

Analysis of the neuronal damage severity and cognitive status in patients after operations on the aortic arch

Kozlov B. N.^{1,2}, Panfilov D. S.¹, Berezovskaya M. O.¹, Ponomarenko I. V.¹, Afanasyeva N. L.¹, Maksimov A. I.¹, Podoksenov Yu. K.^{1,2}, Dyakova M. L.¹, Gusakova A. M.¹, Shipulin V. M.^{1,2}

Aim. To assess the neuronal damage severity and cognitive status in conditions of unilateral antegrade cerebral perfusion through the brachiocephalic trunk during surgical reconstruction of the thoracic aorta.

Material and methods. The study included 144 patients with aneurysm and dissection of the thoracic aorta. Patients underwent reconstructive surgery under cardiopulmonary bypass, unilateral antegrade cerebral perfusion and circulatory arrest. Before and after the intervention, a cognitive status analysis was performed using the Montreal Cognitive Assessment (MoCA), Amatinu test and Schulte tables. The dynamics of neuron-specific enolase (NSE), a marker of neuronal damage, was determined perioperatively.

Results. The duration of cardiopulmonary bypass was 155 [115; 201] min, cardioplegic arrest — 100 [72; 150] min, unilateral perfusion — 20 [15; 51] min, circulatory arrest — 20 [15; 30] min. Hospital mortality was 7% (10 cases). Neurological complications were noted in 12 (8%) cases. All patients in the postoperative period (within 24 hours) showed an increase in NSE compared with baseline values (3,3 µg/L and 2,07 µg/L, respectively, $p=0,0003$), but not exceeding the upper limit of normal (9,9 µg/L). According to the results of psychometric tests, which were carried out upon admission to the hospital and 2 weeks after the operation, there were no negative changes (MoCA test: 24 [21; 26] points — 26 [24; 27] points, $p=0,00001$; Schulte tables: 288 [240; 368] s — 278 [241; 328] s, $p=0,01$; Amatinu sample 264 [216; 297] s — 254 [221; 280] s, $p=0,57$).

Conclusion. Based on the analysis of the perioperative

dynamics of neuron-specific enolase and cognitive tests, unilateral cerebral perfusion through the brachiocephalic trunk is effective and relatively safe. This method of perfusion protection of the brain helps to minimize postoperative neurological complications during operations on the thoracic aorta.

Key words: thoracic aorta, antegrade unilateral cerebral perfusion, circulatory arrest, neuron-specific enolase (NSE), cognitive dysfunction, neurological complications.

Conflicts of Interest: nothing to declare.

¹Cardiology Research Institute, Tomsk; ²Siberian State Medical University, Tomsk, Russia.

Kozlov B.N. ORCID: 0000-0002-0217-7737, Panfilov D.S. ORCID: 0000-0003-2201-350X, Berezovskaya M. O.* ORCID: 0000-0002-6720-3801, Ponomarenko I. V. ORCID: 0000-0003-2494-0104, Afanasyeva N.L. ORCID: 0000-0001-5471-7566, Maksimov A.I. ORCID: 0000-0001-8384-1494, Podoksenov Yu. K. ORCID: 0000-0002-8939-2340, Dyakova M.L. ORCID: 0000-0001-9353-7234, Gusakova A.M. ORCID: 0000-0002-3147-3025, Shipulin V.M. ORCID: 0000-0003-1956-0692.

*Corresponding author: milla2210@yandex.ru

Received: 20.03.2019

Revision Received: 14.05.2019

Accepted: 26.05.2019



For citation: Kozlov B. N., Panfilov D. S., Berezovskaya M. O., Ponomarenko I. V., Afanasyeva N. L., Maksimov A. I., Podoksenov Yu. K., Dyakova M. L., Gusakova A. M., Shipulin V. M. Analysis of the neuronal damage severity and cognitive status in patients after operations on the aortic arch. *Russian Journal of Cardiology*. 2019;24(8):52-58. (In Russ.)
doi:10.15829/1560-4071-2019-8-52-58

Surgical treatment of diseases of the thoracic aorta is a modern urgent problem in cardiac surgery and cardiothoracic anesthesiology. These operations are characterized by large injury and require not only the use of cardiopulmonary bypass (CPB), but also the perfusion and anesthetic protection of the brain. For a long period of time, deep hypothermia without cerebral perfusion was the main method of cerebral protection [1]. Later, various options for perfusion cerebral protection were proposed: bilateral, unilateral antegrade and retrograde perfusion [2].

