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THE CHANGES IN THE STRUCTURE OF COGNITIVE FUNCTIONS AND ANXIETY IN CARDIAC SURGERY PATIENTS DEPENDING ON THE SEVERITY OF CAROTID ARTERIES

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Highlights

• The article revealed that severe (more than 50%) carotid artery (CA) stenosis was associated with significant slowdown of the information selection processes, and these patients were characterized by older age and tendency to an increase in trait anxiety compared to the patients without CA stenosis.

• It was found that the reduced attention and memory was a typical feature of the cognitive status in patients with severe CA stenosis in the early postoperative period of cardiac surgery in comparison with the patients without CA stenosis. At the same time the speed characteristics indicators of the information selection processes in these patients are positively related to state anxiety.

Aim The cardiac surgery patients were studied in order to analyze the postoperative changes in the efficiency of selection information and memory processes depending on the degree of carotid artery (CA) stenosis (including more than 50%) and the age and the role of the trait anxiety indicator assessed before surgery.

Methods The prospective study included 229 patients undergoing elected coronary artery bypass grafting (CABG) or CABG and carotid endarterectomy (CEE). Each study participant underwent clinical, instrumental and extended psychometric examination before cardiac surgery and at 7-10 days after surgery. The evaluation of the extracranial vessels state was carried out before surgery using color duplex scanning. Based on the results of assessing the extracranial vessels state, all patients were divided into three groups: no stenosis (n = 124), CA stenosis less than 50% (n = 69) and more than 50% (n = 36).

Results It was found out that the patients with CA stenoses more than 50% are characterized by a slower reaction under different conditions of visual stimuli selection and by an older age as compared with patients with no stenoses as well as patients with stenoses less than 50%. In the postoperative period of cardiac surgery in comparison with testing before surgery there was an improvement in the information selection stability (an increase in the number of processed symbols per 4 minute of the Bourdon's test ($p<0.00006$)) and short-term memory ($p = 0.03$) only in the group of patients without stenoses. The patients with stenoses of less than 50% had an increase the of the information selection stability but the short-term memory decrease ($p<0.05$) whereas the group with stenoses more than 50% had a decrease in both the stability of information selection and short-term memory ($p<0,05$). Additional factors of cognitive deficit in CA stenosis patients were trait anxiety associated with memory impairment and a history of stroke that related to a decrease in the effectiveness of a complex visual-motor reaction.

Conclusion The comprehensive analysis of the cognitive status of cardiac surgery patients with different severity of CA stenosis showed that an increase in the age and stenosis degree is the factor of the reaction time slowdown under different conditions of information selection. To differentiate groups of patients depending on the severity of stenosis in the postoperative period the testing short-term memory and stability of attention is informative. These indicators improve in the group without stenosis but decrease in the group with pronounced stenosis. The trait anxiety and the history of stroke were the additional factors of memory impairment due to CA stenosis.

Keywords Cognitive functions • Anxiety • Carotid stenosis • Cardiac surgery

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Список сокращений

Acute CVA	– acute cerebrovascular accident	CHD	– coronary heart disease
BW test	– the Bourdon–Wiersma test	CVMT_RT	– reaction time in the complex visual-motor test
BWC	– brain working capacity		
CA	– carotid arteries	FMNP	– functional mobility of nervous processes
CABG	– coronary artery bypass grafting	POCD	– postoperative cognitive dysfunction

Introduction

The steady aging of the population in developed countries is accompanied by age-related changes in the state of health, including the cardiovascular system, atherosclerosis of the heart and brain vessels. Physiological aging of the body leads to changes in the vessel wall architecture and, as a consequence, adaptive mechanisms to maintain normal blood flow conditions and mechanical stress, and/or the degree of the vascular wall tension [1, 2]. Taking into consideration the variety of factors affecting the vascular bed state and different age trajectories of its changes, as evidenced by the occurrence of atherosclerotic vascular lesions not only in the elderly but also at a young age [3], the mechanisms of functionally compensatory or pathological development of stenotic vascular lesions of the brain remain questionable. However, chronological age is one of the prognostic factors of cardiovascular diseases [4, 5].

Cardiovascular diseases cause ischemia and neurodegenerative changes in the brain which lead to changes in the effectiveness of various cognitive processes and the development of cognitive deficits [6, 7]. A review of the results carried out in this direction, indicates different points of view on the degree and specific character of cognitive impairment, which is used to assess cognitive deficits due to the large variety of tools [7–9]. This idea is confirmed by the conclusion from a recent analysis of publications presented in the PubMed database from 1990 to 2019 in order to find the most informative indicators of cognitive resources [10]. The results of neurobiological and psychological studies of the brain cognitive reserves during aging were considered. On the one hand, the instability of the effects shown due to different approaches to determining cognitive functions in normal or pathological aging is noted and on the other hand, recently increasing interest in studying the role of the prefrontal cortex and related inhibitory processes in the nervous system.

When studying the mechanisms of postoperative cognitive dysfunction (POCD) using a comprehensive assessment approach of cognitive status in patients with coronary heart disease (CHD) is informative enough for detecting postoperative cognitive impairment, including the long-term period of coronary bypass surgery (CABG) [11–13]. The studies contained the tests for a comprehensive assessment of cognitive status with complex visual-motor tasks requiring the use of inhibitory functions in the selection of information (neurodynamics), as well as tasks for testing attention and various forms of short-term memory (numbers, syllables, words).

A previously performed study on the neurophysiological mechanisms of POCD in patients with small and moderate (up to 50%) carotid artery stenosis (CA) showed a higher frequency of cognitive dysfunction in terms of neurodynamics and short-term memory compared with the control group. The dysfunction was accompanied by changes in the activity of the cerebral cortex as indicated by an increase in the power of biopotentials in wide range frequencies [14].

It is urgent to continue such a study due to the high POCD incidence because of the use of anesthesia and artificial circulation [15, 16], the need to clarify the diagnostic markers of this pathological condition, as well as its negative impact on the quality of operated patients' lives[17]. It should be noted that the elderly age of patients refers to significant factors in the development of POCD, especially in patients with atherosclerosis CA [11–14].

The aim of this study was to analyze postoperative changes in the efficiency of information and memory selection depending on the degree of preoperative CA stenosis (including lesions of more than 50%) and the age of cardiac surgery patients. An additional task was to clarify the role of the patients' general mental state according to the indicator of personal anxiety measured before the surgery.

Materials and methods

Patients

The prospective study enrolled 229 patients who underwent isolated CABG or CABG in combination with carotid endarterectomy. The study was conducted in accordance with the Declaration of Helsinki standards and was approved by the Ethics Committee of the Research Institute for Complex Issues of Cardiovascular Diseases (Kemerovo, Russia). All the participants signed a voluntary informed consent. The criteria for the inclusion and exclusion from the study were described in detail above [18].

Each participant of the study underwent a standard clinical and instrumental examination. The assessment of the CA condition was carried out before the operation using color duplex scanning on expert-class equipment. To determine the severity of stenosis, NASCET and ECST criteria were used: no stenosis, minor stenosis – less than 30%, moderate – 30–49%, pronounced – 50–69%, critical – 70–99% and occlusion. According to the results of the assessment of the CA condition, three groups of patients were formed: group 0 – absence of stenosis (n = 124), group 1 – stenosis of CA less than 50% (n = 69) and group 2 – more than 50% (n = 36). Table 1 shows the main clinical and anamnestic characteristics of the examined patients.

Psychometric research

Cognitive functions were evaluated in two stages. All patients underwent screening testing using the MMSE (Mini-mental state examination, Short Cognitive Status Assessment Scale), FAB (Frontal Assessment Battery, Frontal Dysfunction Battery) and BDI-II (Beck Depression Inventory, Beck Depression Scale) scales 3-5 days before surgery.

The number of MMSE scores less than 20, FAB less than 11 and BDI–II more than 8 were the grounds for the exclusion from the study. The extended testing of the attention functions, memory and information selection (neurodynamics), as well as personal and situational anxiety on the Status PF software psychophysiological complex was the second stage. Extended psychometric testing was performed on the 7th–10th day of the postoperative period.

