

## ETHICAL ASPECTS, SAFETY ISSUES OF CARDIAC SURGERY AND PREDICTION OF ADVERSE EVENTS

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In cardiac surgery, patient's awareness and consent to surgery are problematic as due to the lack of previous medical background a patient can't understand the processes occurring in the body and effects of exposure on them. Thus, provision of sufficient information by a doctor is a part of safe surgical strategy. An open randomized prospective trial involving 89 patients with stable coronary artery disease (CAD) was conducted. High rate of blood oxidation is believed to be an independent predictor of cognitive dysfunction development during the early postoperative period of coronary artery bypass grafting (CABG). Determination of blood oxidation rate is a tool of risk management during cardiac surgery starting from the stage of preoperative preparation, which is optimal to implement a safe strategy, including psychological and drug-induced support of the patient aimed at prevention of cognitive disturbances.

**Key words:** coronary artery disease, cardiac surgery, safety, oxidative stress

**Author contribution:** Shereshneva MV - review of actual Russian and foreign literature related to the examined issue, identification of the study subject, determination of the goal and objectives, laboratory examination of induced blood oxidation values, mathematical and statistical data processing, making conclusions; Ilyin MV — development of study program, formulation of the study subject, determination of goal and objectives, mathematical and statistical data processing, making conclusions.

**Compliance with ethical standards:** the study underwent ethical expertise and was approved by the Ethics Committee of the Yaroslavl State Medical University of the Ministry of Health of Russia. Prior to inclusion, the patients were explained the study goals and objectives in detail, and a voluntary informed consent was obtained.

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## ЭТИЧЕСКИЕ АСПЕКТЫ, ПРОБЛЕМЫ БЕЗОПАСНОСТИ КАРДИОХИРУРГИЧЕСКОГО ВМЕШАТЕЛЬСТВА И ПРЕДИКЦИЯ НЕБЛАГОПРИЯТНЫХ СОБЫТИЙ

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В области кардиохирургии аспект информированности и согласия пациента на проведение операции представляется проблематичным, ведь не имеющему медицинских знаний больному трудно представить себе процессы, происходящие в организме или последствия воздействия на эти процессы. В связи с этим предоставление врачом всей полноты информации является частью безопасной стратегии хирургического вмешательства. Проведено открытое нерандомизированное проспективное исследование в группе, состоящей из 89 больных стабильной ишемической болезнью сердца. Установлено, что высокая скорость окисления крови является независимым предиктором развития когнитивной дисфункции в раннем послеоперационном периоде при проведении шунтирования коронарных артерий. Определение скорости окисления крови является одним из инструментов управления рисками при выполнении кардиохирургического вмешательства, начиная с этапа предоперационной подготовки, который представляется оптимальным для реализации безопасной стратегии, включая психологическую и медикаментозную поддержку пациента, направленную на предотвращение развития когнитивных нарушений.

**Ключевые слова:** ишемическая болезнь сердца, кардиохирургия, безопасность, окислительный стресс

**Вклад авторов:** М. В. Шерешнева— обзор актуальной отечественной и зарубежной литературы по изучаемой проблеме, формулирование темы исследования, определение его цели и задач, лабораторное исследование показателей индуцированного окисления крови, математико-статистическая обработка данных, формулирование выводов; М. В. Ильин— разработка программы исследования, формулирование темы исследования, определение цели и задач исследования, математико-статистическая обработка данных, формулирование выводов.

**Соблюдение этических стандартов:** исследование прошло этическую экспертизу и было утверждено Этическим комитетом ФГБОУ ВО ