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Patterns of ocular neurovascular reactions

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Aim — to examine factors and determinants of ocular neurovascular reactions (NVR). **Material and methods.** The study included 120 healthy participants of both sexes aged 20.9±0.6 years, who underwent a standard ophthalmic examination. Ocular microcirculation was recorded using laser Doppler flowmetry. Autonomic homeostasis and the intensity of slow-wave oscillations of hemodynamics were of interest. Autoregulation of cerebral blood flow was assessed by transcranial color-coded duplex scanning. **Results.** The dynamics of perfusion control mechanisms (myogenic and neurogenic) have been studied in the young healthy population of Krasnoyarsk. The role of the autonomic nervous system in initiating a particular type of ocular NVR has been identified. The authors have also determined the significance of the nitric oxide production intensity in different types of NVR. **Conclusion.** The type of ocular NVR is determined by parameters of cerebral hemodynamics. Normotonic NVR is associated with effective autoregulation of cerebral blood flow, while hyper- and hypotonic types of reactions — with autoregulatory failure.

Keywords: *eye, ocular neurovascular reactions.*

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Vascular pathology of the eye, caused by both general and local blood flow disturbances, occupies a leading position among ophthalmic diseases. Visual deterioration occurs due to either primary, or secondary decline in the blood supply of the ocular tissues.

To manage the situation, one should determine the extent of hemodynamic disturbance and follow it up throughout all treatment stages.

Pathogenetically appropriate are treatments aimed at improving organ hemodynamics with subsequent restoration of blood flow and metabolism in ocular layers [1]. Despite wide popularity of vasculotropic agents, they, however, are not always effective and sometimes cause negative reactions. The reason is that treatment tactics does not always consider functional state of the vessels and their individual typological features. New knowledge and technologies in ophthalmology and physiology created a distance between clinical experience and theoretical notion of factors that influence organ hemodynamics. Mechanisms of individual physiological responses of ocular vessels to stress remain unclear [2, 3]. In a study on functional changes in the eye and brain associated with different ophthalmic pathology, 50.8% of more than a thousand patients demonstrated hypotonic neurovascular reactions (NVR). An adapted therapy that considers individual features of ocular NVR has proved highly effective in all clinical groups as compared to conventional treatment and enabled an almost threefold decrease in unnecessary consumption of angiotropic drugs (especially, vasodilators).

Identification of mechanisms that determine typological features of ocular vessel response to stress is an important problem of ophthalmology and fundamental medicine.

The aim of this study was to examine factors and determinants of ocular neurovascular reactions to cold stress.

Material and methods

The study included 120 Krasnoyarsk citizens of both sexes aged 20.9±0.6 years. All of them were examined by a physician and recognized as overall healthy. They also had no ocular pathology.

The type of NVR was identified basing on the findings of rheoophthalmography (ROG) with cold stress test.

Ocular microcirculation was recorded using laser Doppler flowmetry (LDF). The meter used was single-channel with emission wavelength of 0.63 μm (red range) [4, 5]. The state of perfusion control mechanisms, myogenic and neurogenic tone in particular (MT and NT, respectively), was judged from blood flow oscillation amplitudes in certain frequency ranges.

Serum nitric oxide levels were determined with modified Griess test (V.B. Karpyuk et al., 2000).

Autonomic homeostasis and the intensity of slow-wave hemodynamic fluctuations (SWHF) were evaluated from heart rate changes at cardiorythmography (CRG) with load tests (mental load and hyperventilation).

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Autoregulation of cerebral blood flow was assessed by transcranial color-coded duplex scanning at mild physical exercise [4].

Cerebral hemodynamic parameters were recorded in the middle cerebral artery before and no later than 15 secs after physical exercise. The increase in peak systolic and end diastolic velocity (PSV and EDV, respectively) in response to functional load was calculated.

Results and discussion

Having analyzed the data collected, we have identified three main types of NVR: normotonic, hypotonic, and hypertonic. There were no cases of non-reactive NVR within the studied healthy population (**Fig. 1**).

