Translated by E.V. Trushina

Review

https://doi.org/10.23934/2223-9022-2023-12-4-637-649

The Role of Nitric Oxide in the Autoregulation of Cerebral Blood Flow and the Pathogenesis of Cerebral Vascular Spasm in Patients with Ruptured Cerebral Aneurysms

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ABSTRACT The presented literature review is devoted to the role of the endothelial relaxing factor – nitric oxide (NO) – in the regulation of cerebral blood flow in patients with ruptured intracranial aneurysms. Modern views on the physiology of NO, methods of regulation and autoregulation of its synthesis are described, experimental and clinical data on the disruption of the production of the endothelial relaxing factor in subarachnoid hemorrhage are presented.

Key words: angiospasm, vascular spasm, SAH, nitrogen monoxide, cerebral aneurysm, inhalation

For citation Prirodov AV, Zhuravel SV, Bakharev EYu, Goncharova II, Zorin PD, Klychnikova EV, et al. The Role of Nitric Oxide in the Autoregulation of Cerebral Blood Flow and the Pathogenesis of Cerebral Vascular Spasm in Patients with Ruptured Cerebral Aneurysms. *Russian Sklifosovsky Journal of Emergency Medical Care*. 2023;12(4):637–649. https://doi.org/10.23934/2223-9022-2023-12-4-637-649 (in Russ.)

Conflict of interest Authors declare no conflicts of interests

Acknowledgments, sponsorship This work was supported by an ANO grant (Agreement No. 1603-32/23c)

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ADMA — asymmetric dimethylarginine
BP — blood pressure
CA — cerebral aneurysms
CBF — cerebral blood flow
cGMP — cyclic guanosine monophosphate
CNS — central nervous system
CPP — cerebral perfusion pressure
CSF — cerebrospinal fluid
DNIC — dinitrosyl iron-sulfur complexes
ECE — endothelin-converting enzyme
eNOS — endothelial synthase
ET-1 — endothelin-1
GSNO — S-nitrosoprotein
ICP — intracranial pressure
iNOS — inducible synthase
nNOS — neuronal synthase
NO — nitric oxide
PDE-5 — phosphodiesterase type 5
RSNO — S-nitrosothiol
SAH — subarachnoid hemorrhage
SMCs — smooth muscle cells
VS — vascular spasm

In 1998, F. Murad, Louis J. Ignarro, and R.F. Furchgott received the Nobel Prize for their discoveries in the field of the influence of nitric oxide (NO, II) on biological systems. Nitric oxide was identified as an endothelial vasorelaxing factor, which plays a leading role in the regulation of resistive vascular tone.

Nitric oxide in the vascular endothelium causes relaxation of vascular smooth muscle cells (SMCs) mediated through the guanylate cyclase signaling system.

From a chemical perspective, nitric oxide is an extremely reactive compound, acting as both an oxidizing and reducing agent.

The production of nitric oxide in the body occurs via two main pathways – enzymatic and non-enzymatic ones. The non-enzymatic pathway is carried out either through nitrite reduction by iron in the composition of hemoproteins at a pH of at least 7, or during reaction of nitrite decomposition, but in a more acidic environment at a pH of no more than 6.8 (for example, in the site of inflammation) [1, 2] (Fig. 1).

Normally, the synthesis of the endogenous form of nitric oxide as a signaling molecule in the human body occurs enzymatically under the action of several classes of specific enzymes - NO synthases (NOS). There are three types of NO synthases: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS); nNOS and eNOS are classified as constitutional synthases, which are constantly present in cells, changing only the intensity of their activity, while the expression of inducible NOS is activated under certain external conditions (Table 1) [3, 4].