Statistical Analysis

The results of the study were processed in the Statistica 13.3 program (SN: JPZ912J057923CNET2ACD-K; StatSoft Inc., USA). The normality of the data distribution was checked according to Kolmogorov–Smirnov criterion while some of the psychometric and quantitative clinical and anamnestic indicators were distributed normally and presented in the form of M±σ. Qualitative clinical and anamnestic indicators are presented in the form of frequency of occurrence n (%). To assess the intergroup differences in qualitative variables the criterion χ^2 was used. The analysis of variance and hierarchical cluster analysis were used to analyze the collected array of psychometric data. For the intergroup comparison of variables that did not meet the criteria of normal distribution, the nonparametric Kraskel–Wallis method was used, correlation analysis was performed using Spearman's criterion. The values of $p<0.05$ were considered statistically significant.

Results

According to the results of descriptive statistics, the cognitive indicators under consideration were a complex visual-motor test (reaction time), the number of errors in the test of the brain performance, the level of functional mobility of nervous processes (reaction time), the number of errors in the test of functional mobility of nervous processes, the number of missed signals (the test of functional mobility of the nervous system), brain performance (reaction time), the number of processed characters during the 1st (workability) and 4th (depletion) minutes of the Bourdon–Wiersma test (BW test); numbers memorizing, syllables and words memorizing met the criteria of parametric data analysis but the indicators of the number of errors and missed signals had a left-sided asymmetry in the distribution.

Table 1. Clinical and anamnestic characteristics of patients planned for cardiac surgery

Variable	group 0, n = 124	group 1, n = 69	group 2, n = 36	p
Age, years, M±SD	57,2±6,35	57,8±6,24	62,9±8,85	0,0003
Men/women, n	120/4	68/1	29/7	0,0001
Education, n (%): secondary high	 91 (73) 33 (27)	 52 (75) 17 (25)	 28 (78) 8 (22)	0,85
Left ventriculi ejection fraction, %, M±SD	57,4±9,27	59,2±7,68	58,1±9,87	0,27
Angina functional class, n (%) 0–I II III	 6 (5) 73 (59) 45 (36)	 5 (7) 35 (51) 29 (42)	 5 (14) 25 (69) 6 (17)	0,06
NYHA functional class, n (%) 0–I II III	 5 (4) 96 (77) 23 (19)	 5 (7) 52 (75) 12 (18)	 6 (17) 26 (72) 4 (11)	0,1
Arterial hypertension, n (%)	110 (89)	61 (88)	33 (92)	0,86
Type 2 diabetes mellitus, n (%)	31 (25)	18 (26)	8 (22)	0,9
Stroke history, n (%)	0 (0)	0 (0)	4 (11)	0,005

Note: *NYHA – New York Heart Association.*

In this regard ANOVA was used as a parametric method for the comparative analysis of the groups (independent factor “group”: group 0, group 1 and group 2; dependent variables: age, anxiety and cognitive indicators measured before and after surgery) as well as its nonparametric analogue – the Kraskel – Wallis method to analyze the number of errors and the number of missed signals in the brain performance test.

The effects, discovered as the result of the analysis, related to the influence of the “group” factor are shown in Table 2. Significant effects of the severity of CA stenosis are due to the fact that group 2 differs from the other two by a slower reaction in different conditions of visual stimuli selection and by a more elderly age of the patients. The decrease in the number of errors indicators in the brain performance test in group 2 compared with group 1 was at the level of p = 0.1.

There was also a tendency to increase trait anxiety in group 2 compared to groups 0 and 1 (41.7±1.1, 39.0±0.6 and 38.9±0.8, respectively; p<0.08) in spite of the absence of significant intergroup differences in situational anxiety.

Taking into account the differences in the clinical and anamnestic characteristics of the three groups, an additional analysis of the possible influence of gender factors or acute cerebrovascular accident (CVA) in group 2 was performed. However, it did not show any significant intergroup differences in these variables.

The main data illustrating the effects of the interaction of the factors "group" and "period" (testing) are given in Table 3.

A tendency to a postoperative decrease in the number of errors in the complex visual-motor test was revealed in group 2 compared to group 0 (p = 0.11). There was also the absence of significant pre- and postoperative differences in both the number of errors in the complex visual-motor test and in the numbers memorizing in group 2. The words memorizing index in group 0 increased in the postoperative period in comparison with the preoperative period (p = 0.03), and in group 1 it decreased (p = 0.1) and turned out to be less than in groups 0 and 1 (with an intergroup comparison of 0.01<p<0.03). The analysis of changes in the number of processed symbols per 4th minute of the Bourdon-Wiersma (BW) test revealed its significant postoperative growth in groups 0 and 1 (p<0.00006) but the absence of such an effect in group 2, and the changes in the same test between groups 2 and 0 turned out to be multidirectional: before the surgery, large values were noted in group 2, after the surgery – in group 0 (0.01<p<0.03).