Most often, the assessment of the effectiveness of various types of perfusion protection of the brain is currently based on various intraoperative instrumental tests (infrared spectroscopy, transcranial dopplerography, electroencephalography), which are mainly indirect. At the same time, laboratory and clinical diagnostics of neurological disorders in the postoperative period is more specific, but it has not been studied enough.

Aim of the study was to assess neuronal damage and cognitive status in conditions of unilateral antegrade cerebral perfusion (ACP) through the brachiocephalic trunk (BCT) during surgical reconstruction of the thoracic aorta.

Material and methods

In the period from August 2008 to April 2018, 144 reconstructions of the thoracic aorta under the conditions of CPB, circulatory arrest (CA) and unilateral ACP through BCT were performed at Tomsk National Research Medical Center. Patient characteristics are presented in Table 1.

Most operations were performed due to aneurysms of the thoracic aorta, and in 31% due to dissection. The most frequently performed prosthetics of the aortic arch were the hemiarch replacement (65%) and the reconstruction of the thoracic aorta using the frozen elephant trunk technology (33%).

In addition to the intervention on the thoracic aorta, 72 (50%) patients required combined operations for concomitant cardiac pathology, including: aortic valve prosthetics — 46 (32%), aortic root replacement according to techniques of T. David — 5 (3%) and Bentall DeBono — 8 (6%), coronary bypass surgery — 14 (10%) patients, mitral valve prosthetics — 1 (0,7%).

To carry out perfusion cerebral protection, an original technique was used to connect the arterial line of the CPB circuit through prosthesis which end-to-side sewn in the BCT [3].

Anaesthetic support was performed as combined anesthesia. Premedication was performed with a nar-

cotic analgesic, benzodiazepine and antihistamine. Induction into anesthesia was performed with fentanyl (3,0-5,0 µg/kg) and propofol (1,5 mg/kg). Pipecuronium bromide (0,1 mg/kg) was used to provide myoplegia. Sevoflurane inhalation (2-3 vol%) was used to maintain anesthesia before and after CPB; propofol infusion (4,0-5,0 mg/kg) was used during perfusion. Analgesia was maintained by fentanyl infusion (3-5 µg/kg/h).

CPB was performed on an S3 console (Stockert, Germany) using Skipper oxygenators (Eurosets, Italy). The perfusion volumetric rate was 2.5 L/min/m². At the CA stage, the volume of unilateral ACP was 8-10 ml/kg/min, while the pressure in the arterial line was maintained in the range of 60-80 mm Hg. To ensure hypocoagulation prior to CPB, heparin was administered at a dose of 3 mg/kg while maintaining an activated clotting time >480 s. For myocardial protection, cold crystalloid cardioplegia was used (Custodiol, Koehler Chemi, Alsbach-Haenlien, Germany). After perfusion, the effect of heparin was neutralized by the introduction of protamine sulfate in a 1:2ratio.

At all stages of operations, an electrocardiogram (ECG) was monitored, invasive blood pressure monitoring in both radial arteries using a 20G arterial cannula (B Braun, Germany), central venous pressure (CVP) using a 12F central venous catheter (CertoFix, B Braun, Germany), nasopharyngeal and rectal temperatures were recorded using an Infinity[®] Delta XL apparatus (Dräger, Germany). We also analyzed the gas, acid-base and electrolyte composition of arterial blood. Catheterization of the bladder was performed to control hourly urine output. Artificial lung ventilation (ALV) was performed on a Primus apparatus (Dräger, Germany).

In addition, cerebral oximetry (rSO₂,%) of the right and left hemispheres was monitored using infrared spectroscopy (INVOS 5100, Somanetics, USA). RSO₂ indices were analyzed at the stages of induction of anesthesia, during CPB before CA, during CA, when warming before CPB weaning, at the end of the operation.

In the blood serum, the level of a marker of neuronal damage, neuron-specific enolase (NSE), was determined by enzyme-linked immunosorbent assay. Venous blood sampling for the study was carried out at two points: the main one in the operating room, after venous access, and the control — at the next morning after the operation. For the study, serum was used, which was centrifuged for 10 minutes. The NSE level of 9,9 µg/L was considered the upper normal limit, the median — 6,5 µg/kg.

