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Association of inflammation, oxidative stress, and deteriorated cognitive functions in patients after cardiac surgery

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Abstract

The study is focused on the connection between cognitive dysfunction, inflammatory processes, oxidative stress, and various associated biological factors. Postoperative cognitive dysfunction is a condition where a patient exhibits a temporary deterioration in cognitive function after surgery, which may include problems with memory, concentration, and overall cognitive performance. While most common among elderly patients, it can occur in individuals of any age. The causes are not fully elucidated, but it is assumed that peripheral trauma during long-term surgical interventions is behind the development of inflammation and the creation of conditions of oxidative stress, which leads to the disruption of the blood-brain barrier and the subsequent development of cognitive impairment. This review aims to describe the detected changes at the level of selected markers of inflammation and oxidative damage in patients, primarily in connection with cardiac surgery.

Keywords: Blood-brain barrier, cardiac surgery, cognitive disorder, inflammation, oxidative stress delirium, ROS, VEGF

INTRODUCTION

According to recent data, more than 300 million surgical procedures are performed worldwide annually, with elderly patients accounting for more than a quarter of the total number of patients[1,2]. Postoperative cognitive dysfunction (POCD) is a complex neurological condition that manifests itself in the deterioration of cognitive functions in patients after surgical procedures. The 1980s saw significant advances in clinical research on cognitive dysfunction following surgery[3,4]. Several studies have begun to closely examine cognitive aspects, including memory and concentration, through neuropsychological assessments even after cardiac surgery[5]. POCD is associated with risk factors that may be critical determinants of the development of neurological events. Oxidative stress, or hypoxia, which is often associated with surgical procedures, contributes to the development of POCD. These processes can trigger inflammatory reactions and the formation of reactive oxygen species (ROS, oxidizing compounds formed from oxygen), causing nerve cell damage and, subsequently, cognitive impairment. microRNAs (miRNAs) are also already an important research direction in connection with POCD, as the regulation of gene expression may play an important role in the pathological alterations associated with cardiac surgery and carotid stenosis.

The paper provides a comprehensive view of the mutual interactions between ROS producers, such as anesthesia, oxidative stress conditions, hypoxia, inflammatory processes, miRNAs, and some of the surgical procedures.

We focused primarily on the resources and role of ROS. Analyzing existing knowledge and identifying ambiguities in the understanding of these relationships will bring a significant contribution to the development of preventive and therapeutic measures aimed at minimizing the occurrence of POCD in the surgical environment.

PERIOPERATIVE NEUROCOGNITIVE DISORDERS

Cognitive function includes the brain's mental ability to acquire, store, process, and extract information[6,7]. It is the ability to understand complex relationships between different information, perform tasks, remember information, use language, solve problems, and make judgments[8]. Several brain regions are involved in cognitive functions, including the hippocampus, prefrontal cortex, striatum, and amygdala[9-11]. The hippocampus is a critical neural region involved in memory regulation and learning processes, allowing individuals to track where objects are located and orient their body position relative to the objects around them.

Memory develops in the hippocampus through a mechanism of long-term potentiation (LTP). Although the mechanisms of initiation and conservation of LTP at various synapses in the CNS are very complicated and contentious, LTP is mediated by high-frequency glutaminergic activation of hippocampal neurons[12]. Quiescent Schaffer cells transmit signals to postsynaptic CA1 collateral neurons containing three kinds of glutamate receptors (Glu2, AMPA, and NMDA). Magnesium blockade of NMDA channels is reversed by recurrent CA1 stimulation, leading to depolarization, receptor activation, calcium inflow, and stimulation of the second messenger. Next, phosphorylation enhances AMPA receptor sensitivity, stability of synapses, and memory formation[12]. Proinflammatory cytokines pronounce deleterious effects on signaling neurotransmitters in the hippocampus, leading to excitotoxic neuronal damage and cognitive deficiency.

The hippocampus is sensitive to proinflammatory cytokines, such as IL-1 or TNF-α, produced in neuroinflammatory processes due to the presence of high concentrations of receptors for such cytokines[13,14].

The occurrence of increased expression of interleukins in the hippocampus has been associated with a decline in cognitive function, even after minor surgical procedures in mice, suggesting a role for the neuro-inflammatory response that is activated after surgical procedures[15-17]. Following cytokine receptor activation, metabotropic Glu2 receptors are downregulated, causing increased AMPA/NMDA signaling and disruption of the LTP process. Meanwhile, HMGB1 (High-mobility group box 1 proteins) can enhance glutamate signaling over NMDA, which causes elevated glutamate flow in hippocampal neurons, and this ultimately leads to glutamate toxicity. In addition, TNF-α can suppress inhibitory neurotransmission through downregulation of GABA receptors, thereby disordering the equity of excitatory and inhibitory neurotransmission, further increasing glutamate toxicity, and leading to apoptosis and cognitive damage[18]. Thus, perioperative stress (various factors in the pre-, intra-, and postoperative period affecting the signaling of inflammation) has a significant impact on CNS homeostasis[19,20], negatively affecting synaptic plasticity, regulation of the cholinergic system, microglial activity, and hippocampal function[21,22].

Perioperative neurocognitive disorder (PND) is a general term that includes cognitive impairments that may occur before or after surgery[23,24]. PND includes debilitating impairments: cognitive function before surgery (referred to as neurocognitive impairment, NCD); postoperative delirium (POD), where patients experience acute changes in mental status; perceptible deterioration recognized within 4 weeks following surgery (delayed neurocognitive recovery); cognitive deterioration recognized within a year after surgery[23,25]. POD causes fluctuations in the state of consciousness and usually occurs 1-3 days after surgery, lasting only a few days[26]. It is essential to differentiate POD from emergent delirium, which affects 8% to 20% of patients after general anesthesia application, particularly at a younger age[27,28]. Conversely, POCD can persist for weeks to several years. POCD refers to cognitive deterioration after surgery, assessed through various neuropsychological tests[25,29].