The analysis of all indicators in group 2, depending on the factors of gender and acute CVA, did not demonstrate the influence of the first but found a lower value of the number of errors in the complex visual-motor test in patients with acute CVA compared

Table 2. General effects associated with the severity of stenosis

Variable	ANOVA		Mean variable values		
	F	p	group 0	group 1	group 2
Age	10,33	0,00005	57,2	57,8	62,9*
Trait anxiety	2,50	0,08	39,0	38,9	41,7
Reaction time in the complex visual-motor test	13,51	0,00001	557	564	642*
Reaction time in the test of functional mobility of nervous processes	8,56	0,0003	447	448	489*
Reaction time in the test of the brain performance	4,42	0,013	435	445	467*
	Kruskal-Wallis Method		Median		
The number of errors in the same test	4,34	0,11	112	118	104
The number of missed signals in the brain performance test	0,82	0,66	74	69	63

Note: ** – significant differences in the mean variable values in group 2 compared with group 0 and group 1 (p<0.04), the median variable values are in parentheses.*

Table 3. Effects of variables interaction: severity of stenosis and testing period

Variable	F	p	Variable values					
			before surgery			after surgery		
			group 0	group 1	group 2	group 0	group 1	group 2
The number of errors in the complex visual-motor test	3,34	0,037	2,0	2,5	2,5	2,3#	2,0	1,7#
The number of processed symbols per 4th min of the Bourdon’s test	12,40	0,00001	67,3#	73,1	91,7#	101,0*#	100,3*	84,4#
Numbers memorizing	3,27	0,040	4,5	4,8	4,2	4,9#	4,4	4,1#
Words memorizing	4,11	0,018	2,7	2,8	2,9	3,0*	2,5#	3.1

Note: ** – p<0.05 the differences before and after surgery; # – between-group differences.*

with those who had not been diagnosed with the stroke (2.2±1.8 and 0.5±0.5, respectively; $p<0.01$ according to the Mann-Whitney criterion).

Thus, the presence of pronounced (more than 50%) CA stenosis is the characteristic of older patients with coronary heart disease and is accompanied by an increase in reaction time to visual stimuli during their selection. With regard to the interaction effects of the group and period factors in the postoperative period, only in group 0 there was an improvement in the stability of information selection (an increase in the number of processed symbols per the 4th minute of the BW test) and short-term memory (words memorizing) in comparison with testing before surgery: in group 1, along with an increase in the stability of information selection, the indicator of words memorizing decreases, and in group 2 it is characterized by a decrease in both the stability of information selection and short-term memory (numbers memorizing). Acute CVA in group 2 is an additional factor that worsens the effectiveness of performing a complex visual-motor reaction.

To clarify the features of the studied variables ratio depending on the severity of CA stenosis, a hierarchical cluster analysis using the Ward method for normalized variables in each selected group was applied. The results, performed for the variables obtained before and after the operation, are shown in the figure.

In all cases, the variables form two clusters but their composition varies depending on the severity of CA stenosis. In group 0 before the surgery one cluster is formed by combining the indicator of trait anxiety, attention and memory indicators, and the second one is formed by the age and efficiency of information selection in visual-motor reactions. In the postoperative period the composition of two clusters is reorganized: age, together with trait anxiety, indicators of the effectiveness of information selection in different conditions and short-term memory, forms a common cluster but the number of errors and reaction speed when performing visual–motor tasks is another cluster.