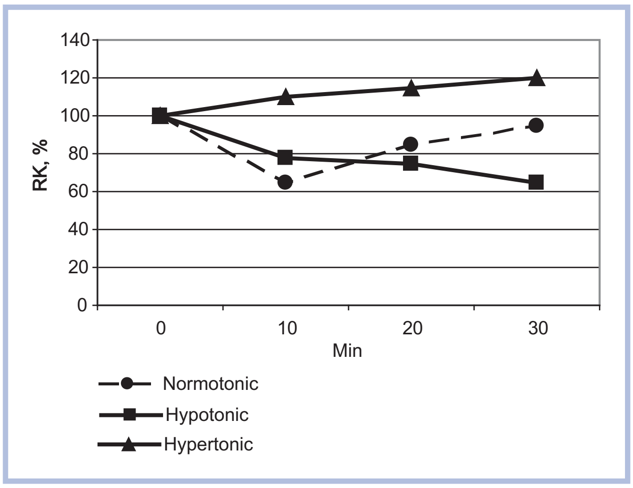

Fig. 1. **Dynamics of the rheographic coefficient (RC) in different types of ocular neurovascular reactions.**

Distribution of the three types of ocular NVR among the young healthy population matches previously documented patterns. Normotonic NVR has been found to predominate in 44.2% of cases, hypotonic — in 35% of cases, and hypertonic — in only 20.8% of cases. These results enable creation of a database of regional 'norms' for typological characteristics of ocular NVR.

Intergroup comparisons of sex composition revealed that normotonic NVR was nearly twice as common among men than women, while the latter prevailed in the hypotonic and hypertonic groups. The finding points out sex differences in the structure of NVR types. Clearly, these differences are due to sex-specific features of neurohumoral homeostasis.

The differences in hemodynamic parameters, as established by ROG, indicated a 1.5-time greater blood filling in normotonic NVR as compared to hypertonic. According to LDF, the highest erythrocyte count was recorded in hypotonic NVR patients, which suggests, despite previous beliefs, that there is no direct relationship between volume and velocity parameters of blood flow by ROG and LDF, respectively. This should be taken into account when interpreting rheoophthalmography cold test results.

Analysis of myogenic and neurogenic amplitudes of microcirculatory oscillations at rest and their changes under cold exposure, revealed with LDF, has yielded interesting patterns. Thus, the hypotonic type of NVR was associated with low MT at rest and its further gradual decrease under functional load. At that, neurogenic oscillations showed average values at rest and mild fluctuations under load. In our opinion, such a combination of myogenic and neurogenic fluctuations may lead to post-load vasoconstriction in hypotonic ocular NVR (**see the table**).

In hypertonic NVR, both components, neurogenic and myogenic, contributed significantly to the basal vascular tone. After cold stress, there was a gradual decrease in neurogenic and myogenic activity on LDF. Presumably, the mentioned shift of microhemodynamic oscillation amplitudes in this type of NVR may lead to vasodilation in response to stress.

Normotonic patients had average myogenic and low neurogenic activity at rest as compared to other NVR types. At that, the myogenic component showed greater stress-related fluctuations than the neurogenic: it increased immediately after an exposure to cold and got reduced at 10 to 20 minutes of the study with no significant changes in neurogenic activity.

The data obtained brings us to the conclusion that both myogenic and neurogenic components are important factors for the formation of basal vascular tone and that their fluctuations determine the type of vascular reactivity to functional load (cold stress).

Having investigated the role of endothelium in the formation of vascular reactivity, we have revealed signifi-

Cold stress induced changes in microcirculatory oscillations on LDF graphs (M±*SD*)

Type of ocular NVR	LDF parameter	Before exposure to cold	Immediately after functional load	10 minutes after functional load	20 minutes after functional load
Normotonic	NT	1.36±0.06	1.33±0.07	1.31±0.06	1.38±0.05
	MT	1.83±0.08	2.55±0.11**	2.34±0.07*	1.93±0.05
Hypotonic	NT	1.58±0.08	1.62±0.05	1.59±0.09	1.63±0.08
	MT	1.51±0.04	1.94±0.06*	2.25±0.07**	2.23±0.11**
Hypertonic	NT	2.19±0.07	1.91±0.08**	1.58±0.06**	1.31±0.07**
	MT	2.25±0.11	1.95±0.08*	1.84±0.07*	1.83±0.06*

Note. Differs significantly from prior-to-stress values (Student's t-test). * — $p<0.05$; ** — $p<0.01$.