Table 1
Clinical and demographic characteristics of patients

Parameter	n
Age, years	56±12
Males, n (%)	97 (67)
Type of aortic pathology	
Aneurysm of the ascending aorta, n (%)	92 (64)
Aneurysm of the aortic arch, n (%)	6 (4)
Aneurysm of the descending aorta, n (%)	7 (5)
Stanford type A aortic dissection, n (%)	24 (17)
Stanford type B aortic dissection, n (%)	15 (10)
Comorbidity	
Hypertension, n (%)	114 (80)
Diabetes mellitus, n (%)	8 (6)
Acute cerebrovascular accident, n (%)	6 (4)
Chronic cerebral ischemia, n (%)	9 (6)
Atrial fibrillation, n (%)	20 (14)

Upon admission to the hospital (source data) and after 2 weeks of surgery patients underwent psychometric tests. We used the following tests: Montreal Cognitive Assessment (MoCA test), correction task (Amatuni test), Schulte tables. The methodology is presented in the Annex.

Statistical analysis of the data was carried out in STATISTICA 13,3 (StatSoft.Inc., USA) software. The normality of indicators' distribution was verified using the Kolmogorov-Smirnov test. Quantitative values were expressed as mean±standard deviation ($M\pm SD$) under normal law of distribution. With an unknown distribution law, the data were presented as the median and 25-75 percentiles (Me [25; 75]). In normal distribution, t-test was used for independent and dependent samples. Comparison of quantitative characteristics with an unknown data distribution was carried out using the Mann-Whitney U-test, Wilcoxon signed-rank test. Qualitative differences between groups in terms of quality were evaluated using Fisher's exact test. Differences were considered as statistically significant at $p<0,05$.

Results

The data of the intraoperative period are presented in Table 2. The initial values of cerebral oximetry against the background of normal gas composition of arterial blood, as well as at the main stage and

Table 2
Intraoperative parameters

Parameters	Result
Operation time, min	325 [260; 405]
CPB time, min	155 [115; 201]
Cardiac arrest time, min	100 [72; 150]
ACP time, min	20 [15; 51]
CA time, min	20 [15; 30]
Moderate hypothermia (25-28°C), n	144

Notet: data are presented as Me [25; 75].

Abbreviations: CPB — cardiopulmonary bypass, ACP — antegrade cerebral perfusion, CA — circulatory arrest.

CA were within the reference values with interhemispheric asymmetry of not more than 3% (Fig. 1).

In the postoperative period, the time spent by patients in the intensive care unit was 3 [2; 9] days. The duration of AVL was 21 [12; 55] h. In connection with respiratory failure, tracheostomy for 3-4 days required in 23 (16%) patients. The duration of AVL in patients of this subgroup was 380 [240; 528] hours.

In total, neurological complications were noted in 12 (8%) cases. In 2 (1,4%) patients, in the early postoperative period, there was signs of acute ischemic cerebrovascular accident, 2 (1,4%) — transient ischemic attack, which stopped within 12 hours without residual focal neurological deficit. In 8 (5%) patients — postoperative delirium was without residual effects.

All patients in the postoperative period (within 24 hours) showed NSE increase in compared with baseline values ($p=0,0003$), but not exceeding the upper limit of normal (Fig. 2).

According to the MoCA test, in patients after surgery there is a statistically significant increase in the total score to 26 [24; 27] ($p=0,00001$). There was also a statistically significant increase in the indicators of visual-constructive skills — combining numbers and letters, copying a cube and clock-drawing test. According to the results of the Schulte table test there is a statistically significant decrease in the total time of passing the test ($p=0,01$). According to the correction task, the attention and psychomotor speed of the patients did not change. Initial and postoperative indicators of psychometric tests are presented in Table 3.

The overall hospital mortality rate was 7% (10 cases). The causes of death were: acute intraoperative myocardial infarction ($n=4$); multiple organ failure,

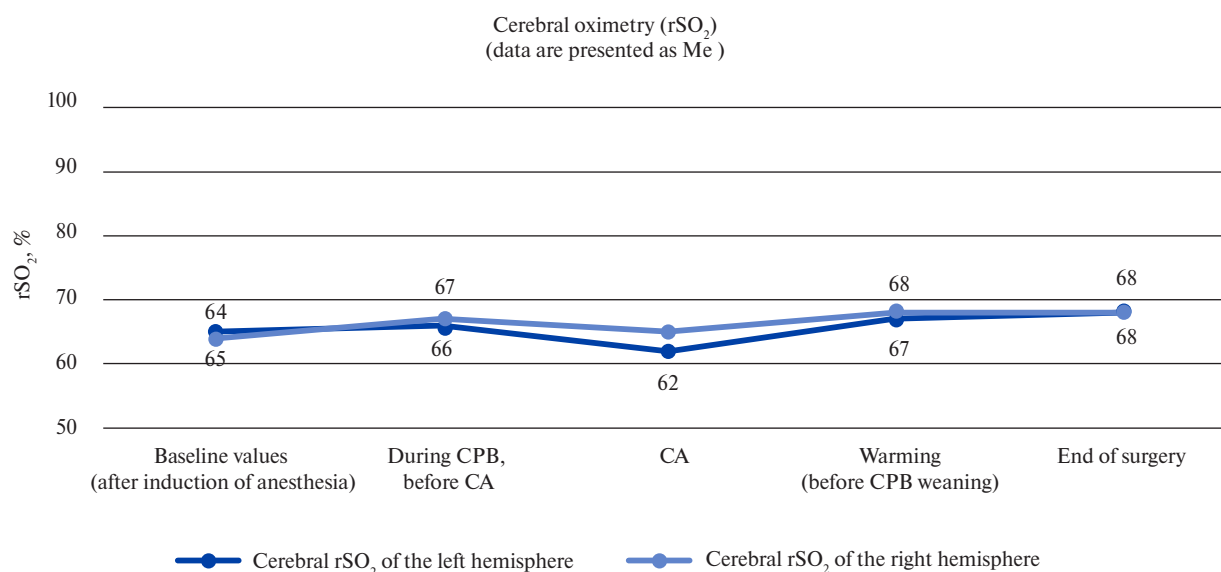


Fig. 1. Parameters of cerebral oximetry (rSO₂) at different surgery stages.

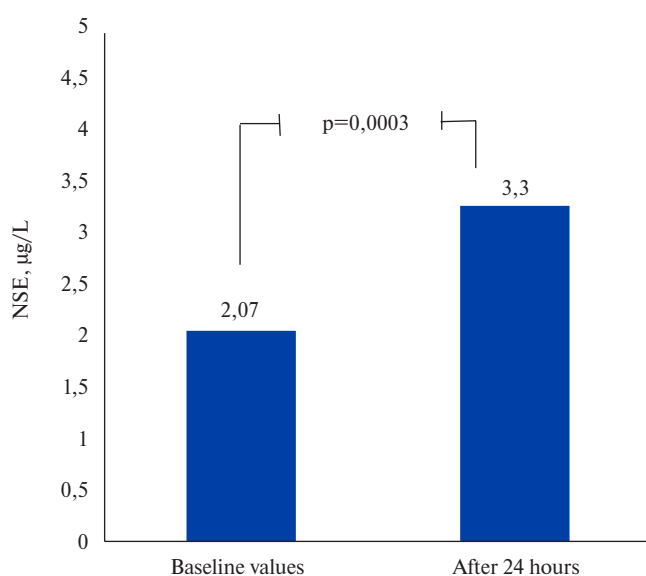


Fig. 2. Perioperative changes of serum NSE level.

Note: data are presented as Me [25; 75].

sepsis (n=5); hemorrhagic shock, DIC (n=1).

Discussion

Currently, there is no unified approach to the choice of the protecting cerebral method during operations on the aortic arch. Deep hypothermia as a cerebral protection in the reconstruction of the thoracic aorta has fewer supporters. That is because along with the low efficiency of cerebral protection, it is associated with the development of coagulopathy,

endothelial dysfunction of the cerebral microvasculature, damage to neurons, an increase in the systemic inflammatory response and an increased risk of organ and systems dysfunctions [4, 5].