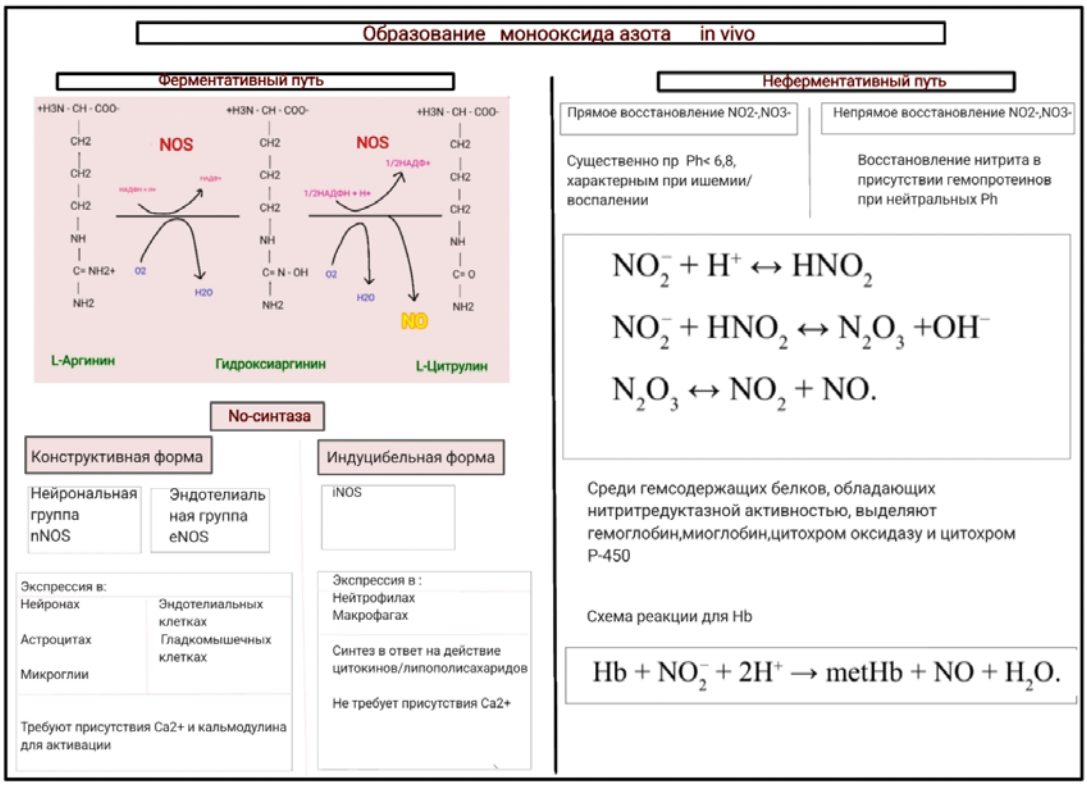

Fig. 1. Enzymatic and non-enzymatic pathways for the formation of nitric oxide in the body

Table 1

Types of nitrogen monoxide synthases (NOS) (according to V.G. Granik and N.B. Grigoriev [3])

Enzyme	Target cells	Enzyme form/ activation pathway
Neuronal NOS (nNOS), NOS-I (155 kDa)	Neurons of the CNS, and PNS, the uterus, muscles	Constitutive form, calcium/calmodulin-dependent
Inducible NOS (iNOS), NOS-II (125 kDa)	Macrophages, liver, smooth muscle, endothelium, heart	Lipopolysaccharide-, cytokine- and glucocorticosteroid-induced, calcium/calmodulin-independent
Endothelial NOS (eNOS), NOS-III (133 kDa)	Endothelium, heart, brain	Constitutive form, calcium/calmodulin-dependent

Notes: CNS — central nervous system; PNS — peripheral nervous system

The substrate for the synthesis of NO in the vascular wall is L-arginine [5—7] (Fig. 2).

In the endothelium of arterioles, the production of nitric oxide is one of the key mechanisms in maintaining basal vascular tone [4, 7]. Nitric oxide binds to guanylate cyclase dissolved in the cytoplasm, thereby increasing the formation of cyclic guanosine monophosphate (cGMP). It activates intracellular protein kinases, which leads to the opening of potassium channels, hyperpolarization of the cell, closure of voltage-gated calcium channels, a decrease in the intracellular concentration of ionized calcium (Ca^{2+}), and relaxation of smooth muscle cells (Fig. 3) [8].

The physiological antagonist in the vascular endothelium is endothelin-1 (ET-1). This polypeptide is synthesized in the vascular endothelium in the form of proendothelin under the influence of endothelin-converting enzyme (ECE) [4, 9]. Endothelin-1, by binding to endothelin type A receptors, promotes the release of calcium from the intracellular store of SMCs, which causes vasoconstriction [4]. A generalized mechanism of vasoconstriction under the influence of ET-1 is presented in Fig. 4.

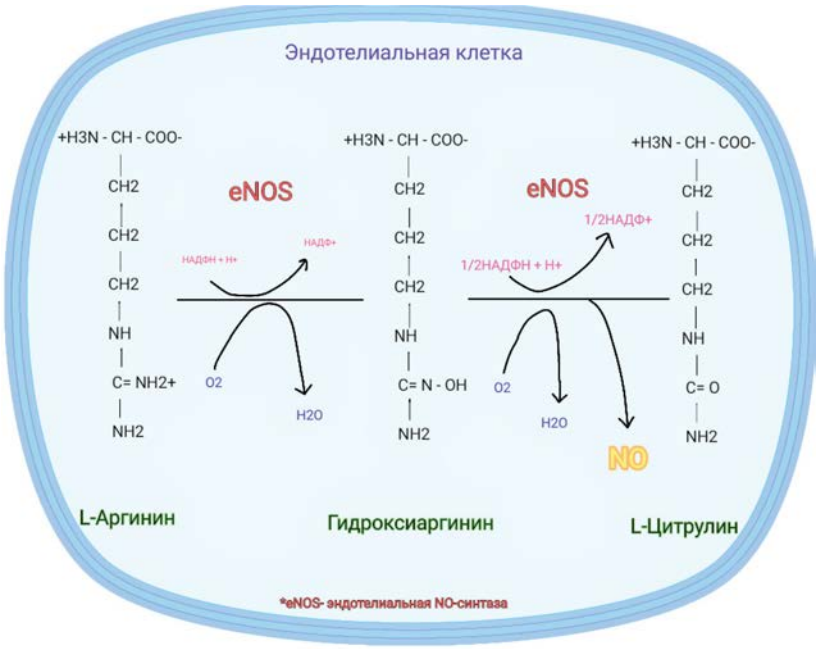

Fig. 2. Formation of endogenous nitrogen monoxide in the endothelium under the action of endothelial NO synthase (eNOS) from L-arginine

Fig. 3. The mechanism of vasodilation of smooth muscle cells of arterioles under the influence of nitric oxide (explanations in the text)
Notes: NOS — nitric oxide synthase; цГМФ — cyclic guanosine monophosphate

Fig. 4. The mechanism of vasoconstriction of arteriole smooth muscle cells under the influence of endothelin-1 (ET-1)

Neuronal NO synthase is located in nitrergic neurons of the central nervous system (CNS) and is involved in cell signaling, nociception, memory, and regulation of other neurotransmitters. Nitrergic neurons in the adventitia of the cerebral arteries play a key role in maintaining the vascular tone of the cerebral arteries and the autoregulation of cerebral blood flow [10–12].

