THE EXPERIMENTAL STUDY OF STRESS-RELATED PATHOLOGICAL CHANGES IN CEREBRAL VENOUS BLOOD FLOW IN NEWBORN RATS ASSESSED BY DOCT

OXANA V. SEMYACHKINA-GLUSHKOVSKAYA^{*,†}, VLADISLAV V. LYCHAGOV^{*},
OLGA A. BIBIKOVA^{*}, IGOR A. SEMYACHKIN-GLUSHKOVSKIY^{*}, SERGEY
S. SINDEEV^{*}, EKATERINA M. ZINCHENKO^{*}, MOHHANAD M. KASSIM^{*,†},
AL-FATLE FATEMA ALI^{*,†}, AL HASSANI LEITH^{*,†},
MARIA V. ULANOVA^{*} and VALERY V. TUCHIN^{*,‡,§}

^{*}*Department of Biology, Saratov State University, Astrachanskaya Str. 83
410012 Saratov, Russian Federation*

[†]*Department of Biology, Al-Mustansiriya University, Baghdad, Iraq*

[‡]*Institute of Precise Mechanics and Control of Russia Academy of Science
Rabochaya 28, 410028 Saratov, Russian Federation*

[§]*Optoelectronics and Measurement Techniques Laboratory
University of Oulu, P.O. BOX 4500 90014
University of Oulu, Finland
[†]glushkovskaya@mail.ru*

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In experiments on newborn rats with stress-related intracranial hemorrhage (ICH) using Doppler optical coherence tomography (DOCT) we have shown that latent stage of ICH (4 h after stress) is characterized by decrease of venous blood outflow and the loss of sensitivity of sagittal vein to vasoconstrictor effect of adrenaline. The incidence of ICH (24 h after stress) was accompanied by progression of early pathological changes in cerebral venous blood flow (CVBF) and development of venous insufficiency. Taking into consideration of this fact, we suggest that the suppression of CVBF related to the severity to the deleterious effect of stress on the brain hemodynamics in newborn rats. These facts allow us to conclude that the venous insufficiency with the loss of vasoconstrictor response to adrenaline is an informative and sensitive component of pattern of CVBF that can be important diagnostic criteria of risk of ICH development in newborns.

Keywords: Doppler optical coherence tomography; stress-related intracranial hemorrhage; cerebral venous blood flow; adrenaline.

1. Introduction

Intracranial hemorrhage (ICH) is defined as the pathologic accumulation of blood within the cranial vault. ICH is the most common type of brain bleeding in preterm newborns (i.e., low birth weight infants weighing less than 1500 g).¹ In recent years, it was believed that in term newborns ICH is relatively uncommon but largest findings suggest that ICH in term newborns is much more frequent than previously thought.^{2,3} The problem is that unlike preterm ICH, ICH in term newborns has different location, multiple etiology, clinical presentation and neurological outcome.^{4,5} The incidence or prevalence of ICH is not known. Only some term infants with ICH present with clinical events, so the true incidence of ICH is difficult to determine.⁶ The lack of diagnostic markers and effective technology for early determination of ICH risk in newborns explains the high rate of neonatal death and less optimistic neurologic prognosis in infants after ICH.^{7–11}

The main reasons for ICH in newborns remain unknown. In our previous experimental study, we have shown that stress is a key provoke factor for ICH in adult rats.^{12,13} Others also demonstrate that stress plays a crucial role in development of ICH.^{14–16} Looney *et al.* hypothesized that in newborns the prenatal stress contributes brain injury and ICH.³ The mechanism responsible for stress-induced ICH are not well understood, but there is strong evidence that stress-related alterations in cerebral blood flow (CBF) may contribute to the pathogenesis of ICH.^{17,18} Our previous results on adult rats with model of stress-induced ICH indicate that cerebral veins are more sensitive and less resistant to deleterious effect of stress than cerebral arteries.¹² Some authors demonstrate that impaired venous hemodynamics is implicated in contributing to the occurrence of ICH in newborns.^{19,20} A number of investigators have shown that ICH in newborns is primary venous.²¹ These facts suggest that pathological changes in cerebral venous blood flow (CVBF) can be important marker and sensitive diagnostic criteria for risk of ICH development in newborns. However, there is limited information regarding the particularities of alterations of CVBF in infants at normal condition and especially during ICH and the parameters of pattern of CVBF that are informative for the prognosis of ICH in newborns.

