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Posthypoxic encephalopathy in patients after cardiac surgery: etiological, pathogenetic, and clinical aspects (a literature review)

Post-hypoxic encephalopathy is a brain damage manifested by neurological, neuropsychiatric, and mental disorders, which is caused by a reduction in cerebral blood flow and by a resultant effect of an episode of hypoxia of various etiology and duration. This complication is most characteristic of patients who have undergone cardiac surgery in view of the high prevalence and severity of clinical manifestations, worse quality of life, the longer length of hospital stay, and the higher cost of treatment and rehabilitation. To determine the individual management tactics for such patients, combining both successful surgical treatment, by reducing perioperative stress, and prevention of cerebral complications, it is necessary to analyze the patterns of their development. The role of pathophysiological risk factors, including preoperative, perioperative and postoperative ones, for posthypoxic encephalopathy, is considered. Its preoperative risk factors include age, gender, concomitant diseases, education level, and cognitive functions before surgery, cardiac morphofunctional changes, and depressive disorders. There are surgery-related (type and duration of anesthesia, operating-suite temperatures, and hyperglycemia) and postoperative (pain syndrome after surgical intervention, sleep disorders, and the environment) risk factors. Emphasis is placed on the technical characteristics of on-pump operations, among which there are cerebral hypoperfusion, microembolism, non-pulsatile flow, and duration of extracorporeal circulation. Classifications of cerebral complications are presented. Different types of brain dysfunction are analyzed to assess their incidence rates, clinical features, and dynamics in the postoperative period.

Keywords: *posthypoxic encephalopathy; neurological complications in cardiac surgery; postoperative cognitive dysfunction.*
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Posthypoxic encephalopathy is a complex of neurological and mental disorders that occur after exposure to hypoxia of varying duration and severity caused by disturbances of pulmonary ventilation, circulation and tissue metabolism, by endogenous intoxication, etc. [1]

Hypoxic mechanisms are triggered and realized in many pathological conditions of various genesis – acute cardiac and pulmonary insufficiency of different etiology, severe trauma, thermal and toxic brain damage, metabolic disorders. The urgency of posthypoxic encephalopathy in patients undergoing cardiac surgery is due to persisting high frequency of cerebral complications, age-related decline in patients' ability to withstand operative stress, lack of comprehensive practical recommendations for prevention of brain damage.

Factors that play a role in developing neurological complications can be divided into preoperative, operation-related and postoperative.

Preoperative risk factors

Age is noted by researchers as one of the most significant risk factors for cerebral complications, associated with a higher incidence of stroke and postoperative cognitive dysfunction [2]. Increased risk of cerebral complications in patients of older age groups is mainly explained by the presence of concomitant diseases, changes in the pharmacokinetic characteristics of drugs used by elderly patients, and their interaction with preparations for general anesthesia [3].

Sex. Despite a variety of strategies undertaken with a protective goal during aortocoronary bypass surgery, women have a higher risk of stroke and death in the early postoperative period compared with men [4]. This may be due to a relatively higher incidence of chronic heart failure and diabetes, and to the fact that women need cardiosurgical interventions at an older age than men, when the protective function of female sex hormones is reduced. As

the research shows, women having specific anatomical features of the coronary arteries and the shunting vein, particularly, thinness and looseness of the vascular wall, often need an emergency surgery, which also affects the incidence of neurological complications [5]. Men have a higher risk of developing postoperative delirium, due to alcohol and psychotropic substances abuse [6].

Concomitant diseases. In 1999, researchers from Papworth Hospital (Cambridge, UK) proposed the EuroScore scale for risk assessment in cardiac surgery, including not only the type of intervention, but also the concomitant diseases [7]. Each factor associated with an increase in mortality in heart operations is assessed in points, and their total score is a risk indicator according to EuroScore. The parameters taken into account include: age, female sex, somatic diseases (chronic lung diseases, septic endocarditis, pulmonary hypertension), laboratory indicators (elevated serum creatinine level), additional indications for surgery (emergency surgery, critical condition of the patient before intervention, manipulations on the thoracic aorta), characteristics of the functional reserve of the myocardium (cardiac surgery and a history of myocardial infarction, left ventricular dysfunction, unstable angina, postinfarction rupture of the interventricular septum). It also takes into account the presence or absence of lesions of the extracardiac arteries, signs of a previous brain injury with a severe neurologic deficit. In addition, it is possible to assess the likelihood of the lethal outcome on the basis of logistic analysis. The frequency of cerebral complications has been shown to have a strong correlation with the result of EuroScore in patients who underwent surgery under conditions of artificial circulation [8].