The third type of specific NO synthase enzyme, inducible NOS (iNOS), is a calcium-independent NO synthase found in macrophages, hepatocytes, fibroblasts and involved in antibacterial, cytotoxic and antitumor activity. The production of endogenous nitrogen monoxide by iNO synthase is ten times greater than the amount of nitric oxide produced by other synthases, which causes toxic effects of monoxide mediated by the formation of reactive nitrogen species and other unstable free radicals [13]. There is evidence of activation of apoptosis processes under the influence of nitric oxide synthesized by iNOS [14].

The resulting nitric oxide in the body is in two forms - free and stored ones. In its free form, endogenous nitrogen monoxide is a short-lived molecule that is rapidly inactivated. The lifetime of free nitrogen monoxide in blood plasma is about 100 ms [3, 12].

The main depots of endogenous nitric oxide are as follows (Fig. 5):

— dinitrosyl iron complexes (DNIC);

— S-nitrosothiols, or S-nitrosoglutathione (RSNO, GSNO);

— S-nitrosohemoglobin (HbSNO).

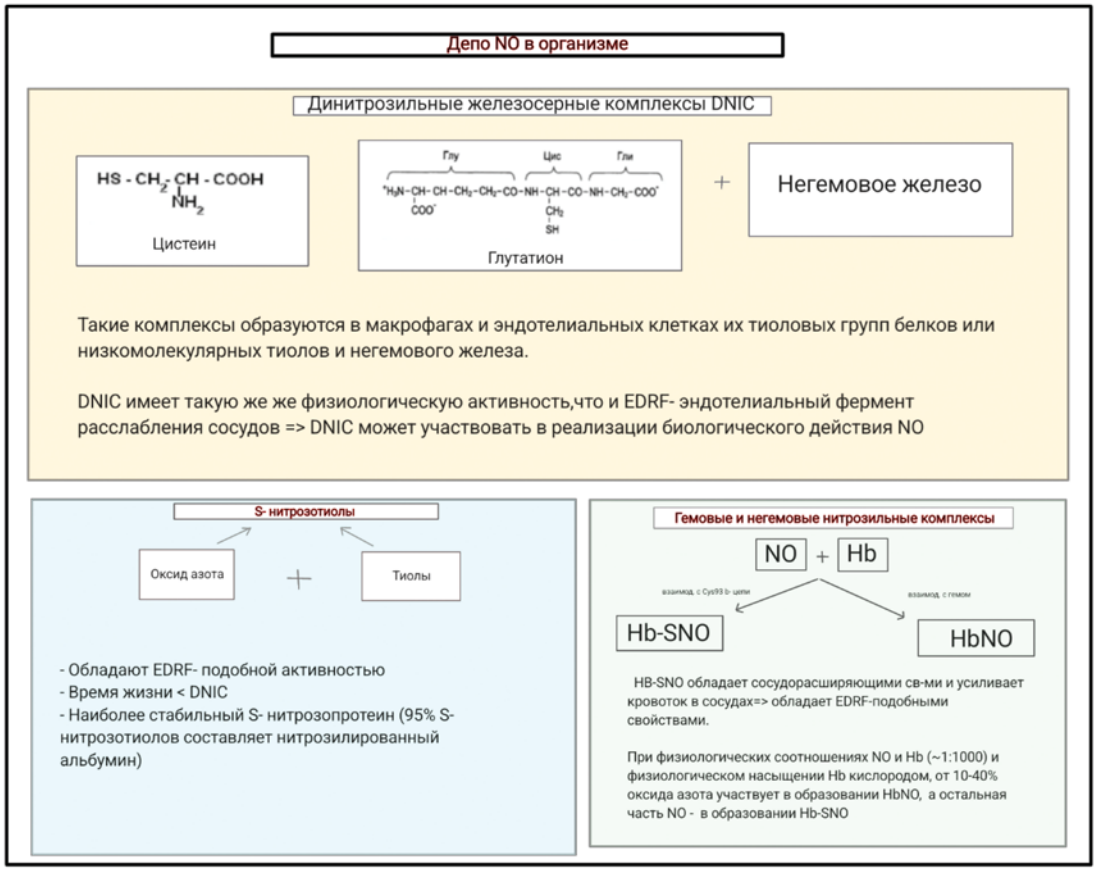

Fig. 5. The main depots of endogenous nitrogen monoxide in the body

Notes: DNIC — dinitrosyl iron-sulfur complexes; Hb — hemoglobin; Hb-NO — nitrosohemoglobin; Hb-SNO — S-nitrosohemoglobin; NO — nitric oxide

Dinitrosyl iron complexes are a stable form of nitric oxide in cells. The formation of DNIC occurs in macrophages and endothelial cells with the participation of thiol groups of proteins or low molecular weight thiols (cysteine or glutathione) and non-heme iron [15, 16]. Nitrogen monoxide can exert its physiological, biological, biochemical effects both in free form and in the form of DNIC. The deposited form of nitric oxide as DNIC has the same activity and stability as free nitric oxide [17, 18].