Sympathetic nervous system plays a key role in regulation of cerebral circulation from early stage of

development organism.^{22–24} Sympathetic vasoconstriction of cerebral vessels has been proposed to be a protective mechanism for the brain, limiting cerebral perfusion and microcirculatory pressure after ICH.^{25–29} Despite intensive investigations in this field, the exact functional role of the sympathetic nervous system in the regulation of the cerebral hemodynamics remains an issue of debate.³⁰ Notice, there is limited information regarding the age particularities of adrenergic control of cerebral circulation.^{26,30}

There are a lot of techniques providing CBF imaging. The most accepted are positron emission tomography (PET),^{31,32} magnetic resonance imaging (MRI) (including functional MRI),^{33–36} Doppler ultrasound and near-infrared spectroscopy (NIRS).^{37,38} MRI provides high-resolution structural images but needs much time for data acquisition and processing and does not supply with information about blood flow parameters. fMRI and PET use radioactive contrast agents to retrieve the data concerning with blood flow and blood volume in the sample and have relatively low spatial and temporal resolution. Doppler ultrasound and NIRS suffer from ambiguity in deconvolution of blood flow velocity and blood flow volume since the raw data usually links to indirect parameters of blood oxygenation level or blood flow level in which both these values enter equally. Besides, Doppler ultrasound and NIRS both cannot provide high spatial resolution functional images. In last years, photoacoustic³⁹ and fluorescence⁴⁰ imaging techniques show potential to visualize microvascular blood flow. However, the tradeoff between penetration depth and resolution is still there. Though multiphoton imaging provides subcellular resolution, scanning area is still limited to hundreds of micrometers, and vice versa the using of acoustic waves improves penetration depths and impairs the resolution. Detailed discussion of advances and limits of imaging techniques listed above can be found in many works.^{41–44} The main idea of these reviews is that in contrast to conventional radionuclide tomography and infrared spectroscopy coherent optical imaging techniques can offer unique combination of characteristics like very high spatial and temporal resolution of functional images, lack of ionizing radiation, variety of contrast techniques, mobility (in order to achieve bedside facility), and finally measuring the blood flow parameters in real units of velocity and geometry of vessels network. Doppler optical coherence tomography (DOCT) is

one of such techniques. Using DOCT one can measure blood flow in vessels and reconstruct vessels map on the base of OCT speckle image analysis.^{45–48}

The objective of this study was to determine the prognostic criteria for pathological changes in pattern of CVBF using DOCT in newborn rats with model of stress-induced ICH.

2. Methods and Materials

Subject. Experiments were carried out in mongrel newborn rats weighing 5–6 g. All procedures were performed in accordance with the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health.³⁵ The rats were housed at $25 \pm 2^\circ\text{C}$, 55% humidity, and 12:12 h light–dark cycle. To induce ICH, newborn rats underwent severe stress — effect of intermittent infrasound (10 Hz, 120 dB) during 2 h. The details of performance of experiment modeling of ICH is described here.⁴⁹

CVBF measuring. The anesthetized rats (thiopental anesthesia, 40 mg/1000 g) with fixed head and scalp incision were immobilized. The measurement of CVBF performed through the fontanel with focus on the superior sagittal vein (the main trunk) (see Fig. 1). The monitoring of CVBF carried out in rats: (1) in normal condition ($n = 12$); (2) in the masked period of ICH (4 h after stress, $n = 20$); (3) during ICH (24 h after stress, $n = 20$). To study the capacity of vascular stress-reactivity, we analyzed the sensitivity of sagittal vein to adrenaline (0.1 mg/kg, Sigma, iv) in healthy newborn rats ($n = 10$) and stressed rats 4 h (without ICH, $n = 14$) and 24 h (incidence of ICH, $n = 14$) after stress.

Fig. 1. The imaging of superior sagittal vein in newborn rats through fontanel. The arrow shows the main trunk cerebral vein.