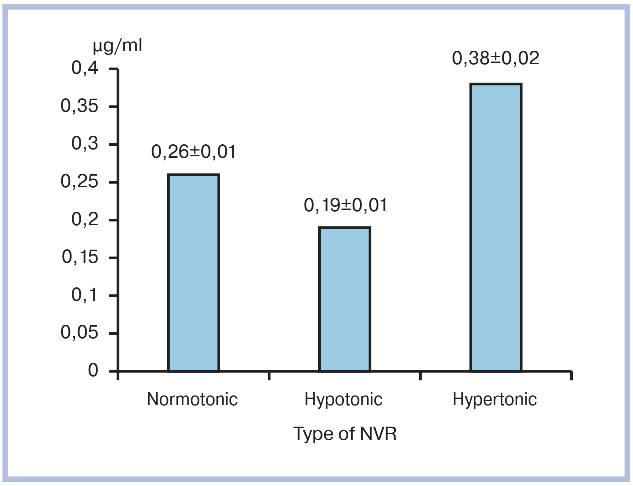

Fig. 2. **Comparison of nitric oxide blood levels in individuals with different types of ocular neurovascular reactions.**

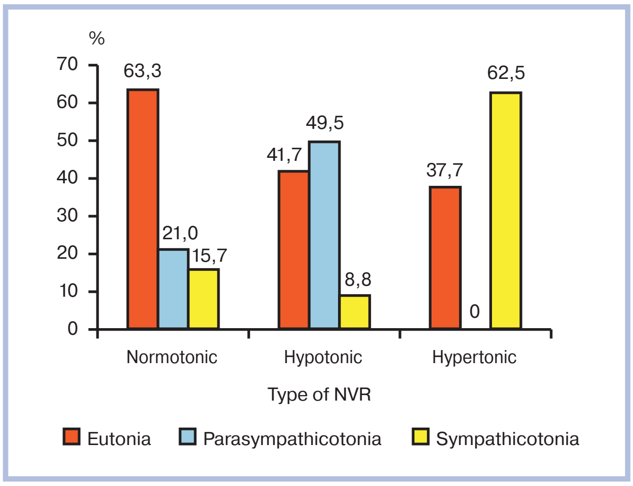

Fig. 3. **Dominance of ANS divisions in different types of ocular neurovascular reactions.**

cant differences in the basal nitric oxide production in individuals with different types of NVR. Thus, normotonic NVR was associated with moderate NO production as compared to other types. Moreover, it fit into the previously established range of normal NO production in healthy young people. Interestingly, the level of NO production in hypertonic NVR was approximately 2 times higher than that in the hypotonic group **(Fig. 2)**.

Nitric oxide is known to be the major endothelial vasodilator and its constant secretion is responsible for maintaining the basal tone [6]. Apparently, hypernitritemia in hypertonic NVR acts as an endothelial counterbalance to neurogenic vasopression and endothelial vasoconstrictors. Stress-triggered vasodilatation, in turn, may be determined by nitroxidergic mechanisms. Low level of NO production in individuals with hypotonic NVR may be due to low basal MT (by LDF). To achieve equilibrium, NO production in blood declines.

Moreover, it is known that vascular reactivity is determined by not only local, but also central mechanisms of regulation. Having studied dominance patterns of the autonomic nervous system (ANS) in the participants, we have revealed the following regularities. In normotonic NVR, ANS acted eutonically in 63.3% of cases, while 21% of participants demonstrated parasympathicotonia and 15.7% — dominance of the sympathetic division of the ANS. In hypotonic NVR, parasympathetic effects prevailed in 49.5% of cases; 41.7% of participants appeared eutonic and only 8.8% showed dominance of sympathetic centers of the ANS. Finally, in hypertonic NVR, sympathetic dominance was documented almost twice as often as eutonic homeostasis. Cases of parasympathicotonia have not been found in this group **(Fig. 3)**.

