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The state of cognitive function in patients with stable coronary artery disease after coronary artery bypass grafting

Aim To study the cognitive function (CF) state in patients with chronic ischemic heart disease (IHD) depending on the method of coronary bypass (CB), with extracorporeal circulation (EC) or on beating heart.

Material and methods Postoperative cognitive dysfunction (POCD) is a frequent complication of CB, and its development may depend on the method of surgery, with EC or on beating heart. This single-center, prospective, nonrandomized study included 196 patients with chronic IHD aged 61.0±5.1 years. Patients were divided into two groups based on the CB method: an EC group (n=11) and a beating heart surgery group (n=85). Mean follow-up period was 26±2.1 mos. The state of CF was evaluated before and after CB (at the hospital stage, at 3, 6, 12, and 24 mos.).

Results The mean duration of CF recovery was 3 mos. only in the group of CB without EC ($p<0.05$), whereas after CB with EC, CF parameters were similar to those during the hospital stage with somewhat reduced values. In 6 mos. after CB, CF normalized to baseline values in both groups (with and without EC). A possible CF decline in patients with chronic IHD after CB depended on the following factors: age older than 60 years ($p<0.05$), diabetes mellitus with glycated hemoglobin >7.5% ($p=0.001$) and 6.5–7.5% ($p=0.03$), smoking ($p=0.04$), atherosclerotic damage of the internal carotid artery ($p<0.05$), and a Charlson comorbidity index >5 ($p=0.03$). The CB surgery either with EC ($p=0.04$) or on beating heart ($p=0.04$) was associated with the development of CD.

Conclusion The results of the study allow identifying patients with chronic IHD and POCD-predisposing factors to recommend them beathing heart CB surgery.

Keywords Chronic ischemic heart disease; coronary bypass; postoperative cognitive dysfunction; extracorporeal circulation

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A common complication of coronary artery bypass grafting (CABG) is postoperative cognitive dysfunction (POCD), which may depend on whether the surgical technique uses cardiopulmonary bypass (CPB) or not [1]. Some authors suggest that the effects of off-pump CABG are primarily physiological and less associated with the development of POCD due to the absence of systemic inflammatory response activation and aortic manipulations. Cognitive impairments following CABG may be of different durations (short-term and long-term) and manifest in various ways: detraction, disorientation, problems with abstract thinking, difficulties in maintaining concentration and memory problems. The incidence of short-term POCD (shorter than 6 weeks) following CABG varies from 20% to 50%, while long-term POCD up to 6 months is observed in 10–30% of cases [2]. POCD occurring in patients after CABG can affect the processes of rehabilitation and social adaptation, as well as reducing treatment compliance.

Aim

To study cognitive function (CF) in patients with chronic coronary artery disease (CAD), depending on a CABG technique (cardiopulmonary bypass and off-pump CABG).

Material and methods

A single-center, prospective, non-randomized study was carried out. The material for the study comprised outcomes of treatment and examination of 196 patients with chronic CAD (mean age 61.0±5.1 years). A «heart team», consisting of a cardiologist and a cardiac surgeon, divided the patients into two groups based on coronary lesion and comorbidity charactersistics. Patients with diffuse coronary lesions were placed in the CPB CABG group. Homogeneous

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groups were formed on the basis of inclusion and exclusion criteria [3].

Inclusion criteria: chronic CAD, indications for myocardial revascularization; coronary atherosclerotic with myocardial ischemia confirmed by relevant investigations.

Exclusion criteria: severe valvular dysfunction; left ventricular (LV) aneurysm; acute myocardial infarction (MI; patients were included in the study not earlier that 3 months after acute MI); severe systolic LV dysfunction (left ventricular ejection fraction (LVEF) <35%); hemodynamically significant carotid atherosclerosis (stenosis >70%) [3, 4].

All patients signed informed consent to participate in the study. The study was approved by the ethics committee of A.N. Bakulev National Medical Research Center for Cardiovascular Surgery.

Patients were enrolled from December 2011 to January 2014. The mean follow-up period for CF after CABG was 26±2.1 months. Intermediate cut-off points of the study were the postoperative in-hospital period, 3, 6, 12, 24 months after myocardial revascularization [4].