We used a commercially available swept source DOCT system (OCS1300SS; Thorlabs, Inc, USA) with operating at 1325 nm central wavelength and 100 nm bandwidth. Longitudinal resolution (in air) was about $12 \mu\text{m}$. Software package supplied with this system allows one to recover Doppler phase map out of the complex form of interference signal resulting from the Fourier transform. The Doppler phase map depicts spatial distribution of moving particles and their velocity. In this map, location of nonzero phase values corresponds to location of vessels in the sample, while magnitude of these phase values relates to blood velocity in the vessels. Because of interferometric data processing, the system implements phase-resolved technique for Doppler frequency shift measurements and phase values are wrapped modulo π . Such wrapped phase map is produced by the out-of-the-box system software. To solve this problem, we have developed custom home-made software using LabVIEW Development System (National Instruments Corporation, USA) for further processing of original phase maps. The processing algorithm consists of the following steps:

- unwrapping phase distribution;
- translation of the phase values into the frequency shift according to the system specification (axial scan rate) and
- translation of the frequency shift into the velocity according to experimental arrangement's specification (central wavelength of swept source, incident angle and sample refractive index).

Velocity of moving cells was calculated using equation:

$$V = \frac{\lambda_0 f_D}{2n \cos \theta}, \quad (1)$$

where λ_0 is the central wavelength of radiation (in vacuum), f_D is the Doppler frequency shift, n is the refractive index, been assumed to be equal to 1.4 and θ is the angle between directions of incident radiation and of cells moving. Equation (1) shows that for particles moving at equal velocities, the major contribution to the Doppler signal give the particles that move at lesser angle against the incident wave. At the same time, incident wave scattered by particles moving perpendicularly to the direction of incidence does not undertake Doppler shift at all. According to the above we assume that waves propagating close to aperture angle of illuminating lens

generate a major part of the Doppler signal (if the particles move perpendicularly to the optical axis of that lens). Since vasculature in the tissue is of the plexiform this assumption is quite rough, but it allows us to make a simplified preliminary analysis of expected results. Aperture angle of output lens LSM03 mounted in the used OCT system is of 7.5° according to specs. That value was used in estimation.

The Doppler frequency shift f_D is calculated as the OCT signal phase change rate:

$$f_D = \frac{\Delta\varphi}{2\pi} f_A. \quad (2)$$

Here $\Delta\varphi$ is the phase difference that can be retrieved from the phase maps produced by the Thorlabs software, f_A is the axial scan rate which is equal to 16 kHz. Since $\Delta\varphi$ is wrapped modulo π , f_D and V are also wrapped terms. Actual values of f_D and V can be recovered using unwrapping procedure.

Statistical analysis. Results were presented as mean $\pm$ standard error of the mean (SEM). The differences from the initial level in the same group were evaluated by Wilcoxon test. Inter-group differences were evaluated using Mann–Whitney test and ANOVA-2 (post hoc analysis with Duncan's rank test). Significance levels were set at $p < 0.05$ for all analyses.

3. Results

In the first step of our work, we analyzed the changes in parameters of CVBF in newborn rats in the different stages of development of stress-induced ICH.

The first 2 h after stress were not accompanied by any changes in CVBF, CVBV was tendentionally decreased 3 h after beginning of experiment but these changes were not statistically significant. About 4 h after stress-off was characterized, there were significant changes in CVBF in all newborn rats despite the fact that they did not demonstrate ICH in this post-stress period. The diameter of main trunk sagittal vein was essentially increased in stressed rats than in unstressed animals (see Fig. 2). So, after stress the lumen of vein was in 2.1-fold higher compared with one before stress (0.48 ± 0.02 mm vs 0.22 ± 0.03 mm, $p < 0.05$). The dilation of superior sagittal vein was accompanied by decrease in speed of blood flow (3.11 ± 0.42 mm/s vs 6.00 ± 0.09 mm/s, $p < 0.05$) reflecting the fall of cerebral venous blood outflow. We did not find progression of above-indicated pathological changes in CVBF during the next 12 h after stress (see Table 1). Thus, 4 h after stress is the important early period for clear visualization of critical alteration in CVBF in newborn rats.

The ICH was accompanied by progression of above-indicated pathological changes in parameters

Fig. 2. The velocity map of main trunk sagittal vein in newborn rat under normal condition (a), 4 h after stress (b) and 24 h after stress (c).

Table 1. The changes in diameter of main trunk sagittal vein and velocity of blood flow under normal condition, during 12 h after stress on newborn rats.