The second most important store of nitric oxide in the body is albumin. Nitrogen monoxide reacts with the SH groups of amino acids of serum albumin, producing S-nitrosothiol, 95% of which is nitrosylated albumin (RSNO, GSNO) [19].

Both forms of stored nitrogen monoxide, DNIC and S-nitrosothiol, are in dynamic equilibrium and have similar effects [7, 20, 21].

Nitric oxide binds to hemoglobin to form S-nitrosohemoglobin (Hb-SNO) and nitrosohemoglobin (Hb-NO) [22, 23]. According to Stamler et al. (1997), oxygenated nitrosohemoglobin, releasing oxygen in arterioles and capillaries, changes its isoform, which leads to the release of nitric oxide and increased blood flow in tissues [24]. In this way, nitric oxide can be released from stores in areas of insufficient blood flow and ischemia.

Thus, due to the deposited forms of nitric oxide, one of the mechanisms of extrapulmonary effects of nitric oxide during inhalation is realized.

PHYSIOLOGICAL AUTOREGULATION OF CEREBRAL BLOOD FLOW

Volumetric cerebral blood flow (CBF) is normally about 50–55 ml/100 g per minute, which occupies about 15–20% of the cardiac output. The brain lacks a nutrient depot, necessitating constant maintenance of cerebral perfusion. CBF is constant over a wide physiological range, which suggests the existence of a complex mechanism of autoregulation.

CBF is provided by cerebral perfusion pressure (CPP) which consists of the difference in mean arterial pressure (MAP) and intracranial pressure (ICP). It is believed that under normal physiological conditions, when CPP parameters change within the range of 50–150 mm Hg, CBF remains constant [25, 26] (Fig. 6).

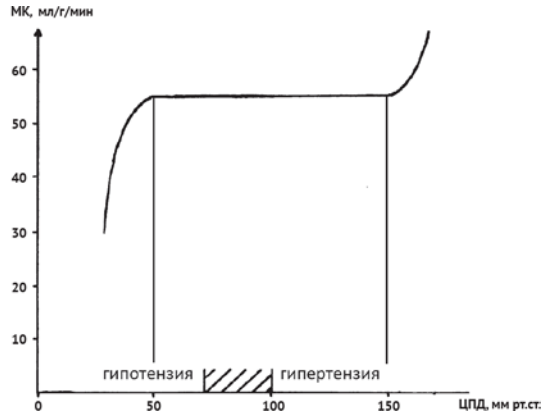

Fig. 6. Constancy of cerebral blood flow depending on blood pressure parameters (ill. by V.V. Krylov et al., (2016) [25] with modifications)

A decrease in CBF levels below 22 mg/100 g per minute is considered critical, leading to damage to the brain substance and the development of ischemia. Autoregulation of cerebral blood flow is based on a unique mechanism for changing the tone of cerebral arterioles and capillaries, which expand or contract with a decrease/increase in blood pressure.

This phenomenon was first experimentally described by Fog M. (1938), when, with changes in blood pressure, a rapid change in the diameter of the pial arteries and arterioles of the brain occurred under direct visual control [27]. Subsequently, this phenomenon was repeatedly confirmed experimentally and clinically [9, 26, 28].

This phenomenon of cerebral vascular tone regulation is based on a change in the activity of L-type calcium channels in the SMCs under the influence of baroreceptors of arterioles: increased blood pressure causes a contraction of the SMCs and a decrease in cerebral perfusion (as a mechanism for protecting the brain from hyperemia), and when blood pressure decreases, the SMCs relax and cerebral perfusion increases [26].

Currently, a large number of factors influencing cerebral perfusion have been established: indicators of systemic hemodynamics, acid-base composition of the blood, level of metabolic activity of the brain, intracranial pressure, humoral factors, parasympathetic nervous system [9, 26]. One of the most important regulatory humoral factors is nitric oxide.

In the CNS, resistive vessels have additional parasympathetic nitrergic innervation, as well as regulation by glia, which ensures finer autoregulation of CBF, and a continuous supply of the required amount of oxygen and nutrients to the brain [9, 10, 12, 26, 29].

The processes of neuronal regulation of cerebral blood flow are shown schematically in Fig. 7.

With an increase in glutamate production, the nitrergic neurons of the adventitia of the cerebral arteries are activated, which leads to nNOS activation, the production of nitric oxide, as well as a number of other vasodilators (prostaglandins). In addition to the release of nitric oxide by nitrergic neurons under the influence of glutamate, astrocytes of the perivascular space release a number of short-lived vasodilators (epoxyeicosatrienoic acid, prostaglandins), and increase the extracellular calcium concentration, which helps reduce the intracellular calcium concentration and dilate arterioles.