Postoperative delirium

POD belongs to the most frequent postoperative complications in over 70% of patients of 60 and more years who underwent surgery in the hospital. The highest prevalence of POD is attributed to cardiac surgery and major orthopedic operations. Multifactorial influences at the tissue and cellular levels are involved in the pathogenesis of POD. The sensitivity of the patient and the presence of triggering risk factors also play an important role. The higher the vulnerability, the smaller the triggering factor that can trigger delirium. The extent of POD development points to brain vulnerability, and its incidence points to the presence of a neurological disorder, like preclinical dementia. Postoperative delirium increases the possibility of POCD in the 1st month after noncardiac surgery, but, on the other hand, there was no association between POD and the occurrence of POCD in the 2nd and 6th months after surgery. Diagnostic criteria for delirium are impaired attention (manifested by a decrease in the ability to concentrate, shift, focus, and maintain attention) and perception (impairment of orientation in the environment). The patient can be excited (hyperactive) or apathetic (hypoactive).

Confusion develops over a short period, typically over hours and days, and represents a change in attention and perception, changes in intensity, often worsening in the evening and at night. Cognitive functions are impaired: it is typically manifested by impaired memory, speech, disorientation, and reduced visual and auditory perception. POD likely has a multifactorial etiology. Different diagnoses such as POD and dementia need to be distinguished. Dementia is a progressive deterioration of cognitive functions. For the diagnosis of POD, there are various psychological investigation methodologies and scales, such as CAM-ICU - Confusion Assessment Method, Richmond scale, *etc.*[30].

Postoperative cognitive dysfunction

POCD is a multifactorial syndrome in patients suffering from post-surgical and anesthetic cognitive weakness[31]. Several studies indicate that POCD follows diverse surgical interventions, more often after cardiovascular than noncardiac surgery[32]. A major concern after cardiac surgery is neurocognitive complications, with POCD reported in 23%-81% of such patients[33,34]. POCD manifests itself in various negative consequences and can affect memory, concentration, ability to process information, language comprehension, social integration, impaired concentration, personality changes, and reduced ability to socialize in severe cases[31,35]. POCD can manifest itself days or weeks after surgery[35], problems persist for months or even become permanent[31,36], and can persist or even develop into Alzheimer's disease, which seriously affects the health status of patients[35].

In the past, POCD was found to occur with a prevalence of 10% to 54% in the early weeks after surgery[37]. The extent of changes in the state and behavior of patients is defined in the period of weeks or even months after induction of anesthesia in the intensive care unit, to several months after surgery[25]. Delayed development of POCD may indicate a poor prognosis. After 3 months, the prevalence ranged between 12%-17%; after approximately 12 months after surgery, the prevalence decreased to 3%[38,39]. POCD is associated with reduced efficiency of daily living, higher mortality, and lower quality of life. The diagnosis of POCD has historically been made through extensive neuropsychological testing. Recently, various cognitive tests have been used more and more[40].

Longitudinal studies following patients who have undergone cardiac or noncardiac surgery have shown that if POCD persists at discharge or long after surgery, both the risk of mortality and the risk of permanent cognitive decline may be increased[41,42]. Intervention measures in patients with a probability of PND can decrease the risk of POCD to 40%[43]. These findings highlight the importance of identifying patients at increased risk of PND, optimizing perioperative management, and conducting long-term monitoring of these patients[43].

CARDIAC SURGERY PATIENTS PRONE TO COGNITIVE DYSFUNCTION

The type of surgery performed is a significant factor in the development of POCD. The consequences differ substantially after cardiac surgical procedures[21]. Cardiac surgery and subsequent intensive care unit time in aged patients is linked to persistent cognitive deficiency and is closely associated with quality of life[44]. Previous scientific research has shown that in adults with physiological cognitive status who underwent noncardiac surgery, the incidence of POCD was 3.9% at 2-3 weeks and 12% at 3 months[29]. Conversely, in adults undergoing cardiac surgery, the incidence of POCD has been shown in up to 60% of individuals, more specifically 33 up to 83% using cardiopulmonary bypass (CPB)[42,45]. The diversity in the occurrence of POCD indicates that different types of surgery present different risk factors for the development of POCD. In part, this may be due to the fact that coronary artery bypass surgery (CABG) is accompanied by dynamic changes in circulation and brain perfusion and has a pronounced period of anesthesia[42]. It was found that the highest frequency of POCD was observed after surgical procedures such as open aorta, transthoracic aortic valve, and coronary bypass[46].

Atherosclerosis has an indisputable place in POCD in cardiac surgery patients as it causes plaque rupture, artery stenosis, and subsequent intraoperative hypoperfusion of the brain, as well as microembolism of the carotid and cerebral arteries[47]. Magnetic resonance imaging of the brain revealed that a compelling part of the elderly had an asymptomatic stroke that altered cerebral autoregulation and predisposed them to POCD[48]. Coronary artery disease is another risk factor for POCD[49] since cognitive function deterioration is similar whether patients were treated surgically or conservatively. In patients with preoperative low

cardiac output, however, surgery improves cognitive function[50]. Atherosclerotic alterations in the vessels of the brain lead to the faster development of brain function disorders[51]. In this context, carotid artery (CA) stenosis plays an important role in influencing autoregulation of cerebral perfusion[52]. It is found that patients with CNS vascular disorders of cognitive impairment often show reduced perfusion in the cerebral cortex, particularly in frontal and parietal areas located at the borders of different vascular zones[53]. These areas of the brain are known as "blood-supplied circuits" and are particularly sensitive to disturbances caused by left ventricular systolic and diastolic impaired function, valvular pathology, and atrial fibrillation, which are common in cardiovascular diseases, as well as during cardiac surgery[51,54,55].

Vascular cognitive disorders are relatively common in senior individuals[56]. A negative impact on cognitive function can be seen even before it causes serious health complications, such as an acute myocardial infarction or stroke. Chronic heart failure can lead to an overall reduction in cerebral blood flow[57]. Up to 19% of patients with coronary disease are affected by cognitive impairment before surgery[58]. Carotid artery stenosis may affect cognitive function before stroke or transient ischemic attack[59]. These changes may be the result of either hypoperfusion of the frontal part of the brain, leading to impaired cerebrovascular reactivity[60] and progressive ischemic changes[61], or embolization from carotid plaques[62], which subsequently lead to the loss of nerve cells. Risk factors for the occurrence of postoperative cognitive decline after heart surgery can be divided into modifiable, partially modifiable, and non-modifiable[63].