Level of education and cognitive functions before surgery. A high level of education in most cases serves as a factor that reduces the likelihood of postoperative cognitive dysfunction. This fact can be explained by the concept of "cognitive reserve". According to this concept, intellectual load during life, the character of professional and leisure activities affect the congenital structural and functional characteristics of the brain, increasing the number of synaptic contacts and forming a buffer function, thereby increasing the ability to withstand damaging effects [9]. Patients with an initially low level of cognitive function, along with older patients, demonstrated the development of postoperative cognitive dysfunction significantly more frequently, which was accompanied by detection of ischemic foci by neuroimaging [10].

Atherosclerotic lesions of the aorta are associated with a higher risk of stroke. Given the need for cannulation of the aorta during cardiac surgery and the possibility of damaging the atherosclerotic plaque with a subsequent episode of embolism, the risk of cerebral complication increases. Thus, in order to prevent episodes of embolism, it is necessary to search for the least affected part of the aorta, which is effectively accomplished by applying additional examination techniques, the most sensitive of which is intraoperative ultrasound aortic aeration [11].

Morphofunctional changes in the heart, such as left ventricular ejection fraction less than 50%, a high degree of dilatation and remodeling of the ventricular cavity are predictors of the development of cardiovascular and cerebral complications. Indeed, a decrease in the level of blood supply to the brain due to cardiac dysfunction leads to low resistance to stress in hypoxic conditions [12].

Depression. Depressive disorders are observed in approximately 20% of patients after coronary artery bypass surgery. Anxious and depressive disorders increase the asthenia of patients, negatively affect the quality of life, the effectiveness of rehabilitation measures in the postoperative period, and also increase the risk of long-term cognitive decline [13].

Factors associated with the operation

Type and duration of anesthesia. Currently, there is no clear answer to the question whether general anesthesia is a triggering factor of exacerbation of existing cognitive impairment, or acts as an independent risk factor [14]. An important role in the development of cerebral complications after cardiac operations is played by the following factors observed in general anesthesia: inhibition of cholinergic transmission and release of pro-inflammatory cytokines, increased permeability of mitochondrial membranes and their dysfunction, increased toxic effects of glutamate and oxidative stress, depletion of energy reserve of the cortex and subcortical formations, activation of apoptosis of nerve cells. Additionally, dysfunction of the walls of small cerebral vessels, impaired metabolism of intracellular calcium, and disruption of associative processes between neurons can be mentioned [15].

Technical factors of the operation. The main pathophysiological factors affecting the likelihood of developing neurological complications in cardiosurgical interventions include hypoperfusion, microembolism, non-pulsatile character and disruption of autoregulation of cerebral blood flow, arterio-venous imbalance, reperfusion mechanism, systemic inflammatory response, damage to the blood-brain barrier [16].

Cerebral hypoperfusion can develop before surgery due to chronic heart failure, a low ejection fraction of the left ventricle which tends to worsen during the application of a device for artificial circulation, aortic clamping with low arterial pressure during the intervention [17].

Intraoperative episodes of embolism may be caused by microaggregates of blood cells appearing after the contact with the materials of the apparatus for artificial circulation (the so-called contact activation of blood coagulation), by droplets of fat, gas bubbles, denatured proteins, particles of plastic material. Arterial macroembolism leads to the development of acute impairment of cerebral circulation and is regarded as the cause of postoperative cogni-

tive dysfunction. Thus, the embolic load, characterized by the number of emboli or episodes of embolism, and the degree of cognitive decline should be inextricably linked; however, the studies of this hypothesis often do not confirm this link, leading to contradictory results [18, 19].