The listed mechanisms of CBF regulation ensure the consistency of maintaining cerebral perfusion, and accurate and rapid regulation, depending on the needs of the brain, and changes in hemodynamic parameters and blood gas composition.

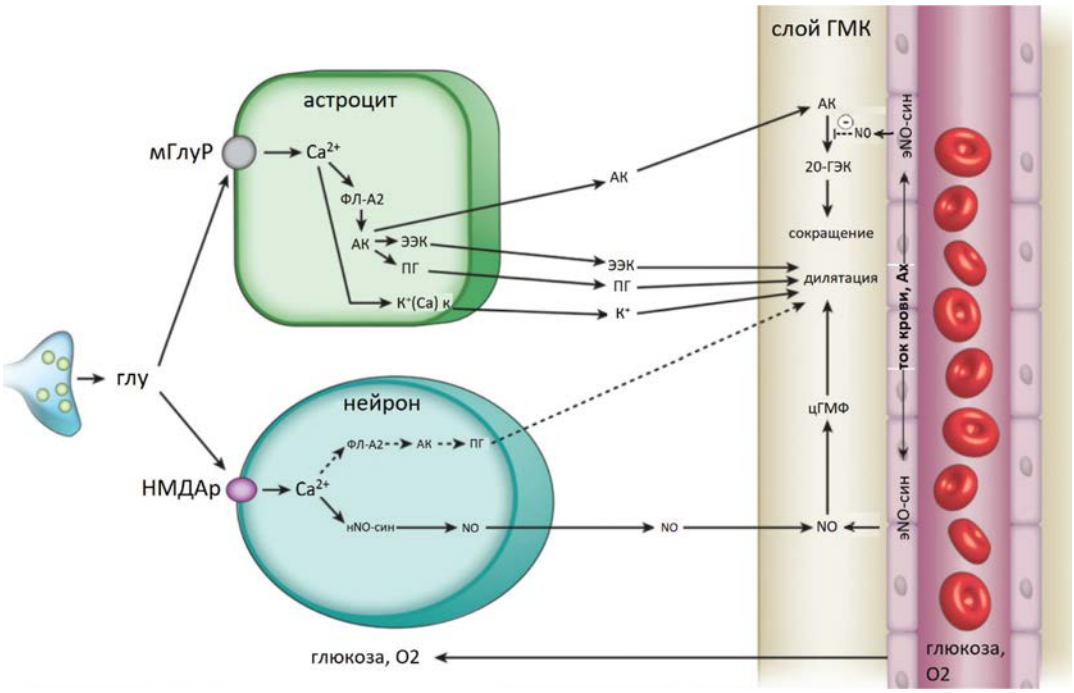

Fig. 7. The mechanism of regulation and modulation of cerebral blood flow and tone of cerebral arteries [ill. by Attwell (2010) [10] modified]
Notes: 20-ГЭК — 20-hydroxyeicosatetraenoic acid; АК — arachidonic acid; Глу — glutamate; мГлуР — metabotropic glutamate receptors of astrocytes; нNO-син — neuronal nitric oxide synthase; НМДАр — N-methyl-D-aspartate type glutamate receptors; ФЛ-А2 — phospholipase A2; ПГ — prostaglandins; эNO-син — endothelial nitric oxide synthase; ЭЭК — epoxyecosatrienoic acid

IMPAIRED NITRIC OXIDE METABOLISM IN SUBARACHNOID HEMORRHAGE

Non-traumatic subarachnoid hemorrhage (SAH) due to rupture of cerebral aneurysms (CA) is a specific form of cerebrovascular accident in which blood enters the cisterns of the base of the brain. A specific complication of basal SAH is cerebral vasospasm (CVS) and cerebral ischemia secondary to CVS. It is believed that CVS develops after 3 days from the moment of SAH, its peak development occurs on the 7–10th day from hemorrhage, and resolution – within several weeks. Cerebral ischemia against the background of cerebral vascular spasm is still the main reason for the unfavorable outcome of treatment of patients with CA rupture in the early postoperative period [25, 30].

It is thought that in SAH, blood entering the basal cisterns of the brain triggers a cascade of pathological processes that lead to the development of CVS and cerebral ischemia. The main spasmogenic factor is hemoglobin and its breakdown products. Oxyhemoglobin binds nitric oxide, which were confirmed in experimental and clinical studies [31–33].

According to Sehba F. (2011), in the first hour after SAH, the level of nitric oxide decreases significantly, which may be due to the binding of nitric oxide by hemoglobin and other active metabolites of blood plasma. During this period, there is a significant decrease in CPP due to contraction of resistive vessels of the brain. There is experimental evidence that the use of NO donors prevents a decrease in CPP in the first hours after SAH [31].

Within several hours after SAH, nitric oxide levels are restored to initial values, mainly due to the activation of inducible and neuronal NOS [31]. The presented data were obtained primarily on experimental models due to the fact that patients with CA ruptures do not have time to come to the doctor's attention so early after SAH [31].

In the next 24–72 hours, a significant increase in the level of nitric oxide in the brain and CSF is noted, which may be primarily due to the activation of inducible NO synthase [31, 34].