Surgical intervention was performed using CABG, which was performed following the standard technique using autoarterial grafts in the CPB and off-pump setting. All patients (n=196) were divided into two groups depending on the CABG method: CPB CABG (n=111; 56.6%) and off-pump CABG (n=85; 43.4%). Patients with chronic CAD following CPB and off-pump CABG were comparable according to most clinical criteria (see Table 1). Patients with diabetes mellitus (DM) were selected for myocardial revascularization subject to preliminary compensation of the disease and treatment correction by an endocrinologist, if necessary. Three patients died in the CPB CABG group during hospital stay [4].

CF was assessed using the Montreal Cognitive Assessment (MoCa) test, covering various cognitive areas: attention and concentration, executive functions, memory, language, visuospatial ability, abstraction, counting and orientation [6]. According to the MoCa test, a CF score of 25 or more is considered to be normal, a score from 19 to 25 represents a moderate decrease in CF, while less than 19 is considered in terms of severe cognitive dysfunction [6]. CF was assessed in patients prior to and immediately following surgery, at 3, 6, 12 and 24 months after CABG.

All patients underwent Doppler ultrasound and duplex scanning of blood vessels using a Philips iE33 device (Netherlands) in the preoperative and postoperative (at 3, 6, 12, and 24 months) periods to determine brachiocephalic atherosclerosis.

As of 2011, all patients received the best possible drug therapy to control blood lipid profile, arterial hypertension and antiplatelet therapy following generally accepted recommendations [7] to achieve low-density lipoprotein cholesterol levels <2 mmol/L and blood pressure levels <130/85 mmHg.

The data obtained were processed using IBM SPSS Statistics 23.0 (IBM Ink., USA) and WinPEPI Portal version 11.61 (J.H. Abramson). The data are presented as M±SD, where M is 1000 bootstrap samples, arithmetic mean, while SD is the standard deviation. Categorical variables are expressed as the absolute values and percentages (n (%)). Qualitative variables were compared using Fisher's exact test. When comparing two groups, statistical analysis of quantitative variables used the Student's t-test and Satterthwaite test for independent samples; when comparing more than two groups, ANOVA with Dunnett's T3 post hoc test and the nonparametric Kruskal-Wallis test was used. A multivariate analysis was carried out to determine independent predictors of cognitive impairment in patients with chronic CAD following myocardial revascularization using CABG. The «cognitive impairment» was used as a binary dependent variable. Features correlated with the dependent variable in pairwise comparison were included in the model as independent variables.

Table 1. Clinical characteristics of patients with chronic CAD depending on the CABG technique

Parameter	CPB CAD (n=108)	Off-pump CPB (n=85)	p
Age, years (M±SD)	60.8±7.6	60.7±7.5	0.927
Male, n (%)	91 (84.3)	59 (69.4)	0.011
More than 12 years of education, n	44 (40.7)	33 (38.8)	0.452
Unemployed, n (%)	65 (60.2)	54 (63.5)	0.373
Diabetes mellitus, n (%)	32 (29.6)	28 (32.9)	0.367
Atrial fibrillation, n (%)	25 (23.1)	21 (24.7)	0.466
Arterial hypertension, n (%)	90 (83.3)	71 (83.5)	0.565
History of CVA, % (n)	2 (1.9)	5 (5.9)	0.136
LVEF, % (M±SD)	51.6±7.0	50.5±5.5	0.236
EuroSCORE II, score	2.0±1.9	2.1±1.7	0.704
SYNTAX, score (M±SD) in multivessel CAD	25.8±5.5	26.2±5.0	0.602
Charlson comorbidity index>5	4.1±1.7	4.1±1.6	0.999

CAD – coronary artery disease; CABG – coronary artery bypass grafting; CPB – cardiopulmonary bypass; CVA – cerebrovascular accident; LVEF – left ventricular ejection fraction; CA – coronary artery.

Differences were statistically significant when p was less than 0.05.