Cardiopulmonary bypass

One of the highlights of cardiac surgery is the use of cardiopulmonary bypass, which can cause neurological problems through inflammatory reactions and microembolisms[64], but all types of surgery carry a high risk of systemic inflammation (excessive defense reaction of the organism to a stressor). In the case of cardiac surgery using cardiopulmonary bypass (CPB), the blood is exposed to foreign surfaces that can induce proinflammatory reactions. This inflammation can cause endothelial dysfunction, leading to leakage across the blood-brain barrier (BBB, semipermeable and selective membrane separating the brain interstitium from the circulation) and tissue edema[65]. Studies have shown a close association of cytokines (for example, TNF-α, IL-1, and IL-6) with neuropathology[66]. These underlying changes are thought to affect the brain regardless of the microembolic burden during surgery[67], and may potentially explain the occurrence of early cognitive decline[68]. Cardiac surgery induces a significant systemic inflammatory reaction, which is manifested by an increased number of leukocytes (leukocytosis) and a significant imbalance in the levels of cytokines and other inflammatory markers[69]. Cardiopulmonary bypass (CPB) is of a non-physiological nature, which induces pathophysiological modifications in the organism and contributes to multi-organ and multi-tissue damage to various extents[70].

The underlying mechanisms of POCD associated with the use of CPB involve a complex combination of factors, including hypoperfusion, emboli, and systemic inflammation[2]. Inflammation is caused by several factors, including the opening of the chest (sternotomy), the use of extracorporeal circulation, the presence of temporary endotoxemia, and aortic clamping. Systemic inflammation can result in increased communication and signaling from the body's periphery to the brain. Consequently, systemic inflammation can trigger the activation of the brain's innate immune cells, specifically microglia and astrocytes, leading to a neuroinflammatory response[71,72].

Carotid stenosis

The carotid artery is the third most common site of atherosclerosis, responsible for 30% of ischemic strokes[73]. The currently valid 2018 European Society of Vascular Surgery (ESVS) and European Society of Cardiology (ESC) recommendations[74] recommend surgery for symptomatic carotid stenosis exceeding 70% according to the criteria of the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[75].

Indications for revascularization of asymptomatic carotid stenosis, i.e. in patients without transient ischemic events within the last 6 months, are less clear and associated with a lower level of evidence.

The potential benefits of revascularizing patients are not so significant compared to the risk of complications if the progress in conservative treatment in recent years is taken into account. The relative risk reduction of a first ischemic vascular event is only 4.6% at 10 years[76], showing that most asymptomatic patients may undergo unnecessary procedures. Some patients have increased risk factors for cerebral ischemia[76]. In such patients, prevention by revascularization could be beneficial. In this context, studies are beginning to look at the effect of revascularization on cognitive function, with the assumption that there may be improvement in pre-existing impairments. Despite initial controversies, there is now a fairly accepted view that asymptomatic carotid stenosis may be associated with cognitive dysfunction[77-79]. In this context, two main hypotheses are presented: cerebral hypoperfusion[80] and microemboli[80]. The mentioned factors can lead to a decrease in cerebrovascular reactivity[81] and changes in brain functional connectivity[78,81].

PATHOPHYSIOLOGY OF COGNITIVE DYSFUNCTIONS

The pathophysiology of POCD is complex and involves various mechanisms[45]. These are primarily neuroinflammatory processes[82], oxidative stress[83], and disorders of the integrity of the BBB[84]. Oxidative stress is associated with an imbalance between antioxidants and free radicals, which is the basis of the pathophysiology numbers of human diseases[85,86]. Subsequently, among the factors that contribute to the mentioned mechanisms are the method of anesthesia administration, the choice of anesthetic agent, insufficient tissue blood supply, and excessive ventilation[87]. Surgery-induced inflammation of the hippocampus is thought to be the main cause of POCD[88]. Lowering damage of neurons can decrease the occurrence of POD[89], while neuronal function is directly related to the preservation of mitochondrial function[90].

We would further focus on pathophysiological mechanisms primarily from the point of view of modulation of oxidative stress conditions not only in the CNS but also in the periphery, which leads to disruption of the BBB.

General anesthesia in terms of modulation of the inflammatory response and oxidative stress conditions

Anesthetics can impair neutrophil and monocyte function, suppress lymphocyte growth, and cause various changes in the release of inflammatory biomarkers[91]. In early scientific research from 2003 and 2011, it was shown that the combination of isoflurane, nitrous oxide, and midazolam can cause brain cell damage, and negatively affect learning and long-term neurocognitive function[92,93]. In the past, several researchers believed that there was no clear relationship between the occurrence of POCD and the choice of different types of anesthesia and anesthetic agents[94].

Anesthesia can be divided into general, which involves the unconsciousness of the whole body, and local, which is aimed at a specific area and preserves the consciousness of the patient[95]. General anesthesia (GA) means a temporary loss of perception and sensitivity. It is often used in major surgical procedures[96]. The states of consciousness that can appear during general anesthesia include unconsciousness, disconnected consciousness, and connected consciousness[96].

It is still uncertain if the effect of anesthesia is fully reversible and the CNS returns to its original state at the end of the anesthetic effect[97]. Adverse effects of GA, such as nausea, vomiting, dry mouth, sore throat or

hoarseness, chills, tremors, confusion, muscle aches, itching, bladder problems, and dizziness, are common. Perioperative neurocognitive disorders, i.e., POD and POCD, are among the prevalent cognitive disorders after GA and surgical procedures[42,98]. The frequency of cognitive impairment associated with GA is significantly higher in two vulnerable groups: young ones and seniors[97]. In elective surgery in elderly patients undergoing noncardiac surgery, the occurrence of POD is approximately 11.6%[99], while it is as high as 60% in children[100]. The frequency of POCD ranges from 30% to 40%[3].

Anesthesia, an integral part of surgical interventions, can also have protective effects[101]. Optimization of anesthetic preparations and alternative selection of anesthetic techniques can prevent unwanted effects on cognitive functions.

Type of anesthetic

Anesthetics may have a dual nature regarding inflammatory responses and the process of POCD[8]. Anesthetic agents can cause excessive production of ROS and impair the antioxidant protection system, which leads to the formation of a large amount of ROS[102]. Additionally, anesthesia induces changes in the cholinergic system and cell apoptosis, thereby contributing to cognitive disorders[103].

The administration of anesthetics is associated with the microglia activation and the emergence of neuroinflammatory processes[104]. Commonnly used anesthetics suppress microglial activation, promote M2 polarization, and exhibit anti-inflammatory effects[105,106]. Substances administered intravenously during general anesthesia have an inhibitory effect on the reticular system of the brainstem via opioid receptors or GABA receptors[107]. According to the Meyer-Overton rule, the effectiveness of anesthetics depends on their ability to dissolve in lipids[108].