Numata S, et al. [6] carried out a comparative analysis of various temperature regimes during operations on the thoracic aorta. It was shown that an admissible protection of the brain and internal organs is provided at a patient's body temperature of more than 28°C. The advantage of moderate hypothermia is associated not only with the hypothermic effect, but also with the reduction in the time required for cooling and warming the patient. In turn, it determines the duration of the CPB as independent risk factor for postoperative central nervous system dysfunction.

Recently, the number of publications has been growing, proving the advantage of ACP over the retrograde variant. So, Okita Y, et al. [7] analyzed the data of interventions on the aortic arch of 8169 patients. It was found that retrograde perfusion is accompanied by a greater mortality and frequency of acute cerebrovascular accident compared with antegrade cerebral perfusion protection. The results obtained by the authors are consistent with the meta-analysis by Tian DH, et al. [5].

Thus, with prolonged and complex interventions on the aortic arch, it is advisable to use ACP [2].

However, the question of choosing the ACP variant remains open. So, Malvidi P, et al. [8], analyzing the data of 3500 operated patients, consider bilateral perfusion as the safest method of cerebral protection.

Table 3

Psychometric test results

Tect	Before surgery	After surgery	p-value
MoCA test, score	24 [21; 26]	26 [24; 27]	p=0,00001
Visual-constructive skills, score	4 [3; 5]	5 [4; 5]	p=0,005
Schulte table (total time), sec	288 [240; 368]	278 [241; 328]	p=0,01
Amatuni test (total time), sec	264 [216; 297]	254 [221; 280]	p=0,57
Amatuni test (fatigue index)	1,09 [0,98; 1,19]	1,10 [1,03; 1,21]	p=0,376

Note: data are presented as Me [25; 75].

In addition, some researchers believe that with an increase in stopping blood circulation for more than 40-50 minutes, it is justified to use bilateral perfusion [9]. It is assumed that this method of neuroprotection has advantages over unilateral one in cases of anomalies of the Willis circle and history of strokes [8].

Angeloni E, et al. [10] presented data from a meta-analysis of 5100 patients operated on the aortic arch using both cerebral perfusion techniques. It was shown that unilateral and bilateral perfusion are accompanied by a comparable frequency of persistent neurological deficit (6,1% versus 6,5%; p=0,8), while transient cerebrovascular accidents were recorded more often with bilateral cerebral perfusion (7,1% against 8,8%; p=0,46). Mortality in the groups did not statistically differ (8,6% versus 9,2%; p=0,78). A higher frequency of neurological deficit in the group of patients with bilateral perfusion is associated with additional manipulations on the modified supra-aortic arteries, which increases the risk of material embolism.

A number of studies have shown that unilateral ACP has an advantage in terms of early survival and postoperative persistent neurological complications. It is important to note that the frequency of permanent neurological complications in bilateral perfusion is 1,6-9,8% [11], and in unilateral — 1,1-4,2% [12].

In the prevention of cerebral complications, along with the cerebral perfusion, its duration is of great importance. So, according to the literature, the duration of cerebral perfusion for more than 40 minutes is associated with postoperative neurological deficit. An increase in its duration to 65 min or more is associated with an extremely high mortality rate [13, 14]. Our study also noted a tendency to increase in neurological complications with increasing cerebral perfusion time.

To date, the assessment of the effectiveness of perfusion cerebral protection is mainly based on

data from instrumental methods such as infrared spectroscopy, transcranial Doppler, and electroencephalography. However, such an analysis is more indirect. For more accurate intraoperative monitoring of neurological status, an analysis of neuron-specific markers, S100, S100B, and NSE proteins, was proposed [15, 16]. It has been empirically established that the most reliable and specific indicator reflecting cerebral injuries during surgical interventions, as well as postoperative neuropsychological disorders, is the NSE [17, 18]. According to the results of our study, all patients in the postoperative period (within 24 hours) showed an increase in NSE compared with baseline values (p=0,0003), but not exceeding the upper limit of normal. Neurological complications were noted in 8% of cases, but only 1,4% of patients had a persistent neurological deficit. Thus, unilateral cerebral perfusion through BCT provides adequate cerebral protection.

In addition to neurological complications, much attention is paid to the problem of postoperative cognitive dysfunctions (POCD), which, being a milder manifestation of neurological disorders, lead to a significant deterioration in the quality of life of patients [19]. A generally accepted definition and clear diagnostic criteria for POCD have not yet been developed; their clinical manifestations are impaired attention, memory, speech, and other cognitive functions, often diagnosed using neuropsychological testing [20-23].