Results

The following early postoperative complications were revealed in the CPB and of-pump groups, respectively: MI (5.4% vs. 0%; p=0.03), bleeding requiring resternotomy (6.3% vs. 0%; p=0.02), multiple organ failure (5.4% vs. 0%; p=0, 03), posthypoxic encephalopathy (8.1% vs. 1.2%; p=0.04). Although in-hospital deaths were reported only in the CPB CABG group in patients with severe multi-vessel CAD, the differences were not statistically significant (2.7% vs. 0%).

It should be noted that the intraoperative indices did not differ statistically significantly between the patient groups (Table 2). CF was assessed using the MoSa test and was followed up for 2 years after CABG (Table 3). Analysis of CF in patients with chronic CAD after CABG showed a slight decrease in CF after both CPB and off-pump CABG. CF only recovered after 3 months of monitoring on average in the off-pump CABG group (p<0.05), while CF parameters after CPB CABG, which corresponded to the hospital period, had slightly lower values on the group average. CF normalized to baseline values in both groups (CPB and off-pump CABG) 6 months after CABG.

We carried out a detailed analysis of changes in the CF aspects depending on the CABG technique (Table 4). Following myocardial revascularization in the CPB and off-pump CABG groups, we observed impairments of regulatory and visuospatial abilities (3.4±1.5 vs. 3.7±1.3, respectively; p=0.145); short-term memory (3.0±1.3 vs. 3.2±1.2, respectively; p=0.274); language (4.3±1.2 vs. 4.5±1.4, respectively; p=0.291); abstraction (1.1±0.4 vs. 1.4±0.5, respectively; p=0.001). Orientation and attention suffered to a lesser extent in the postoperative period, both after CPB and off-pump CABG (see Table 3 and Table 4).

Three month later, CF recovered faster in patients following off-pump CABG than those who had undergone CPB CABG: regulatory and visuospatial abilities (3.8±1.4 vs. 4.2±1.6, respectively; p=0.044), short-term memory (3.3±1.4 vs. 4.1±1.3, respectively; p=0.001). Language and abstraction function improved in 3 months in both groups.

Binary logistic regression coefficients are presented in Table 5. A possible decrease in CF in patients with chronic CAD after CABG depends on the following factors: age over 60 years (p=0.05), DM glycated hemoglobin levels>7.5% (p=0.001) and 6.5–7.5% (p=0.031), smoking (p=0.044), internal carotid atherosclerosis (p=0.001), Charlson comorbidity index>5 (p=0.037).

Discussion

Studies show that CABG surgeries are the most common cause of POCD, whose incidence reaches 37% [8]. While neurological complications following cardiac surgeries are of great concern, the nature of perioperative factors triggering the development of POCD are a matter of dispute. It is believed that POCD may be associated with hypoperfusion, intraoperative brain microembolism and activation of the systemic inflammatory response. Many authors believe that off-pump CABG is better adjusted to human physiology than CPB [9].

Complex cognitive deficits in patients with CAD, which continue to be poorly understood, vary in terms of duration

Table 2. Intraoperative and in-hospital indicators of patients with chronic CAD depending on the CABG technique (CPB and off-pump CABG)

Parameter	CPB CAD (n=108)	Off-pump CPB (n=85)	p
Duration of mechanical ventilation, h (M±SD)	9.9±6.0	8.5±5.2	0.090
Time in intensive care unit, days (M±SD)	1.28±0.5	1.05±0.6	0.074
Time in hospital, days (M±SD)	11.2±5.4	10.8±4.7	0.589

CAD – coronary artery disease; CABG – coronary artery bypass grafting; CPB – cardiopulmonary bypass.

Table 3. Cognitive function according to the MoCa test (score) in patients with chronic CAD at different time points after myocardial revascularization (M±SD)

Parameter	CPB CAD (n=108)	Off-pump CPB (n=85)	p
Before surgery	25.7±2.6	26.2±2.5	0.179
After surgery			
Hospital period	23.6±2.7	24.5±3.0	0.030
In 3 months	23.7±3.0	25.2±3.1	0.001
In 6 months	25.5±2.7	26.0±3.0	0.225
In 12 months	25.3±2.9	26.5±2.8	0.004
In 24 months	25.7±3.0	26.3±3.1	0.176

CAD – coronary artery disease; CABG – coronary artery bypass grafting; CPB – cardiopulmonary bypass.