Further dynamics of the level of nitric oxide during SAH in the CSF has a less detailed description. Woszczyk A. et al. (2003) observed an increase in the level of stable NO metabolites (nitrites and nitrates) in 21 patients with CA

ruptures on days 2–8 after hemorrhage [35]. According to Pluta R. (2005) and Jung (2007), on the 7th day there is a relative decrease in the level of nitrites in the CSF of patients with CVS [29, 36]. Durmaz R. (2008), on the contrary, noted a decrease in the level of nitric oxide in the CSF of 40 patients with SAH compared with the control group of 10 patients. Moreover, the level of nitric oxide metabolites was higher in patients with CVS signs [37]. Kalinkin A.A. et al. (2016), studying the dynamics of nitric oxide in the CSF of 11 patients with CA ruptures, observed a decrease in the level of nitric oxide in 6 patients and no changes in 5 patients, and these parameters did not depend either on the clinical severity of the condition or on the anatomical form of hemorrhage. At the same time, in patients with low levels of nitric oxide metabolites, the incidence of cerebral ischemia was higher [38]. According to Kho G. (2021), based on the examination and treatment of 40 patients with massive forms of SAH, the level of stable nitric oxide metabolites in the CSF, on the contrary, during the first 5 days after SAH statistically significantly increases, and in patients with an unfavorable outcome and vasospasm the level nitric oxide was lower than in patients without vasospasm and cerebral ischemia [39]. Generalized data on the dynamics of nitric oxide are presented in Table 2.

Data on the prognostic significance of stable nitric oxide metabolites (nitrites and nitrates) in tissue fluid were studied in small groups of patients and differ greatly. According to Staub F. (2000), the level of stable metabolites of nitric oxide in the brain substance was significantly higher at the site of ischemia, and an increase in the level of nitrites (but not nitrates) correlated with an unfavorable treatment outcome. Tissue microdialysate measurements were carried out within 3–7 days from the moment of surgery (average 4.6 days) [40]. In 11 patients with CA rupture, Khaldi A. (2001) observed a relationship between the levels of stable metabolites of nitric oxide and partial oxygen tension in tissues ($PbrO_2$) [41]. There was no correlation found between the levels of glucose, lactate, and lactate/pyruvate ratio in this study [41]. Sakowitz O.W. et al. (2001) studied changes in nitric oxide metabolites in 3 patients with CA without hemorrhage and 7 patients with CA rupture. The authors observed a decrease in the level of nitric oxide in tissue microdialysate on days 4–5 and 6–7 after SAH, and the level of nitric oxide was higher in patients with signs of symptomatic CVS and cerebral ischemia. In addition, the level of nitric oxide metabolites correlated with a decrease in glucose concentrations in interstitial fluid, and their increase for lactate. The authors found that, based on the data obtained, it cannot be argued that the cause of cerebral ischemia was an isolated decrease in the level of nitric oxide in the brain matter [42]. A study of nitric oxide metabolites using tissue microdialysis on the material of 7 patients in the acute period of CA rupture showed a two-phase nature of changes in the level of nitric oxide: in the first 7 days, the level of nitric oxide in the tissue microdialysate increased (which correlated with the severity of oxygenation disorders and the level of PbrO2 reduction), and after 7 days the content of stable metabolites decreased [43]. Generalized data on the dynamics of nitric oxide level in tissue microdialysate are presented in Table 3.

Table 2

Dynamics of the content of stable nitric oxide metabolites in the cerebrospinal fluid in patients with cerebral aneurysm rupture

Author	Year	Nature of changes in nitrogen oxide
Suzuki Y.	1997	NO levels increase within 14 days in patients with SAH and patients with massive hemorrhage (Fisher 3); the increase in NO levels is more pronounced than in patients with non-massive hemorrhage (Fisher 2)
Khaldi A.	2001	Nitric oxide levels did not differ between patients with and without CVS; there is no correlation between NO levels and partial oxygen tension in brain tissue ($PbrO_2$)
Woszczyk A.	2003	NO levels are statistically significantly higher in patients with SAH and symptomatic CVS than in patients without symptomatic CVS
Pluta R.M.	2005	NO level decreases by the 7^{th} day from the moment of hemorrhage
Durmaz R.	2008	NO levels are reduced in patients with SAH compared to control patients. NO levels increase to a greater extent in patients with angiographically verified CVS than in patients without angiographic CVS
Kalinkin A.A.	2016	NO levels are reduced or unchanged in patients with SAH. No relationship was found between NO levels, the severity of patients on the Hunt-Hess scale, and the severity of SAH according to the Fisher scale. Reduced NO levels are a risk factor for the development of cerebral ischemia
Kho G.S.	2021	NO levels increase in patients in the first 5 days after SAH; in patients with CVS, NO levels decrease to a greater extent than in patients without CVS

Notes: CVS — vascular spasm; NO — nitric oxide; SAH — subarachnoid hemorrhage

Table 3

Dynamics of the level of stable nitric oxide metabolites in tissue microdialysate in patients with cerebral aneurysm rupture

Author	Year	The nature of changes in NO levels
Staub F.	2000	nitrite levels were higher in the ischemic area and correlated with the incidence of unfavorable outcome
Khaldi A.	2001	a decrease in NO levels correlated with a decrease in partial oxygen tension in brain tissue (PbrO2)
Sakowitz O.W.	2002	NO levels decreased in patients with SAH compared to the control group; in patients with symptomatic CVS, NO levels were higher than in patients without signs of cerebral ischemia
Hosmann A.	2020	NO level increased in the first 7 days after hemorrhage and decreased on days 7–14. In the first 7 days, the NO level correlates with a decrease in partial oxygen tension