Non-pulsatile blood flow allows maintaining the oxygen and acid-base balance, blood lactate concentration at the required level. However, such perfusion provokes the processes of endothelial dysfunction and systemic vasoconstriction, both during the operation and in the early postoperative period, leading to an aggravation of cognitive impairment [20].

In conditions of artificial circulation, the cerebral blood supply depends to a greater extent not on the blood pressure, but on the perfusion flow rate, which is subject to numerous influences, leading to limitation and disruption of autoregulation of cerebral circulation, activation of hypoxia mechanisms [21].

Duration of artificial circulation of more than 120–180 minutes can be regarded as a clinical model of acute global cerebral ischemia [22]. We have found a correlation between the duration of the use of the artificial circulation apparatus and the time of the appearance of the first signs of consciousness after the operation, as well as the severity of dysfunction of the stem structures and the cerebellum, and the degree of cognitive dysfunction according to the results of neuropsychological testing [23].

Temperature regimen during surgery. It is known, that the protective effect of hypothermia is realized by slowing the metabolism, reducing the need for oxygen, reducing the release of excitatory neurotransmitters, inflammatory factors and products of lipid peroxidation. However, adverse effects are electrolyte imbalance, hypovolemia, immunosuppression and changes in the pharmacokinetic parameters of the drugs used perioperatively [24].

Hyperglycemia is often observed intraoperatively, both in diabetic and non-diabetic patients. The mechanism of this phenomenon is associated with transient resistance to insulin under the conditions of operative stress. Hyperglycemia is considered to be a risk factor for neurological complications due to activation of anaerobic metabolism, excitotoxicity, formation of reactive oxygen species. It has been proved that intraoperative increase of blood glucose level to more than 9.0 mmol / l is a predictor of hyperaggregation of erythrocytes [25].

Postoperative factors

Postoperative pain and sleep disturbances. Preparations of the opioid group are widely used for relief of postoperative pain, but they are associated with gross interference in the structure of the «sleep–wake» cycle. Sleep disturbances reduce the threshold of sensitivity to pain, which, in turn, worsens sleep even more, increasing the need for prescribing opioid analgesics, thus forming a vicious cycle. Additional undesirable effects of opiates include increasing the level of blood acetylcholine, triggering the mechanisms of excitotoxicity, causing a decrease in cognitive function based on the results of neuropsychological testing [26].

Factors associated with staying in a hospital, including change of the habitual setting, noise of technical devices for monitoring, have been shown in a few studies to have adverse effects on sleep and cognitive function. [27].

Postoperative atrial fibrillation is one of the most common complications of cardiosurgical interventions and occurs in 5% – 40% of cases. Patients who experienced atrial fibrillation in the postoperative period, have attention disturbances and slower sensorimotor processes compared with patients without disturbances of the heart rhythm [28].

Variants of brain dysfunction

There are several classifications of central nervous system complications that arise after cardiosurgical interventions.

I. Classification proposed by Shaw PJ, 1986 [29]: 1) Central nervous system complications: fatal brain damage, non-fatal diffuse encephalopathy (decreased level of consciousness, intellectual dysfunction, behavioral changes), seizures, ocular complications, stroke, spinal cord injury; 2) Peripheral nervous system complications: damage to the brachial plexus, peripheral neural disorders.

II. The systematization proposed by Wolman L.R. et al., 1999 [30]: type I: death due to stroke or hypoxic encephalopathy, non-lethal stroke, transient ischemic attack, stupor or coma; Type II: impairment of intellectual function, confusion, agitation, disorientation, memory impairment, non-metabolic convulsive seizures without signs of focal brain damage.

III. Classification of adverse cerebral outcomes, proposed by the American Heart Association for on-pump coronary artery bypass, 2011 [31]: 1) stroke; 2) postoperative delirium; 3) postoperative cognitive impairment. This variant of systematization has received the widest distribution in clinical and scientific practice because of its ease of use.

Perioperative stroke

Stroke is an acute disorder of the cerebral circulation, characterized by a sudden (within a few minutes, hours) appearance of focal and / or cerebral neurological symptoms that persist for more than 24 hours or lead to the patient's death in a shorter period of time due to cerebrovascular pathology [32].

