 21.1	2.6 ± 2.2
	p (1–2)	0.855	0.411	0.817	0.046*	0.273	0.035*
	p (1–3)	0.855	0.312	0.472	0.521	0.041*	0.366
	p (2–3)	1	0.034*	0.087	0.163	0.0008*	0.013*

* Difference is statistically significant

sia). We used a complex of the neuromonitoring «Centaurus» (Ver. 2.0, Nizhniy Novgorod State Medical Academy, Russia).

Statistical analysis

Cerebral vascular resistance was calculated by the formula modificated by P. Scheinberg [26]:
CVR = eCPP/CBF,
where CVR is cerebrovascular resistance (mmHg × 100 g × min/ml),
eCPP is estimated cerebral perfusion pressure (mmHg),
CBF is cerebral blood flow (ml/100 g/min).

Noninvasive cerebral perfusion pressure was calculated by the formula M. Czosnyka [27]:
eCPP = MAP × Vd/Vm + 14,
where eCPP is estimated cerebral perfusion pressure (mmHg),
MAP is mean arterial pressure (mmHg),
Vd is diastolic flow velocity rate of middle cerebral artery (sm/sec),
Vm is mean flow velocity rate of middle cerebral artery (sm/sec).

Reference range CVR was chosen according Scheinberg P. 1.54 ± 0.24 mmHg × 100 g × min/ml [26]. The comparisons between the groups were performed by using the Student's t-criterion and the criterion χ^2. The program Statistica 7.0 (StatSoft Inc., Tulsa, OK, USA) was used for the analysis. A significance level of $p < 0.05$ was determined.

Results

In the 1st group the "angiographic" CVS was unilateral in 30 cases and bilateral in 11 cases, and in three cases it extended to segments of the anterior cerebral artery. In 15 cases the CVS was mild, in 21 cases it was moderate and in 5 cases it was severe. The "angiographic" CVS coincided with the 'dopplerographic' CVS in all patients with the severe CVS and in 5 patients with the moderate CVS. In the 2nd group in 28 cases the "angiographic" CVS was revealed on the side of the removed hematoma. In 10 cases it was developed on the side opposite to the removed IH and in one case it was bilateral and included in addition to M_{1-2} also segments A_{1-2}. In 13 cases the CVS was mild, in 16 cases it was moderate and in 10 cases it was severe. The "angiographic" CVS coincided with the "dopplerographic" CVS in 9 patients with the severe and moderate CVS.

Mean values and standard deviations of the data are summarized in Table 2

Mean values of CVR was significant higher ($p = 0.05$) in both the first and second group (with or without traumatic hematomas) in comparison with reference data ($p < 0.05$). The CVR in the second group was statistically significant higher than in the first group especially on the side of the former hematoma ($p = 0.035$). There were significant difference in CVR between the perifocal zone of the former hematoma and the opposite locus of the contralateral hemisphere ($p = 0.013$).

At the same time, the vasospasm development on the side of the removed IH enhanced even more the the vascular resistance. On average, CVR was 4.45 ± 2.5 mmHg × 100 g × min/ml in perifocal zone of the former IH, while on the opposite side (where there were no hematomas and a vasospasm did not develop) it was 2.46 ± 1.4 mmHg × 100 g × min/ml ($p = 0.0011$).

The vasospasm emergence on the side opposite to the removed IH due to multidirectional CVR changes, which did not have statistically significant differences between them and the reference value. However, small series (10 cases) have not enabled us to do some significant conclusions. In addition, no significant effects of different types of IH on the CVR value were found.

Discussion

It has been established that the narrowing of cerebral arteries developing after traumatic subarachnoid hemorrhage may result in the reducing cerebral blood flow more distal than the spastic segment and depending on the state of the autoregulation, which may lead to brain ischemia and cerebral infarction [28–31].

There are some conflicting data on CVS as the cause of the cerebral ischemia development after SAH. According to some reports, only in 20–30% of patients with the "angiographic" CVS some cerebral ischemia symptoms would develop [32]. Furthermore, the localization of the secondary ischemia is almost in 25% of cases does not coincide with the territory of the spastic artery [32–34].

However, other researchers have reported the high correlation between the "angiographic" CVS and the secondary ischemia development. So, according to R. Crowley only 3% of cerebral ischemia cases with SAH are either not followed by vasospasm, or it may be referred to a mild one [35].

Despite the fact that the foregoing data mainly describe the dynamics of aneurysmal subarachnoid hemorrhages, they quite fully reflect the total variety of cerebral microvascular reactions aimed at maintaining the adequate perfusion with the available CVS, including a posttraumatic CVS [36–38].