There is an indication regarding the depth of anesthesia in association with POCD disorders. Increased concentrations of inhaled anesthetics can increase the permeability of the BBB[109]. A controlled anesthetic with bispectral index monitoring was used in the Cognitive Dysfunction after Anesthesia (CODA) study. The results showed that in elderly patients undergoing major surgery, achieving and maintaining BIS values between 40 and 60 during surgery minimized the events of a deep anesthetic state. This was linked with a reduced risk of delirium during the initial care and cognitive decline 3 months after surgery. BIS monitoring contributed to faster recovery from anesthesia. Patients monitored by BIS demonstrated a faster return to consciousness after anesthesia compared to the usual care group, showing faster eye-opening and faster discharge from the postanesthesia care unit[110]. On the other hand, other studies report the opposite findings, that a deeper level of anesthesia protects against delirium and POCD[109]. In older adult patients, anesthesiologists should monitor age-appropriate end-expiratory concentrations of inhaled anesthetics, maintain optimal values of cerebral perfusion pressure, and use EEG to monitor brain function[43].

A proper anesthetic strategy can protect patients from cognitive impairment during the perioperative period[103]. An important aspect of POCD is the thorough examination of the optimal method of administration of anesthetics based on the type of drug and its dosage[111].

The role of oxidative stress in perioperative neurocognitive disorders

Oxidative stress is a critical cause in the pathophysiology of diverse cognitive disorders. The occurrence of POCD may be promoted by oxidative stress and hypoxia in the brain region, as well as changes in the phenotype, and receptor expression of microglia and astrocytes in situations of inflammatory conditions[112]. High oxygen concentrations were shown to be harmful to various body systems, such as the cardiovascular, nervous, respiratory, and gastrointestinal[113]. Surgical interventions can disrupt this delicate

balance, interfering with autophagy in the hippocampus and promoting oxidative damage[114].

Increased oxidative stress in the hippocampus was observed in animals after surgery, and affected by postoperative cognitive impairment[83,115]. It can result in damage to the extracellular matrix and trigger cell necrosis and apoptosis[116]. In the presence of necrotic cells and damaged extracellular matrix, several components are released that activate inflammatory processes. Research suggests a positive correlation between the severity of cognitive impairment and levels of ROS and NO[117].

Significant sources of ROS production behind neurocognitive dysfunctions

ROS is directly involved in cognitive impairment by damaging neurons[118]. In rats with induced POCD, isoflurane anesthesia was found to increase the expression of NOX2 (a major source of ROS) and impair contextual fear memory seven days after incision. These findings suggest that hippocampal induction of oxidative stress could be connected with the POCD[119]. The prevalence of POCD in cardiac surgery can reach 70%, regardless of optimal oxygen saturation[32]. ROS regulates the expression of genes responsible for protection against oxidative stress and can interact with important cell signaling molecules such as MAP kinases, PI3 kinases, and protein tyrosine phosphatases[120]. This interaction induces signal cascades that affect various cellular processes, including cell proliferation and survival[121].

ROS can affect all biological structures[122]. They contribute to neuroinflammation, accumulation of amyloid protein (Aβ), excessive phosphorylation of tau protein, and mitochondrial dysfunction[119]. According to Abdallah *et al.*, the profile of polyunsaturated fatty acids in erythrocyte plasma membranes is sensitive to oxidative damage due to sustained exposure to ROS in the bloodstream[123]. This results in a serious decline in the lifespan of circulating erythrocytes. Under pathological conditions such as cardiovascular diseases, diabetes mellitus, and the aging process, the frequency of oxidative damage to erythrocytes increases[85]. Zhong *et al.* identified greater severity of carotid disease association with a higher tendency of cognitive deficiency during a ten-year follow-up[124].

NOX enzymes

NOX is a family of NADPH oxidases representing molecules transferring electrons through membranes. The electron acceptor is O_2 forming superoxide radical ($O_2^{\bullet-}$). Neurons respond to ROS, which are primarily generated by NADPH oxidase 2 (NOX2). NOX2 is the most abundant enzyme and is generally present in phagocytic cells, especially in the thymus, small and large intestine, spleen, pancreas, placenta, prostate, and testis tissues. It is also present in smaller amounts in cells without the ability to phagocytose, such as neurons, cardiomyocytes, skeletal muscle myocytes, hepatocytes, endothelial cells, and hematopoietic stem cells. In phagocytes, it is present in intracellular membranes and on the plasma membrane. In inactive neutrophils, it is located primarily on the membranes of intracellular components, especially secondary and tertiary granules, and after activation, it is translocated to the plasma membrane. However, it is also activated in granules. In other phagocytic cells, the subcellular distribution differs. In non-phagocytic cells and smooth muscle cells, it is located near the nuclear cytoskeleton, in the hippocampus, and the membranes of synaptic sites. NOX2 expression is inducible, for example, in phagocytes by interferons, in myofibroblasts by carotid damage, in cardiomyocytes after an acute myocardial infarction, or by angiotensin II (in adipocytes, aorta, heart, pancreatic islets). However, the amount of NOX2 can also be influenced by angiotensin II at the post-transcriptional level[125].

An NADPH oxidase inhibitor, apocynin, was tested on mice that underwent an experimental laparotomy with isoflurane anesthesia. This drug has shown the ability to reduce the impairment of contextual memory and fear that are induced by surgery as a concomitant brain pathology[126]. Inhibition of NOX2, which is

involved in oxidative stress, may be proposed as a preventive and healing POCD strategy[127].

Iron and the production of reactive oxygen species

Ferroptosis is caused by impaired iron metabolism, amassing products of lipid peroxidation, decreased glutathione, glutathione peroxidase 4, and reduction in mitochondria[128]. Recent research by Masaldan *et al.* suggests that ferroptosis and iron imbalance in the nervous system may be underlying mechanisms of cognitive impairment and neurodegeneration[129]. Optimal heart function requires adequate regulation of iron levels in the human body[130]. Iron deficiency is the most common condition associated with malnutrition in humans, affecting up to 75% of heart failure patients[131]. In the last 10 years, however, ferroptosis, due to impaired iron homeostasis, has played a significant role in the pathophysiology of many cardiovascular diseases, along with atherosclerosis, drug-induced heart failure, myocardial ischemia-reperfusion, cardiac injury, sepsis-induced cardiomyopathy, arrhythmias, and diabetic cardiomyopathy[130]. Particularly, cardiomyocytes were provably affected[132]. Cardiomyopathies associated with iron metabolism disorders are the main matter of mortality and comorbidity in patients suffering from hemochromatosis[133].