An analysis of our own data showed that reconstructive surgery on the aorta does not adversely affect cognitive functions, but even vice versa, leads to an improvement in counting, praxis, neurodynamic functions, attention and concentration skills, which is confirmed by an increase in the total score of the MoCA test after surgery. The operated patients showed a statistically significant increase in the indices of visual-

constructive skills — combining numbers and letters, copying a cube and the clock-drawing test. According to the results of the Schulte table test, a reduction in the time spent for passing the test was noted, which indicates improved stability and attention, increased work efficiency, warming-up, psychological stability. Improvement in cognitive functions appears to be associated with improved cerebral blood supply, as well as a decrease in hypoxia after surgery.

Conclusion

Based on an analysis of the perioperative changes of NSE and cognitive tests, unilateral cerebral perfusion through BCT is effective and relatively safe. This method of perfusion cerebral protection helps to minimize postoperative neurological complications during operations on the thoracic aorta.

Conflicts of Interest: nothing to declare.

Annex

Montreal Cognitive Assessment (MoCA) is used for assessing of various cognitive skills: attention

and concentration, executive functions, memory, speech, visual-constructive skills, abstract thinking, counting and orientation. The time for holding is approximately 10 minutes. The maximum possible score is 30; 26 points or more is considered as normal.

Correction task is a method of stability and attention focusing studying. The patient is provided with a correction task form, which presents numbers from 0 to 9 in random order. Patient is invited to look at these numbers line by line, from left to right, and cross out “6” and “9”. After the test is completed, the task is checked for correctness according to a special “key”. The total number of errors is analyzed, as well as the number of errors made in the first and second half of the table.

Schulte table determine attention span and changes of performance. The test subject is offered five tables in turn, on which the numbers from 1 to 25 are arranged in random order. The test subject seeks for, shows and names the numbers in ascending order. The total test time is estimated and the average value for each square is calculated.