It has been previously shown that cerebral microcirculation undergo significant changes (especially in the compression of the brain by IH), which remain even after hematoma's removal [21, 39].

At the same time, it is known that enveloped hematoma as well as the concomitant injury are factors that provoke the posttraumatic CVS development [3–5].

Thus, the study of the cerebrovascular resistance state during the CVS formation in the acute period of head injury is obviously important for its prevention and timely diagnosis [40].

This study has shown that with a developing CVS in the acute period (on the 2^{nd}–3^{rd} day after the accident) of a concomitant craniocerebral injury the CVR significantly increases as compared to the normal data.

One of the common causes of the increasing CVR is the development of a cytotoxic and vasogenic cerebral edema causing the compression of pial vessels [41, 42].

The indirect proof for this hypothesis is the identification of CT signs of cerebral edema in all 80 patients. However, by PCT we have not carried out the blood-brain barrier breakdown study, we could not distinguish zones of ischemic injury and vasogenic edema [43].

Because of this limitation in our study we have not be able to investigate the correlation between the change in CVR, the CVS development and the secondary ischemia.

Another reason for the increasing CVR may be a regional microvascular CVS due to the formation of a large amount of blood degradation products fallen into the subarachnoid cisterns. This effect is realized through the auto-oxidation of haemoglobin to methaemoglobin with the release of iron ions, which in their turn cause the formation of superoxide radicals. Superoxides are supposed to cause a change in the nitrogen oxide concentration and the peroxide damage to the endothelium of pial vessels, thus causing the microvascular CVS development [44–46].

We have not used in our study the laser Doppler flowmetry (that was another limitation in our work) and consequently we could not directly examine the state of microvessels. However, taking into account that the "dopplerographic" CVS have coincided with the "angiographic" CVS in the most severe patients of the both groups, we assume that in this forth part of the patients (24%-in 1^{st} group, 23%-2^{nd} group) the symptomatic character of a spasm took place, which was typical for its microvascular CVS [47, 48].

Another cause of the microvascular bed compression may be astrocytic endfeet swelling. Such swelling evolving in the first hours after injury may persist for a week thereafter [49, 50].

Finally, the compression of pial vessels both in a brain injury and in a vasospasm is associated with the dysfunction of pericytes-cells located in the basal pericapillary membrane. It was shown that the narrowing of arterioles and capillaries occurs because of the disturbance in the expression of endothelin-1 and pericytial receptors, types A and B, as well as the migration of over 40% of pericytes from the basal membrane [51–54].

All these factors as it has been shown above may result in the reduction of the total capillary bed lumen and accordingly to the increasing CVR [55, 56].

It should be noted that the CVS formation after the elimination of the brain compression by enveloped IH changes even more the CVR value [57].

We have ascertained that with the CVS development on the side of the removed IH the CVR remained significantly higher than on the opposite side.

Some researchers note that the compression of the capillary network in the perifocal zone to IH may reach such a value, thereunder the vessel will collapse completely even though a certain vasomotor tone remains. Such value is individual and is called the critical closing pressure [58].

It results in the sudden reduction of the number of functioning capillaries and in the increasing CVR on the side of the vascular spasm and compression [50, 57].

Under such circumstances, in order to maintain perfusion in the perifocal zone with CVS available, the opening of mi-

crovascular (arterio-venous, veno-venous, arterio-arterious, precapillary) shunts and the development of the supracapillary and intracapillary bypass phenomena may occur [59].

Perhaps it is the development of a capillary bypass syndrome that may explain such a paradoxical result we have obtained, when the estimated eCPP value on the side of the removed IH and a CVS has appeared to be higher than MAP. Thus, the present results suggest that the formation of the CVS after a severe concomitant craniocerebral injury cause the prominent increase in the CVR.

The most "vulnerable" for adverse vasospasm effects is a perifocal zone of enveloped hematomas where the CVR increases even more. It indicates gross disorders of the cerebral microcirculation in this zone. The findings of our investigation may have the practical significance for optimizing the selection of individual regimens for brain edema therapy and vascular treatment with CVS available, which would prevent the development of cerebral perfusion disorders in patients with concomitant craniocerebral injury.

Conclusion

The peripheral resistance of brain vessels in the cerebral vasospasm development in the acute period of a concomitant craniocerebral injury significantly increases as compared to the norm. The CVS formation in the perifocal zone after the removal of an enveloped hematoma is followed by a significant increase of the CVR as compared to the symmetric area of the opposite hemisphere.

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