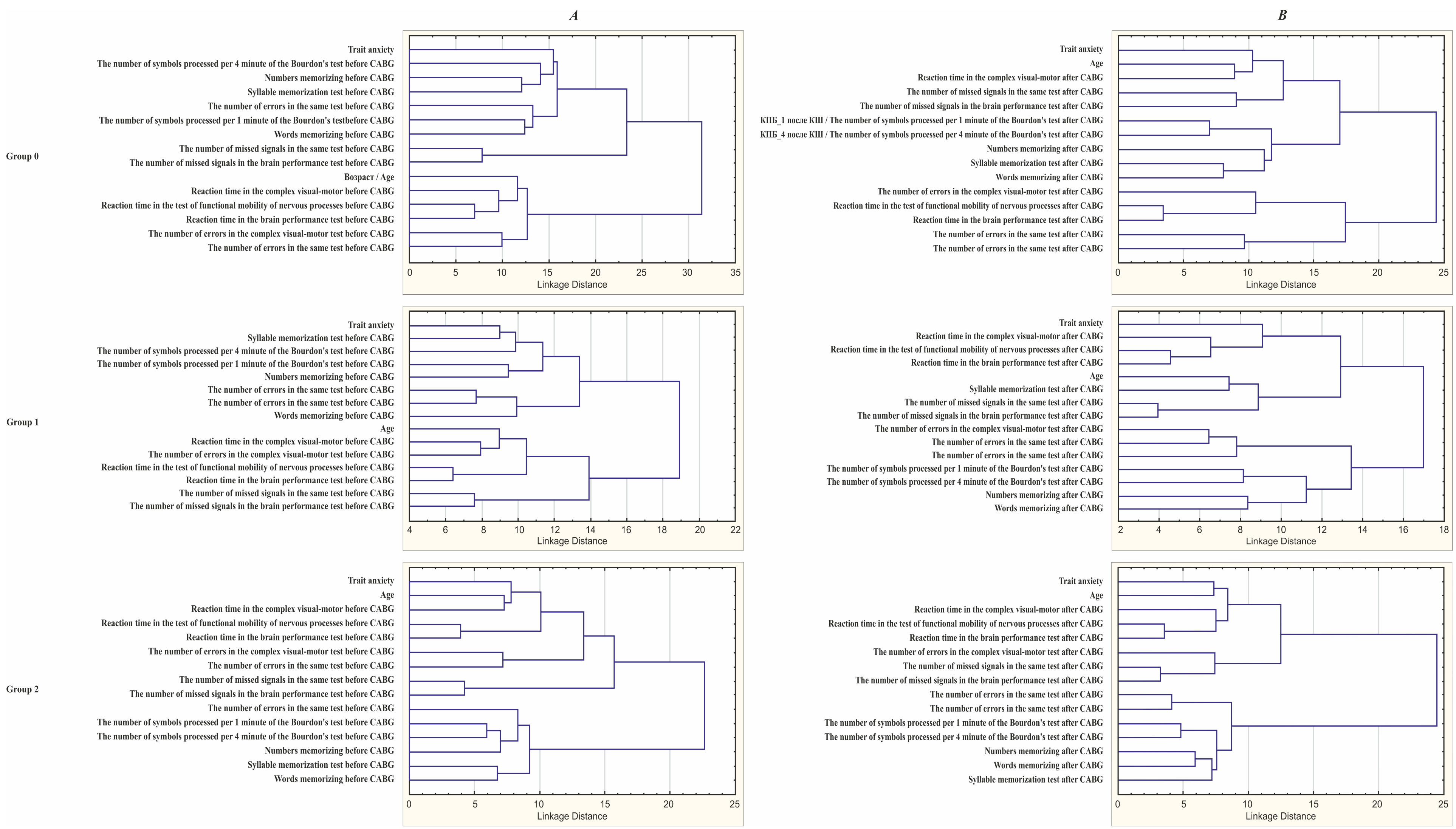
In group 1, the composition of clusters before surgery was similar to that in group 0 and differed from group 2 by a closer relationship of trait anxiety with the indicators of short-term memory and attention. The cluster composition in group 2 differs from what is presented for group 0: firstly, by a closer relationship between age, trait anxiety and the speed characteristics of choice reactions, and secondly, by the absence of fundamental postoperative changes. Apparently, the postoperative improvement of blood supply to the brain in the absence of CA stenosis in group 0 is accompanied by a reorganization of cognitive indicators, whereas, with less than 50% stenosis, they are weaker than in group 0, and in group 2 there are no fundamental changes in the system of cognitive indicators recorded before the surgery and on the 7^{th}–10^{th} day after it: age, personal anxiety and the speed of visual-motor reactions form one cluster, indicators of attention and memory form another.