Acute disorders of cerebral circulation, diagnosed in patients who underwent cardiosurgical intervention, occupy a leading position in the structure of nosocomial strokes. Among patients after coronary artery bypass grafting, this cerebral complication occurs with a frequency of about 5%, and is one of important causes of a decrease in the quality of life and mortality in the postoperative period [33].

In the study of etiopathogenetic features of stroke in cardiac surgery [34], based on the retrospective analysis of case histories, the following results were obtained: ischemic stroke was observed in 93.1% of cases; transient ischemic attack – in 6.9% of cases. The majority of patients had cardioembolic stroke subtype (74.1%), less often atherothrombotic (9.3%), lacunar (1.9%), or cryptogenic (1.9%) subtypes, other causes accounted for 12.96%, including hemodynamic subtype in 1,9% of cases. With a high degree of confidence, it can be stated that the predominance of the cardioembolic stroke subtype is associated with the adverse effects of intraoperative factors, particularly microembolism, and the severity of cardiosurgical pathology. The development of stroke in most cases is observed during the first three days after surgery. Age over 70 years, history of acute cerebral circulation disturbances and kidney failure are considered to be the most important risk factors for the development of postoperative stroke [35].

It is interesting to note, that in patients with two or more risk factors, cardiosurgical intervention on the working heart was accompanied by a lower incidence of stroke, compared with the use of artificial circulation devices [36]. However, other authors argue that the risk of cerebral complications is associated with any kind of heart or aortic surgery, and the fact of using artificial circulation devices does not necessarily lead to a high probability of stroke [37]. The question of whether the risk of stroke depends more on the type of intervention, or duration of the use of cardiopulmonary bypass, remains the subject of discussion. It has been demonstrated that the duration of artificial circulation of more than 120 minutes may be regarded as an independent risk factor for acute impairment of cerebral circulation [38].

A study of atherosclerotic vascular lesions in patients who had a stroke after a cardiac surgery has shown that assessing the morphological status of the carotid arteries alone does not provide comprehensive information about the risk of stroke. It was concluded that for the timely initiation of preventive measures, information on the state of the neck vessels in the preoperative period should be complemented by the study of the intracranial arteries; and that MR angiography has a greater diagnostic value than duplex scanning [39].

Thus, the specific features of stroke after cardiac surgery include the cardioembolic subtype and an increased risk of instability of the systemic hemodynamics. Late clinical diagnosis, possible limitations of neuroimaging (e.g, metal staples for sternal stapling), frequency of subcompensated concomitant diseases, contraindications to thrombolytic therapy are important factors[16].

Postoperative delirium

Postoperative delirium is an acute psychotic state that lasts for a short time after surgery and is manifested as confusion not associated with an existing or developing neurocognitive disorder (such as dementia or stroke) [40]. Its main characteristics are qualitative disorder of consciousness, hallucinations, psychomotor agitation, disturbances of the sleep-wake cycle.

In cardiosurgical practice, delirium occurs in about 30% of patients; this is the highest rate in comparison with other types of surgery [41]. It typically develops in the early postoperative period – within 3 days. Despite the fact that this complication is a transient condition, it has been shown to be associated with a high risk of hospital infections, distant cognitive impairment, mortality, and prolonged hospital stay [42].

Depending on the specific clinical manifestations, three subtypes of delirium are distinguished: hyperactive, hypoactive and mixed. The hyperactive type is characterized by pronounced psychomotor activity, increased excitability, anxiety, persistent and loud speech. The hypoactive type is manifested in attention disturbances, detachment, apathy, decreased motor activity, and quiet monotonous speech. In a mixed type, the patient's activity level may vary. It is believed, that delirious psychomotor agitation with concomitant productive symptoms reflects the initial stage of pathological changes in the macro- and microstructures of the central nervous system, leading to an increased risk of irreversible dystrophic changes in the brain structures. Patients who have developed delirium in the postoperative period are characterized by a threefold increase in the risk of long-term cognitive impairment within 12 months after the operation, and tenfold – for several years. Compared to patients who have not experienced delirium, they often need the help of others in their daily activities. [43].