	Normal condition	1 h after stress	2 h after stress	3 h after stress	4 h after stress	8 h after stress	16 h after stress
Diameter, mm	0.22 ± 0.03	0.20 ± 0.01	0.23 ± 0.02	0.30 ± 0.04	0.48 ± 0.02^a	0.44 ± 0.05^a	0.50 ± 0.09^a
Blood flow velocity, mm/s	6.00 ± 0.09	5.84 ± 0.06	5.91 ± 0.07	4.88 ± 0.05	3.11 ± 0.42^a	3.37 ± 0.19^a	3.00 ± 0.22^a

^a $p < 0.05$ vs basal levels.

of CVBF (see Fig. 2). So, in newborn rats with ICH the diameter of main trunk sagittal vein was greater in 3.0-fold compared with unstressed animals (0.67 ± 0.07 mm vs 0.22 ± 0.03 mm, $p < 0.05$) and in 1.4-fold vs stressed rats without ICH (0.67 ± 0.07 mm vs 0.48 ± 0.02 mm, $p < 0.05$). The fall of speed of blood flow in dilated cerebral vein was more pronounced in rats with ICH than in stressed rats without ICH and especially compared with healthy rats (see Table 1).

In the second step of our work, we investigated the sensitivity of sagittal vein to adrenaline in healthy and stressed newborn rats on different stages of ICH development (see Table 2). In healthy rats, adrenaline infusion was accompanied by constriction of sagittal vein (see Fig. 3). So, adrenaline induced the decrease in diameter of main trunk sagittal vein (0.10 ± 0.04 mm vs 0.20 ± 0.02 mm, $p < 0.05$).

Table 2. The changes in diameter of main trunk sagittal vein and velocity of blood flow before and after adrenaline injection in newborn rats under normal condition, 4 h and 24 h after stress.

	Normal condition	4 h after stress	24 h after stress
Before adrenaline injection			
Diameter, mm	0.20 ± 0.02	0.42 ± 0.05	0.59 ± 0.04^b
Blood flow velocity, mm/s	5.82 ± 0.06	3.27 ± 0.02	2.48 ± 0.07^b
After adrenaline injection			
Diameter, mm	0.10 ± 0.04^a	0.47 ± 0.03	0.63 ± 0.04^b
Blood flow velocity, mm/s	6.01 ± 0.09	3.42 ± 0.04	2.59 ± 0.08^b

$p < 0.05$ vs: ^abasal levels; ^bbetween stressed rats.

The speed of blood flow had tendency to be increased after adrenaline treatment but these changes in CVBF were not statistically significant (6.01 ± 0.09 mm/s vs 5.82 ± 0.06 mm/s).

Surprisingly, the stressed newborn rats did not demonstrate reactivity to adrenaline that we observed already on the masked period of ICH. Indeed, adrenaline injection to the stressed rats without ICH (4 h after stress) was not accompanied by any changes in diameter of main trunk of sagittal vein and speed of blood flow (0.47 ± 0.03 mm vs 0.42 ± 0.05 mm and 3.42 ± 0.04 mm/s vs 3.27 ± 0.02 mm/s, respectively). The treatment of newborn rats with ICH by adrenaline did not cause any changes in parameters of CVBF (0.63 ± 0.04 mm vs 0.59 ± 0.04 mm — diameter, 2.59 ± 0.08 mm/s vs 2.48 ± 0.07 mm/s — speed of blood flow).

4. Discussion

Collectively, in this study using DOCT we examined the parameters of CVBF and analyzed the vascular stress-reactivity of sagittal vein (adrenaline test) on different stages of development of stress-induced ICH in newborn rats. Our results show that the deleterious effect of stress on the cerebral venous hemodynamics in newborn rats developed during 24 h, during the first 4 h after stress (masked period of ICH) newborn rats did not demonstrate ICH but the CVBF was significantly changed. In this period, we observed increase in diameter of sagittal vein with the fall of blood flow velocity. Thus, latent stage of ICH was accompanied by dilation of superior sagittal vein reflecting decreased venous blood outflow. In the next day after stress ICH

Fig. 3. The velocity map of left branch of sagittal vein before (a) and after (b) adrenaline infusion in newborn rat.