The variables correlation analysis registered before and after the surgery in the three studied groups and anxiety indicators demonstrated their different relationships. It is presented in Table. 4. Considering that the indicators of the number of errors and number of missed signals in the brain performance test had a left-sided asymmetry in the distribution, Spearman correlation analysis was used to compare all the studied parameters.

According to the results obtained, significant associations were found only for situational anxiety in group 0: positive with the number of errors and negative with the reaction time both before and after the surgery. In group 1 before the surgery positive associations of anxiety and indicators of cognitive functions were only at a trend level. However, the comparison of situational anxiety correlations and preoperative number of missed signals in the functional mobility test in groups 0 and 1 revealed their significant differences at $p = 0.003$. The same effect of opposite sign correlations of anxiety indicators and reaction time was found in these groups and in the analysis of postoperative indicators of cognitive functions but in group 0 it is presented for situational anxiety and in group 1 – for the trait one.

In group 2, prior to the operation, higher trait or situational anxiety corresponded to a smaller number of errors when performing the task in the brain performance test and a decrease in numbers memorizing reproduction. The postoperative period is characterized by a positive relationship between trait anxiety and reaction time/number of missed signals, a negative relationship between both trait anxiety and short-term memory and between situational anxiety and the number of errors in the functional mobility of the nervous processes test (see Table 4).

Therefore, it can be concluded that only pronounced (more than 50%) CA stenosis leads to a significant slowdown in the reaction formation during information selection and patients of group 2 are characterized by an older age and a tendency to increase trait anxiety compared with group 0. A distinctive feature of group 2 is a postoperative decrease in the volume of attention, whereas in group 0 that indicator increased. An additional factor in the postoperative growth of errors when performing a complex visual-motor reaction is the presence of acute CVA in the anamnesis of group 2 patients. Memory deterioration was also noted in group 2 in comparison with group 0 while the structure of the interrelations of cognitive indicators does not fundamentally change and the speed indicators of information selection are positively associated with trait anxiety. According to the results of all stages analysis, group 1 with stenosis less than 50% occupies an intermediate position between groups 0 and 2, and is characterized by a postoperative increase in attention volume but a decrease in memory.



Dendrograms for analyzed variables obtained before (A) and after cardiac surgery (B) in the groups of patients with different degrees of CA stenosis.
Note: *CABG – coronary artery bypass grafting.*

Discussion

The slowing down of the sensorimotor reaction found in group 2 when performing various tasks requiring signal selection is consistent with the results of other studies. Pronounced CA stenoses lead to motor reaction and attention disorders in comparison with the control group [6, 19]. Another effect, consistent with the literary data, is the association of severe stenosis and age [4, 5] which are considered as additional aggravating factors of cognitive decline caused by brain hypoxia due to severe cardiovascular disease and surgery [8, 20].

The postoperative period in group 0 is characterized by an increase in the stability of attention and memory indicators, as well as the reorganization of cognitive functions according to the results of cluster analysis which can be associated with some improvement in blood supply to the brain, shown on the 6th day after CABG [21]. If CA stenosis up to 50% is detected, the effect of postoperative cognitive processes recovery in group 1 refers only to the stability of attention but in group 2 (stenosis of more than 50%) is not observed at all. It should be noted that, when tested before the surgery, the studied groups differed only in terms of workability and attention span in group 2 compared with group 0 but after the surgery intergroup differences were found in four cognitive indicators pointing at a more effective recovery of cognitive activity in group 0 compared with groups that had the diagnosed CA stenosis. The only exception is the higher number of errors in the complex visual-motor test indices in group 0 compared with group 2, which requires further investigation of the features of inhibitory functions in patients with coronary heart disease, possibly due to the regional specifics of CA stenosis.