These data are consistent with the results of LDF. Hypertonic ocular NVR is associated with mostly a high-amplitude neurogenic component of the basal tone of intraocular blood vessels. Depression of the neurogenic oscillation amplitudes in response to functional load in

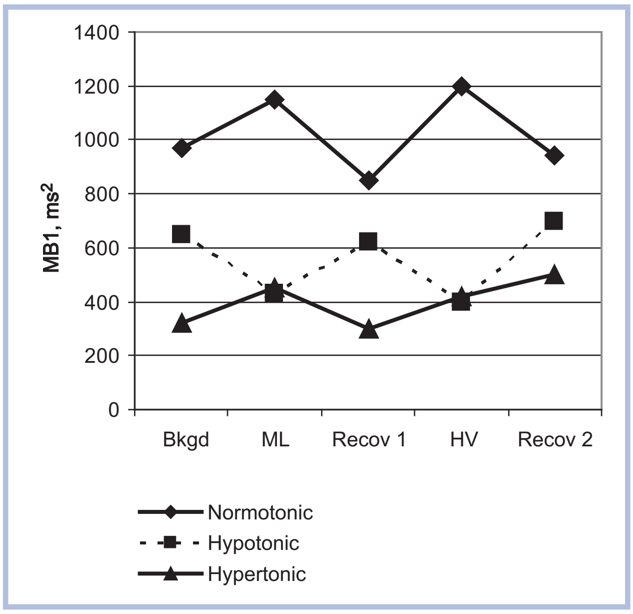

Fig. 4. **MB1 dynamics on CRG in different types of ocular neurovascular reactions.**

Bkgd — the initial MB1 value; ML — mental load; Recov 1,2 — the first and the second recovery periods; HV — hyperventilation.

this group is, apparently, due to exhaustion of adaptive reserves of the autonomic neural regulation.

Thus, normotonic NVR is significantly more often found in individuals with eutonia of ANS centers, while hypotonic NVR is characteristic of parasympathicotonia, and hypertonic — of sympathetic dominance.

The said differences in autonomic regulation patterns in individuals with different types of NVR, firstly, indicate the significance of this factor for the formation of vascular reactivity, and, secondly, may determine further differences in adaptive resources of organ hemodynamics.

Having explored different formation mechanisms of typological features of ocular NVR, we have established