Notes: CVS — vascular spasm; NO — nitric oxide; SAH — subarachnoid hemorrhage

It can be assumed that such differences in the dynamics of nitric oxide levels and the heterogeneity of clinical data are due to a number of reasons. First, it is impossible to assess nitric oxide levels directly due to its extremely high chemical reactivity. All of the above studies are based on determining the level of chemically stable metabolites of nitric oxide, primarily nitrites and nitrates. This approach does not allow us to differentiate the point of application of nitric oxide: whether it is nitric oxide produced by nNOS and eNOS synthases that is an endothelial vasorelaxant factor, or it is nitric oxide produced due to iNOS activity that exerts its cytotoxic effects. In addition, it can be assumed that tissue microdialysis data can vary significantly in patients depending on the location of the sensor installation (intact brain substance, penumbra zone, ischemic zone), since it is often not possible to predict where the zone of ischemic damage to the brain substance due to CVS will form.

The activity of different types of nitric oxide synthases is known to change in SAH. In the adventitia of the cerebral arteries, there is a decrease in the number of nitrergic neurons and nNOS activity, which is associated with the toxic effects of blood and oxyhemoglobin that entered the basal cisterns of the base of the brain [44, 45]. Thus, we can say that one of the mechanisms for the development of cerebral ischemia against the background of CVS is impaired autoregulation of cerebral blood flow due to a decrease in the activity of nitrergic neurons and neuronal NO synthase.

According to Pluta R.M. et al., during a decrease in nNOS activity, an increase in the level of eNOS expression in the endothelium of cerebral arteries is observed, which is probably one of the protective and compensatory mechanisms [29, 44, 45]. The dynamics of changes in the activity of neuronal and endothelial NOS are described in detail in the works of Pluta R. et al. (2005) and is presented in Fig. 8.

Hino A. et al. (1996), when studying the level of eNOS expression in monkeys during experimental SAH, on the contrary, observed a decrease in the level of eNOS expression in the cerebral arteries on the 7th day after hemorrhage, and increased level of eNOS expression in brain tissue.

When studying the level of NOS expression in brain tissue of patients with CA rupture occurred during surgical treatment, Berra et al. (2007) observed an increase in the expression level of eNOS, and the level of overexpression was higher in patients in severe clinical condition [46].

Despite the increase in the expression level of endothelial NO synthase, there is experimental evidence of a decreased vasodilating effect of NO on cerebral arteries in conditions of SAH [47, 48]. This phenomenon is based on two development mechanisms:

— an increase in the activity and level of expression of phosphodiesterase type 5 (PDE5) in the cerebral arteries, which leads to a decrease in the amount of cGMP and vasoconstriction;

— an increase in the amount of asymmetric dimethylarginine (ADMA), which is a physiological inhibitor of NOS.

According to Inoha et al. (2002), during experimental hemorrhage in dogs, an increase in PDE5 expression confirmed by immunohistochemistry data was observed on the 7th day of experimental hemorrhage [49]. Similar data on an increase in the activity (but not the level of expression!) of PDE5 in the SMCs of cerebral arteries were presented by Han et al., 2012. There are experimental [50, 51] and clinical [52, 53] data on the use of the PDE5 inhibitor sildenafil to reduce the severity of CVS and improve cerebral perfusion in patients with SAH. Dhar et al. (2016) reported evidence of no effect of sildenafil on cerebral perfusion in 12 patients with SAH. Thus, data on the clinical use of PDE5 inhibitors are contradictory and require further research [54].