developed in all stressed rats. Notice that incidence of ICH was characterized by progression of pathological changes in CVBF. The relaxation of sagittal vein and decrease in blood flow velocity were more pronounced in rats with ICH than in stressed rats without ICH (masked period) and especially compared with healthy rats. These facts allowed us to conclude that stress induced gradual suppression of cerebral venous blood outflow and development of venous insufficiency. Others also demonstrate that decrease in cerebral venous blood outflow is implicated in contributing to the occurrence of ICH in newborns.^{19,20} Some studies show that impairment of CVBF with low cerebral perfusion pressure are associated with ICH and poor outcomes after brain injury in children.^{26,50–52} The current 2003 Pediatric Guidelines recommend preventing or rapidly treating venous insufficiency and cerebral hypotension in children.⁵³ The clinical data suggest that the ICH in newborns is primary venous.²⁰ Thus, suppressed CVBF is closely correlated with ICH in newborns.

The one commonly employed strategy to increase CVBF and cerebral perfusion pressure is to use vasopressors (adrenaline, norepinephrine, dopamine or epinephrine).^{54,55} Yet, there are no studies describing vasopressor use or comparing vasopressor effectiveness in the setting of pediatric ICH and brain injury. To study the effect of sympathetic vasopressors on CVBF in newborn rats during development of ICH, we analyzed the sensitivity of sagittal vein to adrenaline in normal rats and stressed rats without ICH (4 h after stress) and with ICH (24 h after stress). In healthy rats, adrenaline induced the decrease in diameter of sagittal vein with tendency to increase in blood flow velocity that suggest about vasoconstriction of cerebral vein. Interestingly notice, after severe stress the pathological changes in CVBF in newborn rats were accompanied by the loss of sensitivity to adrenaline. Indeed, we observed that sagittal vein did not respond to adrenaline independently on the stages of development of ICH. These results suggest about the low functional capacity of sympathetic system in newborn rats that can be attributed to immaturity of adrenergic neurons and synapses in the brain in newborn rats. Adrenergic-related vasoconstriction effect is realized by activation of different types of alpha-adrenoreceptors. In experiments on newborn rat has been shown that density of alpha-adrenergic receptors in brain is very low during the first week

after birth. Between day 7 and 14 there is a rapid increase in the density of alpha-adrenoreceptors. Adult levels are reached by the end of the second week.^{56–58} Thus, the loss of sensitivity of cerebral veins to vasoconstrictor effect of sympathetic agonist – adrenaline under severe stress influences can be one of an important mechanism underlying pathological changes in CVBF and the decrease in resistance to development of ICH.

Collectively, our results show that the decrease in CVBF related to the severity to the deleterious effect of stress on the brain hemodynamics. The masked period of ICH (4 h after stress) was characterized by early changes in CVBF due to the decrease in venous blood outflow. The incidence of ICH (24 h after stress) was accompanied by progression of early pathological changes in CVBF and development of venous insufficiency. Our results are consistent with the findings of other researches who show that suppressed CVBF, hypotension and low cerebral perfusion pressure are associated with poor outcomes after ICH in children with brain injury.^{59–68} In adult patients with subarachnoid hemorrhage, investigators demonstrated that the fall CBF with oxygen desaturation is associated with a poor neurological outcome.⁶⁹ Progressive decrease in CBF have been reported in patients with subarachnoid hemorrhage for three weeks after bleeding, and the decrease in blood flow is related to a worsening in clinical grade.⁷⁰ The same results are obtained from animal data with experimental model of ICH.⁷¹

5. Conclusion

In summary, in experiments on newborn rats with stress-related ICH using DOCT we have shown that latent stage of ICH (4 h after stress) is characterized by decrease of venous blood outflow and the loss of sensitivity of sagittal vein to vasoconstrictor effect of adrenaline. The incidence of ICH (24 h after stress) was accompanied by progression of early pathological changes in CVBF and development of venous insufficiency. Taking into consideration of this fact, we suggest that the suppression of CVBF related to the severity and to the deleterious effect of stress on the brain hemodynamics in newborn rats. These facts allow us to conclude that the venous insufficiency with the loss of vasoconstrictor response to adrenergic agonists are an informative and sensitive components of pattern of CVBF that

can be important diagnostic criteria of risk of ICH development in newborns.

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