The immediate mechanism that leads to the formation of reactive particles is the presence of free iron in the cell, which triggers the Fenton reaction. Cells maintain a highly reduced state, so any available metal ion should only exist in a reduced form[134]. The Fenton reaction, in which the formation of a hydroxyl radical with a high reduction potential occurs, takes place only if a "free" transition metal is present. Free iron can occur due to impaired function of transport and storage proteins for iron. However, more common are induced conditions of oxidative stress, when the superoxide anion radical is formed through both regulated and unregulated mechanisms[135]. $O_2^{\bullet-}$ with an existence of 2-4 μs is subject to either non-enzymatic one-electron reduction or dismutation. In case of excessive production, especially in mitochondria, it causes oxidation of [4Fe-4S]-clusters of enzymes, which releases iron. The oxidation of Fe-S centers is expressed in the reactions (1) and (2). The oxidized center loses Fe because the sulfide ligand binds Fe^{3+} more strongly than Fe^{2+}.

$$[2Fe^{2+}2Fe^{3+} - 4S] + O_2 + 2H^+ \rightarrow [2Fe^{2+}3Fe^{3+} - 4S] + H_2O_2 \quad (1)$$

$$[2Fe^{2+}3Fe^{3+} - 4S] \rightarrow Fe^{2+} [3Fe^{3+} - 4S] \quad (2)$$

The increased production of enzymes containing [4Fe-4S] clusters then increases the availability of free iron, causing damage to structures through hydroxyl radicals ($HO^{\bullet}$), up to the occurrence of spontaneous mutations. Another disadvantage of oxidative modification of proteins is their susceptibility to proteolytic degradation[134].

Research on ferroptosis induced by abnormal iron metabolism and distribution suggests that neuronal death in the hippocampus is responsible for the occurrence and progression of postoperative cognitive dysfunction[136]. Inhibiting ferroptosis in the CNS effectively ameliorates cognitive deficits, while promoting ferroptosis can exacerbate cognitive impairment in animal experiments[137]. Thus, ferroptosis appears as a potential therapeutic target to improve cognitive decline associated with neuroinflammation[138]. The formation of excessive amounts of ROS and damage to cellular structures can be prevented by iron chelators such as deferiprone, deferoxamine, ciclopirox, and 2,2-bipyridyl[128,129]. Deferoxamine reduces the extent of myocardial infarction and neurological deficits in rats after ischemia[139] and in human patients[140]. Rosenthal *et al.* reported that deferoxamine significantly improved neurological status and reduced mortality in rats subjected to cardiac arrest for 6.5 min[141]. Deferoxamine also exhibits a positive effect on neurological function in a collagenase-induced intracerebral hemorrhage model[142].

LOX and COX enzymes

Lipoxygenases (LOX) are enzymes containing non-heme iron that enable the formation of hydroperoxides from polyunsaturated fatty acids to other biologically active metabolites (for example, arachidonic or linoleic acids to linoleic and arachidonic hydroperoxides) prostaglandins, prostacyclins, thromboxanes, leukotrienes. LOXs insert oxygen into the corresponding carbon position and form hydroxyeicosatetraenoic acids (HETEs). Most LOXs, notably 5-LOX and 12-LOX, utilize arachidonic acid. Reticulocytes (15-LOX) and other types of LOX also catalyze the transformation of other lipids, the same as membrane phospholipids, losing their stereospecificity. However, the products of oxidation can be cholesteryl hydroperoxides, hydroperoxides, epoxides, hydroxycholesterol derivatives, isoprostanes, and aldehydes that react with proteins and are cytotoxic[143].

Isoenzymes of cyclooxygenase (COX-1 and COX-2) catalyze the prostaglandin formation from arachidonic acid[144]. COX-1 is constitutive and associated with physiological functions, while COX-2 is inducible and plays a key role in inflammatory processes[145]. Upregulation of COX-2 is through tissue degradation products, lipopolysaccharides, and also inflammatory cytokines (IL-1beta, IL-15, and TNF-α). Among them, IL-1beta is considered the most potent inductor of COX-2 during inflammation. MAPK (mitogen-activated protein kinase) pathway and peroxynitrite are also involved[146]. However, the mere presence of higher NO levels suppresses COX-2 induction, as can glucocorticoids in the spinal cord[147].

COX-2 was expressed at the postsynaptic dendrites and excitatory terminals of cortical and spinal neurons in the brain in stable amounts[148]. Much attention has been paid to the induction of COX-2 in the context of neurodegeneration and mental disorders linked to neuroinflammation, which, to some extent, contributed to the progression of POCD[149]. In response to the activation of synapses, COX-2 can produce prostaglandin E2 (PGE2), which also undergoes synaptic transport and stimulates glutamate release from presynaptic neurons[148]. Increased glutamate release may reduce the number of GABA small cells[150]. Within the hippocampus, PGE2 plays a key role as a mediator of COX-2-mediated synaptic transmission and plasticity. PGE2 stimulates amyloid (Aβ) production in microglia, astrocytes, and neurons *in vitro* and *in vivo*, which is known to adversely affect brain function[148].

Commonly used analgesics are cyclooxygenase (COX-2) inhibitors after surgery[151], reducing the production of prostaglandins in peripheral and central tissues[152]. These anti-inflammatory and analgesic effects may protect against POCD progression. Animal studies suggest that COX-2 inhibitors represent appropriate means for neuroinflammation and cognitive dysfunction after surgery[153].

However, with increased ROS production, only suppression of COX activity may not be sufficient. Arachidonic acid can be oxidized by ROS, forming prostaglandin-like products[154]. PGE2 and PGF2 can produce oxidatively changed lipoproteins mimicking prostaglandin effects[155]. Body temperature, nociception, expression of inflammatory and other genes can also be affected by their effect. It was confirmed that this form of oxidation of LDLs is capable of forming both COX and LOX products (for example, PGD2 and 11β-PGE2 and 12-, 15-, and 5-HETEs)[156,157].