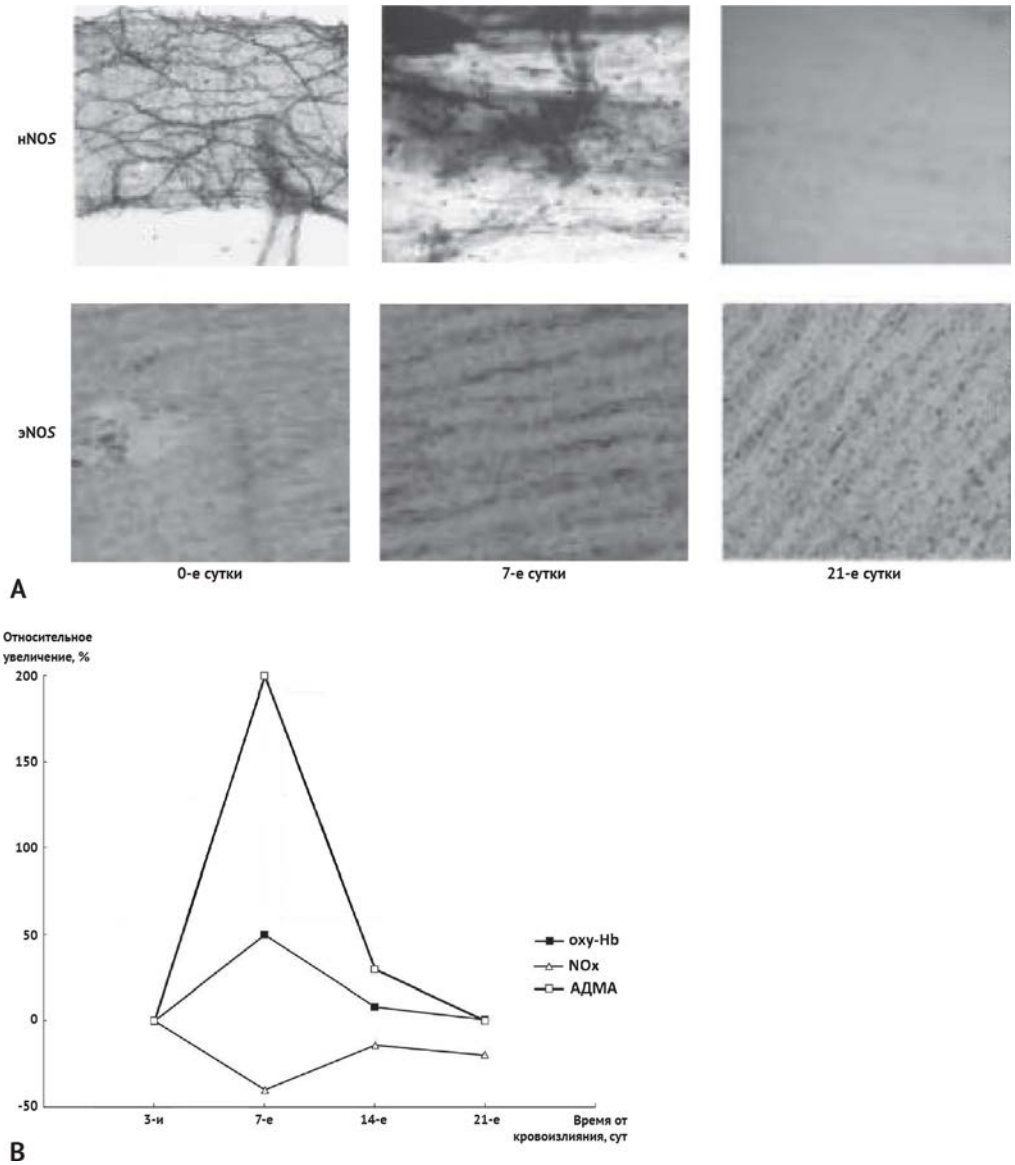

Fig. 8. Dynamics of changes in the level of neuronal and endothelial NOS in the wall of cerebral arteries (micrographs) (A) and the level of oxyhemoglobin, nitric oxide metabolites, and asymmetric dimethylarginine (ADMA, a physiological inhibitor of NOS) in the cerebrospinal fluid (CSF) (B). According to immunohistochemical studies, there is a significant decrease in the level of nNOS in the adventitia of the arteries by the 7th day, which persists up to 3 weeks from the moment of hemorrhage. Expression of eNOS, on the contrary, increases significantly by the 7th day from the moment of hemorrhage. The level of stable nitric oxide metabolites in the CSF on the 7th day from hemorrhage is significantly reduced, and the level of hemoglobin breakdown products, ADMA, is increased [ill. by Pluta R, 2005 with modifications].
Notes: eNOS — endothelial nitric oxide synthase; nNOS — neuronal nitric oxide synthase; NOX — stable metabolites of NO in the CSF; oxy-Hb — oxyhemoglobin; АДМА — asymmetric dimethylarginine

Another mechanism for the development of endothelial dysfunction is associated with an increase in the level of ADMA in the CSF during SAH. ADMA is a physiological competitive inhibitor of NOS and is formed as an intermediate metabolite of protein metabolism [29, 36]. Increased ADMA in SAH was shown in experimental [23, 55] and clinical studies [36, 56]. According to clinical research, the greatest increase in the level of ADMA in the CSF is observed in patients with CA rupture on days 7–9 after hemorrhage; and the degree of its increase correlates with the incidence of unfavorable clinical

outcome [36, 56]. The mechanism for increasing ADMA levels remains unclear, and is presumably associated with the development of oxidative stress in the subarachnoid space [29].

CONCLUSION

The presented data indicate the key role of nitric oxide in the regulation of cerebral blood flow both in normal conditions and in subarachnoid hemorrhage. The dynamics of changes in the content of nitric oxide in the brain matter, cerebrospinal fluid, and the walls of cerebral arteries during subarachnoid hemorrhage does not have a detailed description, and data from clinical studies demonstrate different dynamics of these indicators. It can be assumed that the ambiguous nature of the dynamics of the content of nitric oxide in the cerebrospinal fluid, brain matter and cerebral arteries is associated with parallel processes occurring in different directions during subarachnoid hemorrhage: on the one hand, there are cytotoxic effects of nitric oxide synthesized under the influence of inducible synthase; and on the other hand, there is a violation of its metabolism in the wall of cerebral arteries, where vasorelaxing effects are manifested. The creation of methods for the prevention and treatment of cerebral vasospasm, aimed at correcting these disorders, has the potential to solve the problem of preventing cerebral ischemia in subarachnoid hemorrhage.

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Received on 31/01/2023
Review completed on 19/06/2023
Accepted on 26/09/2023