References

1. Griepp RB, Luozzo G. Hypothermia for aortic surgery. *J Thorac Cardiovasc Surg.* 2013;145(3):56-8. doi:10.1016/j.jtcvs.2012.11.072.
2. Misfeld M, Mohr F, Etz C. Best strategy for cerebral protection in arch surgery — antegrade selective cerebral perfusion and adequate hypothermia. *J. Ann Cardiothorac Surg* 2013;2(3):331-8. doi:10.3978/j.issn.2225-319X.2013.02.05.
3. Kozlov BN, Panfilov DS, Ponomarenko IV, et al. The new technique of unilateral antegrade cerebral perfusion during aortic arch surgery. *Russian Journal of Cardiology and Cardiovascular Surgery.* 2015;8(1):30-4. (In Russ.) doi:10.17116/kardio20158130-34.
4. Kornilov IA, Sinelnikov YuS, Soyнов IA, et al. Risk assessment of renal and neurological complications in newborn after aortic reconstruction. *Patologiya krovoobrashcheniya i kardiokhirurgiya.* 2015;19(1):84-9. (In Russ.) doi:10.21688/1681-3472-2015-1-84-89.
5. Tian DH, Wan B, Bannon PG et al. A meta-analysis of deep hypothermic circulatory arrest versus moderate hypothermic circulatory arrest with selective antegrade cerebral perfusion. *J. Ann Cardiothorac Surg.* 2013;2(2):148-58. doi:10.3978/j.issn.2225-319X.2013.03.13.
6. Numata S, Tsutsumi Y, Monta O, et al. Acute type A aortic dissection repair with mild-to-moderate hypothermic circulatory arrest and selective cerebral perfusion. *The Journal of cardiovascular surgery.* 2015;56(4):525-30.
7. Okita Y, Miyata H, Motomura N, Takamoto S. A study of brain protection during total arch replacement comparing antegrade cerebral perfusion versus hypothermic circulatory arrest, with or without retrograde cerebral perfusion: Analysis based on the Japan Adult Cardiovascular Surgery Database. *J. Thorac. Cardiovasc. Surg.* 2015;149(2):65-73. doi:10.1016/j.jtcvs.2014.08.070.
8. Malvindi PG, Scarscia G, Vitale N. Is unilateral antegrade cerebral perfusion equivalent to bilateral cerebral perfusion for patients undergoing aortic arch surgery? *Interact Cardiovasc Thorac Surg.* 2008;7(5):891-7. doi:10.1510/icvts.2008.184184.
9. Misfeld M, Mohr F, Etz C. Best strategy for cerebral protection in arch surgery — antegrade selective cerebral perfusion and adequate hypothermia. *Ann Cardiothorac Surg.* 2013;2(3):331-8. doi:10.3978/j.issn.2225-319X.2013.02.05.
10. Angeloni E, Benedetto U, Takkenberg JJ, et al. Unilateral versus bilateral antegrade cerebral protection during circulatory arrest in aortic surgery: a meta-analysis of 5100 patients. *J Thorac Cardiovasc Surg.* 2014;147(1):60-7. doi:10.1016/j.jtcvs.2012.10.029.
11. Ozatik MA, Kocabeyoglu S, Kücük SA, et al. Neurochemical markers during selective cerebral perfusion via the right brachial artery. *Interact. Cardiovasc. Thorac. Surg.* 2010;10(6):948-52. doi:10.1510/icvts.2009.228858.
12. Bakhtiyar F, Dogan S, Zierer A, et al. Antegrade cerebral perfusion for acute type A aortic dissection in 120 consecutive patients. *Ann. Thorac. Surg.* 2008;85(2):465-9. doi:10.1016/j.athoracsurg.2007.10.017.
13. Belov YuV, Charchyan ER, Akselrod BA, et al. Cerebral and visceral organ protection during aortic arch surgery. Intraoperative tactics and monitoring details. *Patologiya krovoobrashcheniya i kardiokhirurgiya.* 2016;20(4):34-44. (In Russ.) doi:10.21688-1681-3472-2016-4-34-44.
14. Di Eusanio M, Schepens MA, Morshuis WJ, et al. Antegrade selective cerebral perfusion during operations on the thoracic aorta: factors influencing survival and neurologic outcome in 413 patients. *J. Thorac. Cardiovasc. Surg.* 2002;124:1080-6.
15. Bockeria LA, Garmanov SV. Surgical treatment of aneurysms of the ascending aorta and aortic arch with the use of selective antegrade cerebral perfusion. *Annaly Khirurgii.* 2013;3:23-30. (In Russ.)
16. Shi-Min Yuan. Biomarkers of cerebral injury in cardiac surgery. *Anatol J Cardiol.* 2014;14(7):638-45. doi:10.5152/akd.2014.5321.
17. Schaefer ST, Koenigsperger S, Olotu C, Saller T. Biomarkers and postoperative cognitive function: could it be that easy? *Curr Opin Anaesthesiol.* 2019;32(1):92-100. doi:10.1097/ACO.0000000000000676.
18. Sosnovsky EA, Puras JV, Talypov AE. Biochemical markers of head injury. *Russian journal of neurosurgery.* 2014;(2):83-91. (In Russ.) doi:10.17650/1683-3295-2014-0-2-83-91.
19. Newman MF, Grocott HP, Mathew JP, et al. Report of the substudy assessing the impact of neurocognitive function on quality of life 5 years after cardiac surgery. *Stroke.* 2001;32(12):2874-81. doi:10.1161/hs1201.099803.
20. Bokeria LA, Golukhova EZ, Polunina AG, et al. Cognitive functions after on-pump operations at early and delayed postoperative follow-ups. *Kreativnaya kardiologiya.* 2011;(2):71-88. (In Russ.)
21. Shnayder NA, Shprakh VV, Salmina AB. Post-operative cognitive dysfunction. *Krasnoyarsk: KrasGMA,* 2005 p. 96. (In Russ.)
22. Rasmussen LS, Larsen K, Houx P, et al. The assessment of postoperative cognitive function. *Acta Anaesth. Scand.* 2001;45(3):275-89. doi:10.1034/j.1399-6576.2001.045003275.x.
23. Novitskaya-Usenko LV. Post-operative cognitive dysfunction in an anesthesiologist's practice. *Medsina neotlozhnykh sostoyaniy.* 2017;4(83):9-15. (In Russ.) doi:10.22141/2224-0586.4.83.2017.107418.