NOS enzymes

The reactive forms of nitrogen are NO· and peroxynitrite ($ONOO^-$). Nitric oxide synthase (NOS) synthesizes nitric oxide by transferring electrons from tetrahydrobiopterin (BH_4) to L-arginine, producing L-citrulline and NO in a reaction that requires the presence of oxygen and NADPH[158]. In the case of insufficient levels of tetrahydrobiopterin (BH4), NOS is disconnected, which transfers electrons from L-arginine to oxygen, creating a superoxide radical that immediately reacts with NO to form a powerful

oxidizing agent, the peroxynitrite anion[159]. The peroxynitrite anion subsequently further reduces BH4 levels within the cycle, leading to increased formation of the peroxynitrite anion[159].

Nitric oxide (NO) is important in many physiological processes[160]. Under inflammatory conditions, excessive production of NO triggers neurodegenerative processes[161], including microglial activation, neuronal cell apoptosis, and oxidative stress[162]. Increased levels of NO can negatively affect cognitive functions[163]. NO levels are considered a risk factor for Alzheimer's disease and early POCD[164].

eNOS and nNOS isoforms within endothel and neurons produce short-lived levels of NO[165]. iNOS does not occur under physiological conditions. Its expression is induced by LPS endotoxin stimulation and various cytokines (e.g., TNF-α, IL-1)[148]. iNOS production is induced by various stimuli and serves as a dominant proinflammatory and devastating mediator in inflammatory diseases[165]. iNOS affects synaptic plasticity and causes problems in brain functions, including cognitive impairment[166]. NOS inhibition through the substance L-nitroarginine methyl ester, which reduces the formation of NO, can help alleviate brain dysfunctions[167]. Reversal of NO-related signaling pathways alleviated cognitive impairment and inflammatory responses following carotid artery surgery in mice[168]. Excessive production of NO is considered a pathogenic signal related to the diagnosis of POCD[148,168].

Hypoxia

Hypoxic, ischemic, and anemic mechanisms can lead to an insufficient supply of tissues with oxygen[169,170]. Each of these categories is independently associated with cognitive decline, which is common in old age. There is evidence to suggest that aging may exacerbate the effects of hypoxic stress[171]. Ischemic hypoxia, which refers to insufficient oxygen supply to tissues due to limited blood flow, is most often linked to cognitive decline[172]. In surgery, ischemia is usually a result of acute or chronic embolic events or insufficient perfusion[172]. Embolic, ischemic, and hemorrhagic strokes are widely recognized as important factors contributing to cognitive failure[171]. Cognitive and behavioral disorders can affect multiple areas. Local brain damage can affect functional networks[171].

Hypoxia readily affects brain function[173]. The lesions that form the core of POCD likely affect the hippocampus, which is extremely sensitive to hypoxic damage[174]. In ischemia-reperfusion injury, the permeability of the BBB changes, leading to an increased flow of substances from the blood vessels into the brain tissue and thus worsening the damage to neurons[175]. Research has shown that in elderly patients undergoing cardiothoracic surgery, hypoxia-induced brain damage is associated with a disadvantageous prognosis[70]. In addition, major surgical procedures, especially in elderly patients, may involve methods that reduce oxygen delivery, including fluid overload, atelectasis, acute anemia, hypoperfusion, and hypoventilation[171]. Postoperative sleep-disordered breathing (sleep apnea), as well as narcotics, contribute to perioperative hypoxemia[176].

The response of cerebral vessels to hypoxia is manifested by dilation[177]. In anemia, there is a significant increase in cerebral blood flow because the body needs more oxygen for the brain[178]. Such an overall response does not appear to be significantly affected by aging. There is evidence indicating that restraints in regional cerebrovascular supply may contribute to cerebral hypoxia and ischemia in a variety of situations, such as severe anemia, hypotension, low cardiac output, and the state of cerebral intravascular obstruction and extracranial in nature[171]. An absence of effect on outcomes was observed with deliberate isovolemic blood dilution in the treatment of acute ischemic stroke, implying that this measure neither worsens nor improves outcomes[179].

Many scientific studies have reported that hypoxia causes systemic and central inflammation, with hypoxia-induced neuroinflammatory responses initiated through HIF-α[180]. Neuroinflammatory responses can be neuronal or glial and are associated with POCD[171,181]. The effects of hypoxia can be reduced by erythropoietin[182]. These parallels support the idea that cerebral hypoxia could underlie the mechanisms leading to POCD[171,183].

In response to hypoxia, hypoxia-inducible transcription factor 1-alpha (HIF-1α) accumulates, whereas HIF-1β is expressed continuously[184]. HIF-1α activates genes for cellular adaptation to hypoxia and vascularization. Among the genes are a regulator of angiogenesis, vascular endothelial growth factor (VEGF)[185], and vascular permeability-increasing matrix metalloproteinases (MMPs)[186]. MMPs attach to collagen and tight junctions of brain endothelial cells, causing disruption of the BBB[187]. Inhibition of HIF-1 α led to increased apoptosis in the hippocampus and poorer cognitive performance[188]. Induction of HIF-1α increases glycolysis through activation of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3)[189], which is an enzyme of glycolysis[190]. Increased expression of PFKFB3 potentiates neuroinflammatory reactions during hypoxia.

Several research studies have shown that HIF-1α influences the response to oxidative stress through different mechanisms[191]. HIF-1α provides direct protection against oxidative stress by targeting mitochondria[192]. Mitochondrial ferritin can protect brain cells from hypoxia-induced death[193]. This protective mechanism consists of capturing free iron and preventing redox damage caused by oxygen[194]. HIF-1α can increase the expression of FtMt to prevent redox damage that can be caused by oxygen[195].

Inflammation

Especially in elderly individuals, an increased occurrence of the expression of inflammatory cytokines and inflammatory cells is observed in the CNS, in combination with an increased sensitivity to the induction of inflammatory reactions after stressful situations. This fact leads to the deterioration of cognitive functions in elderly people[35,82,196]. Inflammation and activation of the immune system are key mechanisms contributing to POCD[36,112]. Surgery and anesthesia trigger inflammatory processes in the body of elderly patients, and subsequently, peripheral inflammatory cytokines can damage the blood-brain barrier, which allows increased penetration of inflammatory substances and macrophages into the brain[36,66].