The features of the emotional regulation of cognitive processes in patients with coronary heart disease in particular, frequently occurring increased anxiety, including those associated with hospitalization [22], are of particular interest. The predominant relationship of cognitive indicators with situational anxiety in group 0 and trait anxiety in group 2 indicates that prolonged brain ischemia due to severe cardiovascular disease can contribute to the formation of a stable state of anxiety and concomitant changes in the functions of sensory perceptual systems with an increase in their sensitivity to incoming stimuli – this process can be both adaptive and maladaptive due to inadequate assessment of their potential danger [23]. The association of greater situational anxiety and acceleration of sensorimotor reaction in group 0 before surgery should be considered rather maladaptive, since it is accompanied by an increase

Table 4. Trait and state anxiety correlations with cognitive indicators

Variable	group 0		Variable	group 1		Variable	group 2	
	Rs	p		Rs	p		Rs	p
Before surgery								
State anxiety & reaction time in the complex visual-motor	–0,22	0,013	Trait anxiety & reaction time in the brain performance test	0,19	0,116	Trait anxiety & the number of errors in the same test	–0,33	0,046
State anxiety & the number of errors in the same test	0,28	0,001	Trait anxiety & syllable memorization test	0,22	0,068	State anxiety & the number of errors in the same test	–0,36	0,030
State anxiety & the number of missed signals in the same test	–0,26	0,004	State anxiety & the number of missed signals in the same test	0,20	0,094	State anxiety & numbers memorizing	–0,42	0,010
State anxiety & the number of errors in the same test	0,24	0,008						
After surgery								
State anxiety & reaction time in the test of functional mobility of nervous processes	–0,21	0,030	Trait anxiety & reaction time in the complex visual-motor	0,27	0,030	Trait anxiety & reaction time in the complex visual-motor	0,47	0,004
			Trait anxiety & the number of errors in the same test	–0,28	0,038	Trait anxiety & reaction time in the test of functional mobility of nervous processes	0,34	0,040
			State anxiety & the number of symbols processed per 4 minute of the Bourdon's test	0,25	0,050	Trait anxiety & number of missed signals in the same place	0,34	0,043
						Trait anxiety & numbers memorizing	–0,35	0,035
						State anxiety & the number of errors in the same test	–0,35	0,039

in the number of errors in the selection of stimuli. The disappearance of the relationship between situational anxiety and the number of errors in the postoperative state while maintaining a negative correlation of situational anxiety and sensorimotor reaction time may already indicate an adaptive improvement in executive attention control, as it was found out in case of increased cardiovascular activity as a result of physical exertion [24].

There is some evidence that anxiety affects the effectiveness of short-term memory, disrupting mainly the executive component of engram reproduction [25, 26]. Consequently, the negative associations of situational and trait anxiety with different types of memory found in group 2 can be considered as the confirmation of this point of view, and precisely in conditions of severe brain ischemia, since in group 0 such a relationship is not observed, and in group 1 there is a tendency to the opposite positive relationship of trait anxiety and syllable memorizing (see Table. 3).

The negative relationship between anxiety indicators and the number of errors in information selection most likely reflects the generalized effect of anxiety on inhibitory processes in the brain and the general slowdown in sensorimotor reaction time in group 2 caused by a violation of functional neural networks in CA stenosis [27, 28].

It has been shown that such disorders lead to instability in the cognitive deficits manifestation, which can be predicted using the brain functional connectivity method to assess ischemia and reperfusion of its individual regions [29].

Conclusion

Cognitive functions comprehensive analysis in cardiac surgery patients with different severity of CA stenosis shows that an age increase and the degree of CA stenosis are the factors which slow the formation of a response in different conditions of information selection. In the group with severe CA stenosis (more than 50%) CABG leads to a decrease in cognitive status in comparison with the groups without diagnosed stenosis or with its moderate severity. To differentiate the groups of patients with coronary heart disease depending on the severity of stenosis in the postoperative period, it is informative to test short-term memory and attention stability, the indicators of which improve in the group without stenosis but decreases in the group with severe stenosis. Additional factors of cognitive deficit in CA stenosis are the trait anxiety associated with memory impairment, and the history of acute CVA associated with the decrease in complex visual-motor reaction effectiveness.

Conflict of interest

O.M. Razumnikova declares no conflict of interest. I.V. Tarasova declares no conflict of interest. O.A. Trubnikova declares no conflict of interest. O.L. Barbarash – Deputy Editor-in-Chief of the journal "Complex Issues of Cardiovascular Diseases".

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Author Contribution Statement

TOA – data collection and interpretation, editing, approval of the final version, fully responsible for the content

TIV – data collection and interpretation, editing, approval of the final version, fully responsible for the content

ROM – contribution to the concept and design of the study, data interpretation, manuscript writing, approval of the final version, fully responsible for the content

BOL – data interpretation, editing, approval of the final version, fully responsible for the content

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