The most sensitive predictors of delirium development after cardiac surgery are: age over 70 years, initial cognitive deficit, atherosclerosis of the ascending aorta, previous history of stroke and atrial fibrillation, risk of operation according to EuroSCORE more than 5%, left ventricular ejection fraction less than 40%, diabetes mellitus and depressive disorders [44].

According to the results of numerous studies, the probability of delirium development does not correlate with the severity of postoperative cognitive dysfunction [45]. There are conflicting data on the relationship between the development of delirium and duration of the use of an apparatus for artificial circulation [46]. The risk of delirium development was shown to correlate with the duration of aortic clamping during surgery [47].

Postoperative cognitive dysfunction

Postoperative cognitive dysfunction is a change in the functional and morphological state of the cerebral cortex mainly of the vascular genesis, which is observed in the postoperative period and is characterized by a decrease in memory, difficulty in concentrating, impairment of speech and other higher cortical functions [48].

Postoperative cognitive dysfunction, often of a persistent nature, reduces patients' compliance, their quality of life, social and household adaptation [49].

The prevalence of cognitive impairment after coronary artery bypass grafting is high: it develops in 50% – 80% of patients in the early postoperative period, in 20% – 50% in 2 months and in 10% – 30% of patients 6 months after the operation [50].

The structure of cognitive impairments in the postoperative period is described in numerous publications. The most frequently observed impairments are disorders of attention, speech, counting, memory, a tendency to slow thinking, difficulty in spatio-temporal organization and abstract thinking. Cognitive function in the attention domain is more frequently disturbed than memory. Of the memory impairments, one third of the patients had disturbances of delayed reproduction, and, less often, in recognition. According to L.A. Bokeria et al. [51], a short-term memory impairment is the most prominent manifestation of postoperative cognitive dysfunction. In addition, after operations on the open heart, disturbances of nonverbal memory and visual-spatial construction are the most pronounced [52].

Contradictory data were obtained when investigating the problem of recovery of the disturbed functions. A number of authors argue that the phenomena of cognitive decline are subject to gradual regression in the postoperative period (within several months) [53]. Other authors note that cognitive dysfunction may persist for several months and even years, and a disorder of the auditory memory can be regarded as a predictor of such persistence [54]. Some researchers have shown aggravation of cognitive impairments and their faster transformation into persistent disorders. Thus, in patients who underwent coronary artery bypass surgery, the prevalence of dementia was significantly higher in the period of 7.5 years after the operation than in general population [55]. The authors believe that this result is heavily influenced by the initially low result of neuropsychological testing and the presence of cerebrovascular diseases. Other predictors of long-term and persistent cognitive decline include such factors as age over 70 years, duration of aortic clamping, and the use of an artificial circulation device [56].

Conclusion

The results of the analysis of literature devoted to the study of etiological factors, pathogenetic mechanisms and clinical features of posthypoxic encephalopathy in patients after cardiosurgical interventions indicate that the factors contributing to the onset of cerebral complications are diverse. Along with the factors of the operation itself, factors characterizing the adaptive capabilities of patients (age, sex, concomitant diseases, education level, etc.) deserve attention, as well as environmental factors. A special place is occupied by technical features of operations performed using an apparatus of artificial circulation. On the one hand, they allow to effectively carry out the process of myocardial revascularization; on the other hand, hypoperfusion, embolism and other factors can cause different variants of brain dysfunction.

Current classifications of cerebral complications developing after operative treatment of cardiac pathology, as well as unrelenting interest of researchers to this problem, point out to its significance.

Postoperative stroke is the most serious complication of cardiosurgical interventions, characterized by high prevalence. Its specific features, such as a predominantly cardioembolic subtype and contraindications to thrombolytic therapy, indicate the need for timely preventive measures, including the impact on possible risk factors, especially intraoperative ones.

The problem of postoperative cognitive impairment continues to be extremely prevalent and relevant, because of a decrease in the quality of life of patients, and a decrease in adherence to treatment. After using surgical methods of treatment, the manifestations of coronary heart disease become less pronounced, and it is cognitive dysfunction that causes a change in the optimal level of daily activity and, thus, becomes an important problem for both neurologists and physicians.

Thus, further studies of the causes and mechanisms of perioperative damage to the structures of the central nervous system will allow to optimize surgical interventions, and are of paramount importance.

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