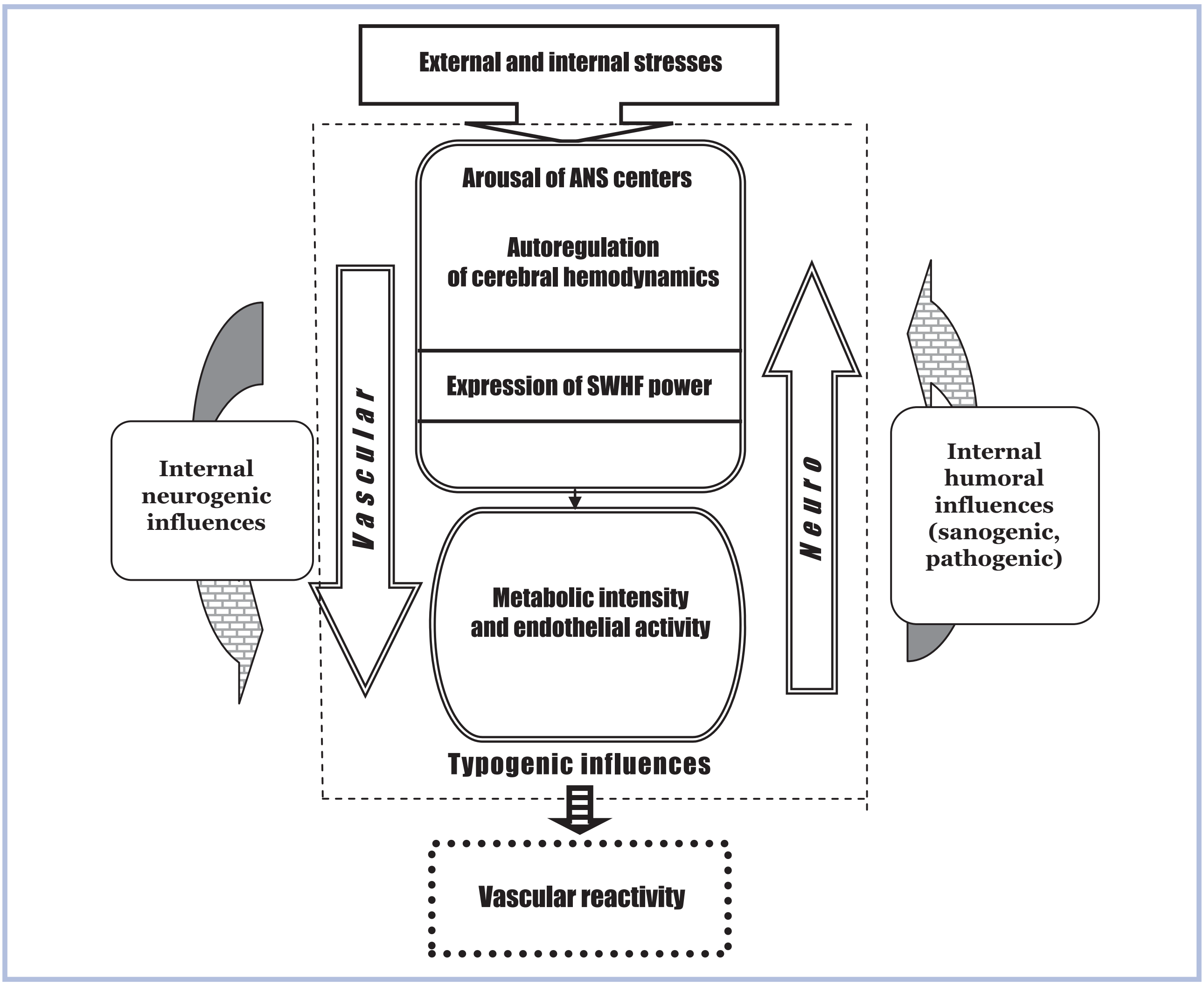

Fig. 5. **Hypothetic scheme of typological formation of ocular neurovascular reactions.**

differences in the intensity of SWHF and its reactivity in individuals with different types of NVR [7].

The power of SWHF at rest and under functional load in individuals with normotonic NVR indicates the presence of substantial adaptive capacities of organs and systems of the body. In hypotonic and hypertonic NVR, the profile of SWHF power changes under functional load lied below the range of average normal values for healthy young adults, thus indicating a certain 'energy deficit' in this type of NVR (**Fig. 4**). Apparently, such a deficit may significantly limit the adaptability of the organism to different stresses.

Hence, neurophysiological processes responsible for peculiarities of SWHF along with other factors play an important role in the formation of particular features of vascular reactivity, including ocular hemodynamics. These factors have a significant impact on individual regulation of energy metabolism.

The extent of autonomy of ocular vascular reactivity in terms of its formation mechanisms is still being discussed, and therefore, we considered it expedient to investigate the influence of the consistency of cerebral autoregulation on the formation of typological features of vascular reactivity.

It has been revealed that individuals with normotonic NVR show a higher load-related increase in parameters of cerebral hemodynamics as compared to other groups. In hypotonic and, especially, hypertonic NVR, velocity changes are less dynamic.

Thus, the normotonic type of ocular NVR is formed against the background of effective autoregulation of cerebral hemodynamics, while the two extreme types of NVR are associated with varying degrees of autoregulatory failure (**Fig. 5**).

Conclusion

A normotonic ocular reaction develops against the background of adequate reactivity of the myogenic component of the intraocular vascular tone. It also requires a balance of the effects of endothelial factors, eutonia of the ANS, sufficient SWHF power, and consistency of cerebral autoregulation. Therefore, this particular type of ocular NVR should be associated with maximum resistance to ophthalmic diseases and stressful events.

Hypotonic type of NVR is formed under the influence of low myogenic tone and against the background of low production of endothelial vasodilators (NO), parasympathicotonia, reduced SWHF power, and low efficiency of cerebral autoregulation. This type of NVR is associated with severely limited adaptation reserves and low resistance to stress factors. As to the development of vascular dysfunction, hypotonic NVR are prognostically less favorable than normotonic.

Hypertonic reactions of ocular hemodynamics are largely due to high neurogenic and myogenic basal tones and sympathetic dominance within the ANS balance, inadequate SWHF, and failure of circulatory autoregulation. Such neurohumoral influences contribute to the lack of adaptation reserves under stress load in individuals with hypertonic NVR.

The authors declare no conflict of interests.

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