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of symptoms, severity and variety of clinical manifestations. Early, acute short-term postoperative disorders occuring in the form of delirium are observed in 40–46% of cases in patients after major cardiac surgeries [10].

While the origins of POCD have yet to be fully explained, various systemic inflammatory reactions associated with surgical and anesthetic management are known to trigger cognitive impairments following CABG; these include intraoperative hemodynamic disturbances, such as hypotension and, thus, hypoperfusion, as well as microembolism compromising brain circulation that occurs during surgery [11].

While only a few studies have been performed on this problem in human patients following CABG, more extensive data on this problem obtained from animal experiments show that the inflammatory response system plays an essential role in determining cognitive impairments [12]. The data were obtained on the activation of signaling cascades of tumor necrosis factor-alpha (TNF-α) and nuclear factor kappa-beta (NF-κβ) after peripheral surgeries in mice. The release of proinflammatory cytokines violated the integrity and increased the permeability of the blood-brain barrier, promoting the migration of macrophages into the hippocampus and leading to subsequent memory impairment. Further animal experiments showed that anti-inflammatory activation of the cholinergic cascade prevented the development of POCD in mice [12]. These findings indicate that extensive surgical procedures under general anesthesia and repeated surgical interventions increase the risk of POCD. However, the effects of general and/or local anesthesia on more significant CF impairments are not yet fully understood [13]. In studies carried out by Kline et al. [14], magnetic resonance imaging (MRI) revealed a decrease in the volume of gray matter, atrophy of the hippocampus and an enlarged lateral ventricle for 5–9 months following major surgery.

Although there are no clear guidelines for the diagnosis of cognitive impairments, the most common methods are the MoCa test, the MMSE score, the Schulte test, and neurophysiological diagnosis, including electroencephalography and neuroimaging (computed tomography and MRI) [15]. Functional MRI, while representing a cutting-edge technology for diagnosing morphological and metabolic disorders of the brain, has limitations, including high cost. All methods used to examine CF have their focuses and are applicable in various clinical situations. The MoCa test used to assess POCD is the most straightforward and objective diagnostic method for examing a range of cognitive impairments.

POCD is currently addressed in terms of three main triggers: patient characteristics, as well as surgical and anesthetic management. Older age, lower levels of

Table 4. MoCa scores of cognitive function areas soon after CPB or off-pump CABG (M±SD)

Cognitive function area	Parameter	Maximum possible score	CPB-CABG		Off-pump CABG	
			1 month	3 months	1 month	3 months
Regulatory, visualspacial ability	Drawing, copying	5	3.4±1.5**	3.8±1.4**	3.7±1.3*	4.2±1.6*, **
Memory (short-term)	Delayed recall	5	3.0±1.3**	3.3±1.4**	3.2±1.2*, **	4.1±1.3*, **
Language	Naming animals, repeating phrases, words beginning with a specific letter, fluency	6	4.3±1.2*, **	4.7±1.5*	4.5±1.4*	5.0±1.5*
Attention	Repeating numbers, concentration, serial counting	6	4.8±0.8	5.1±0.6	5.0±0.9*	5.5±0.8*
Abstraction	Explaining, generalizing, abstraction	2	1.1±0.4*, **	1.4±0.3*	1.4±0.5**	1.6±0.2
Orientation	Orientation	6	5.8±0.4	6.0±0.0	6.0±0.0	6.0±0.0
Total score		30	23.6±2.9	23.9±3.0	24.4±3.4	25.0±3.3

CABG – coronary artery bypass grafting; CPB – cardiopulmonary bypass.
* – statistically significant differences within the group in 3 months, p<0.05;
** – statistically significant differences between the groups in the corresponding interval, p<0.05.