If the equilibrium between anti-inflammatory and proinflammatory signals is disturbed, microglia become chronically activated, leading to the excessive release of proinflammatory factors, specifically cytokines, and the gradual development of neurodegenerative changes such as atrophy and loss of neuronal function[5,197]. Microglia can actively release HMGB1[198]. HMGB1 binds to microglial receptors and activates inflammatory pathways, promoting microglial activation[199]. Long-term activation of chronic neuroinflammation increases the supply of immune cells from the periphery over the BBB, further accelerating the neuro-inflammatory and neurodegenerative process[5,200]. In a state of neuroinflammation, there is increased permeability of the BBB, which allows greater incursion of peripheral immune cells into the CNS[201]. The acute neuro-inflammatory response usually serves to protect the CNS, minimizes further damage, and contributes to the maintenance of tissue balance[200,201]. Chronic neuroinflammation can lead to severe damage to the neuronal environment, disturb its homeostasis, and damage the balance between reparative and proinflammatory processes[202].

NF-κB is bound to NFκB inhibitor (IκB) in the cytosol and is, therefore, inactive. However, phosphorylation of IκB by IκB kinase causes NF-κB release, its translocation to the nucleus, and leads to proinflammatory cytokine upregulation[203]. The subsequently produced proinflammatory cytokines IL1, IL6, and TNFα

promote the release of HMGB1, and further amplification of the inflammatory response. In addition, IL-1 and TNFα reactivate NFκB, leading to increased upregulation of the COX-2 isozyme[204,205], which re-triggers local prostaglandin synthesis[206].

Circulating proinflammatory cytokines in the peripheral circulation subsequently affect BBB permeability. This leads to increased COX-2 and MMP activity, enabling proinflammatory cytokines to enter CNS[66,207]. There is compelling evidence between the increase in serum proinflammatory cytokines and the occurrence of POCD *in vivo* as well as in clinical studies[208]. Impaired memory was observed in patients with a significant increase in IL-6 levels. This cognitive dysfunction lasted up to one month after surgery[209]. Surgery-triggered release of HMGB1 may contribute to inflammatory cytokine activation, and increased amyloid beta and Tau phosphorylation[210,211].

The central cholinergic anti-inflammatory pathway is connected to consciousness and memory formation[212]. Cholinergic regulation of the mtROS/NLRP3/IL-1β inflammasome pathway plays an important role in cognitive functions[213,214]. Stimulation of α7nAchR by agonists can suppress the production of inflammatory mediators in various organs[215]. This process can lower the pathological processes evoked by the inflammatory response and improve the immune function[216,217]. An α7nAchR agonist can enhance anti-inflammatory mediators releasing and reduction of changes to peripheral and brain tissues[217].

The MIP-1 family plays an important role in T-cell migration across the endothelium. Research has shown that higher levels of MIP-1A and MIP-1B are present in patients with cardiovascular disease through a complex cytokine profile[218]. Increased levels of the mentioned factors support theories that turbulent blood flow in incompetent veins has a proinflammatory effect[219]. MIP-1a can attract macrophages and neutrophils to areas of tissue damage. Increased blood levels of MIP-1a have been associated with mood changes and impaired cognition[220]. Experimental studies showed that MIP-1a contributes to the development of neuropathic pain[221].

Additionally, fibrinogen can induce inflammatory responses by increasing the levels of IL-6, TNF-α, monocyte chemoattractant protein (MCP-1), macrophage inflammatory protein-1 (MIP-1a and b), MMP-1, MMP-9, and Toll-like receptors (TLR)[222,223]. For that, fibrinogen can trigger the focal adhesion kinase (FAK), MAPK, and NFκB pathways[223].

Blood-brain barrier damage

The mechanism of BBB disruption is caused by the action of inflammatory mediators [Figure 1], which are induced by peripheral surgical trauma[224]. Peripheral proinflammatory cytokines affect BBB through upregulation of the COX-2 enzyme and another group of enzymes, MMPs, allowing their entrance to CNS[225]. BBB is formed by a tight junction of transmembrane proteins (occludins, claudins, and junctional adhesion molecules) between neurovascular endothelial cells. This structure allows only passive diffusion of water, gases, and small fat-soluble molecules. However, upregulation of COX-2 by IL 1 and TNFα in neurovascular endothelial cells[226] promotes local synthesis of prostaglandins and impairs BBB permeability[66,227]. TNF-α increased MMP-9 transcription, allowing extracellular matrix protein degradation and BBB damage[228,229]. TNFα, IL-1β, and IL-6 were found in higher concentrations in the hippocampus of rats as well as in human cerebrospinal fluid after surgery, suggesting BBB impairment. Elevations of cytokines in the CNS have also been associated with memory impairment in mice and cognitive impairment in humans as measured by various neurocognitive measures.

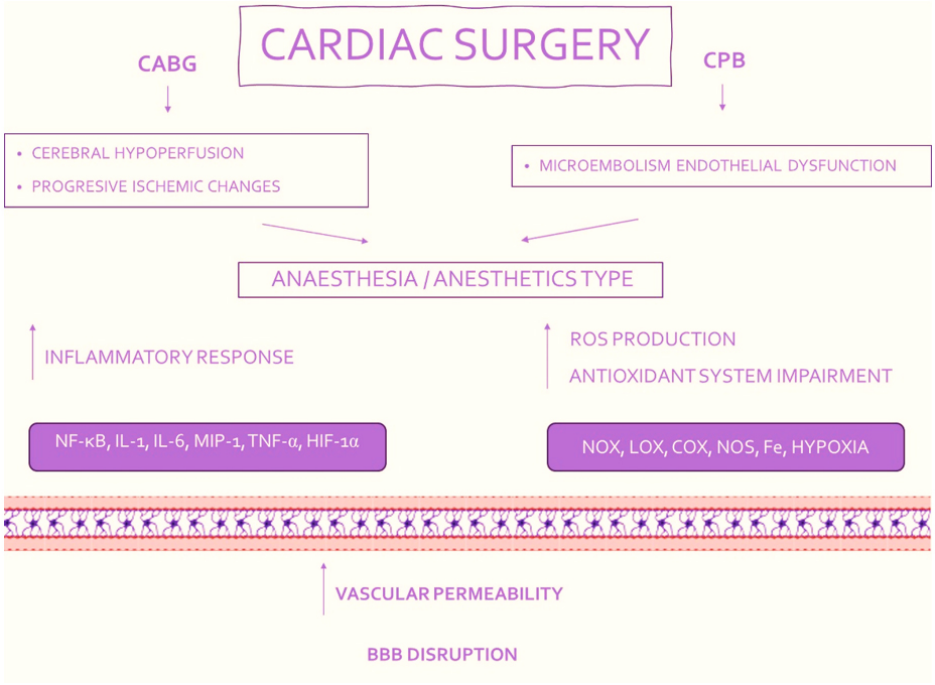

Figure 1. The effect of factors from the peripheral circulation during cardiac surgery on the disruption of the blood-brain barrier and the escalation of inflammatory processes in the brain tissue, which lead to impairment of cognitive functions. BBB: Blood-brain barrier; CABG: coronary artery bypass surgery; COX: cyclooxygenase; CPB: cardiopulmonary bypass; LOX: lipoxygenase; NOX: NADPH oxidases.

Upon BBB damage, bone marrow-derived macrophages (BMDM) entered the CNS via monocyte MCP-1, which interacted with the BMDM surface[230]. BMDMs entered CNS and continued to release proinflammatory cytokines, activating the transcription of the NF-κB signaling[231] and thereby promoting the activity of microglia, thus amplifying the neuroinflammatory response. In a mouse model, preoperative depletion of BMDM was found to reduce the incidence of POCD[232], suggesting that BMDM migration may play an important role in POCD. BMDM could freely enter the CNS due to damage to BBB and trigger deregulation of immune activities. The immune system was connected in the CNS with the periphery through the BBB, which contributed to the worsening of neuroinflammation, and brain tissue injury, contributing to POCD[183].

RNA

Changes at the gene level are involved in the pathogenesis of POCD[233]. The expression profiles of non-coding RNAs (e.g., lncRNAs, miRNAs, and cirRNAs) and mRNAs in mouse hippocampus were investigated by chip technology and PCR analysis. Compelling differences were found in the POCD group, suggesting that non-coding RNAs can contribute to the pathogenesis of POCD[234-236]. The role of non-coding RNA in the pathogenesis of POCD can be explained by its ability to regulate the expression of relevant genes. It is about the creation of regulatory networks of the so-called competitive endogenous RNA (ceRNA) that affects gene expression at the post-transcriptional level. These networks are formed between long non-coding RNA (lncRNA), circular RNA (cirRNA), and messenger RNA (mRNA) and involve binding to the microRNA (miRNA)[237,238].

circRNA

With the development of RNA sequencing (RNA-seq) technologies, it was discovered that there is a class of non-coding RNAs (ncRNAs) known as circular RNAs (circRNAs)[239,240]. With increasing age, there is an increase in the level of circular RNAs (circRNAs), which accumulate in synapses and other neuronal tissues. Increased accumulation of circRNA is associated with the occurrence and development of neurodegenerative and psychiatric diseases, as reported by several previous studies[241,242]. In addition, circRNA is related to neurotransmitter function, neuronal maturation, and synaptic activity, according to previous research[243-245]. CircRNA is found in mammalian brains and contains a close association with neurological functions[239,240].

In contrast to classical linear RNAs, circRNA (cyclic RNA) represents a subset of endogenous non-coding RNAs with a closed loop-like structure and exhibits high resistance to degradation[246]. CircRNAs are closed covalently looped molecules that lack 5′ ends or 3′ poly-A tails. They are generated through reverse splicing of pre-mRNAs[239,247]. Current studies highlight that circular RNAs (circRNAs) can act as competitive endogenous RNAs (ceRNAs) - binding to microRNAs (miRNAs) to eliminate their inhibitory effect on target mRNAs via miRNA binding sites[248,249]. The regulatory network formed by the interaction of circRNAs, miRNAs, and mRNAs is called the ceRNA network. Recent studies have focused on circRNA research and show that circRNA-linked ceRNA networks play an important role in the pathogenesis of diseases such as Alzheimer's disease (AD), stroke, and other neurological disorders[250,251]. These findings provide new insights into the molecular relationships associated with POCD[252].

CircRNAs play an important role in cognitive disorders such as Alzheimer's disease. Downregulation of circCwc27 can lead to improved cognitive function in mice suffering from Alzheimer's disease[253]. Plasma circRNA-089763 is positively correlated with the incidence of POCD[235,236]. A total of 210 circRNAs were identified with differential expression in the serum of POCD patients after screening by microarray analysis. Such circRNAs include, for example, HSA_circRNA_001145, HSA_circRNA_101138, HSA_circRNA_061570[254], circRNA_28795, circRNA_44122, circRNA_44122, circRNA_22058, circRNA_22058, and circRNA42559, which are crucial factors in POCD[255]. Recent research has revealed that certain circular RNAs (circRNAs) show abnormal expression in the hippocampus and play an important role in postoperative cognitive impairment (POCD) through a microRNA (ceRNA) competition network[255].

miRNA

It was found that microRNA has a role in the origin and development of POCD[256]. MicroRNAs (miRNAs) represent a group of short single-stranded non-coding RNAs that play a key role in suppressing the expression of target genes by either degrading mRNAs or preventing their translation[257]. To date, scientists have discovered more than 700 types of miRNAs. As a part of scientific studies, several miRNAs have been found to have the ability to influence processes in neurons and the area of the immune system[88,258]. miRNAs were found to be either closely related to cognitive processes, nervous system development, learning and memory, or cancer and inflammation[259-261].

CONCLUSION

The development of neurocognitive dysfunctions after cardiac surgery is a relatively common phenomenon. Many other risk factors can lead to and contribute to the pathogenesis of cognitive dysfunctions after surgical interventions, such as genetic polymorphisms, ethnicity, nutritional status, physical fitness, substance abuse, liver dysfunction, or diabetes mellitus.

It is important to recognize the pre-, peri- and postoperative risks especially for the possibility of applying preventive strategic measures that should help eliminate the development of neurocognitive impairment, such as the selection of appropriate premedication, adjustment of psychological status, length of surgical procedure, amount and type of anesthetics/anesthesia, maintenance of body temperature and hemodynamics, administration of compounds that suppress inflammation, but also melatonin agonists and dopamine antagonists. We tried to approach the factors that are significant sources of reactive oxygen and nitrogen species because they are modifiable factors. It does not represent a treatment strategy, but a choice of appropriate antioxidant adjuvants can affect the patient's condition.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study: Kočan L, Vašková J
Data analysis and interpretation: Sabolová G, Kočan L, Rabajdová M, Rapčanová S, Vašková J
Data acquisition, technical support: Sabolová G, Rabajdová M, Rapčanová S
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All authors declared that there are no conflicts of interest.

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Consent for publication

Not applicable.

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