Table 5. Multivariate logistic regression analysis: parameters associated with cognitive decline after CABG

Parameter	Nonstandard factor	Standard factor	95% CI	p
Sex	-0.009	0.17	0.001–1.54	0.633
Age (> 60 years)	0.188	2.14	1.29–3.03	0.002
Smoking	0.014	1.89	1.05–5.97	0.044
DM type 2 with HbAc 6.5–7.5%	0.029	2.09	1.15–3.33	0.031
DM type 2 with HbAc >7.5%	0.316	4.88	2.03–8.38	0.001
Charlson Comorbidity Index>5	0.087	2.01	1.03–3.25	0.037
Arterial hypertension	0.147	0.43	0.01–5.19	0.099
ICA stenosis	0.345	6.92	1.91–28.77	0.001
Atrial fibrillation	-0.022	0.02	0.01–9.36	0.936
CPB-CABG	0.010	1.87	1.03–2.67	0.047
Off-pump CABG	0.011	1.85	1.01–3.33	0.044

CABG – coronary artery bypass grafting; DM – diabetes mellitus; HbAc – glycated hemoglobin;
ICA – internal carotid artery; CPB – cardiopulmonary bypass; CI – confidence interval.

education, a history of alcohol misuse, various cardiovascular and cerebrovascular diseases can also be determinative [16]. Surgical triggers include major surgical interventions, including repeated ones, as well as the various complications that may be associated with major surgery [17]. Intraoperative hemodynamic disturbances of varying severity combined with hypotension, as well as consequent hypoperfusion and organ ischemia, including the use of long-acting anesthetics, are among those causes attributable to anesthesia.

In our work, we also tried to identify determinants possibly associated with the development of POCD, such as age over 60 years, DM, smoking, internal carotid atherosclerosis with stenosis of any degree, and multimorbidity. Open surgery, including CPB CABG (p=0.04) and off-pump CABG (p=0.04), was associated in this study with the development of cognitive dysfunction.

Our data are comparable with the results of many studies of this problem. Lahariya et al. [18] demonstrated the dependence of cognitive deficit, such as delirium, in patients with acute myocardial infarction after CABG on the Charlson comorbidity index (odds ratio (OR) 3.30; 95% confidence interval (CI): 2.14–5.09; p<0.001). Several studies of cognitive dysfunction [19] with a total of 5,033 patients showed the following causes of its development: lack of physical activity (OR 1.28; 95% CI: 1.01–1.63 in male patients) and concomitant DM (OR 2.98; 95% CI: 1.56–5.68 in male patients) are associated with impaired verbal memory; persistent smoking was associated with poor verbal memory (OR 1.40; 95% CI: 1.09–1.81 in male patients), lack of attention (OR 1.56; 95% CI: 1.20–2.03 in male patients) and psychomotor retardation (OR 1.58; 95% CI: 1.23–2.03 in male patients) [20]. LVEF<35% was a significant predictor of persistent POCD in patients after both CPB and off-pump CABG [21, 22].

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Some researchers [23] argue that POCD can persist for a long time. The proportion of patients with cognitive impairments increased 44.8% to 54.5% within 3 months of follow-up. Cognitive deficits may last for more than 6 months after CABG in some patients. Lyketsos et al. [24] showed in their study (n=5,092) that CF decreased to a greater extent 5 years after surgery in patients after CABG compared to patients without a history of CABG. There are various data on the effects of CPB. For example, Farhoudi et al. [25] found no differences in CF between patients following CPB and off-pump CABG. The minimal effect on the aorta during off-pump CABG reduces the risk of developing cerebral microembolism leading to POCD. The MoCA test assesses various types of cognitive abilities, including orientation, short-term memory, executive functions, language and visuospatial abilities. In this regard, the MoCA test can be a useful screening tool for diagnosing cognitive impairments in some neurological diseases.

Conclusion

The incidence of transient cognitive dysfunction, observed following coronary artery bypass grafting in patients with chronic coronary artery disease for 3 to 6 months, depends on the coronary artery bypass grafting technique used. Possible factors associated with the development of postoperative cognitive dysfunction were determined: age over 60 years, smoking, diabetes mellitus with glycated hemoglobin levels of ≥6.5%, internal carotid atherosclerosis and a Charlson comorbidity index>5. The origin of postoperative cognitive dysfunction is complex and variable. More profound cognitive dysfunction, which develops in patients after coronary artery bypass grafting with cardiopulmonary bypass, requires further research. However, our findings can be used to identify patients with chronic coronary artery disease and factors contributing to the development of postoperative cognitive dysfunction and recommend that they undergo off-pump coronary artery bypass grafting.

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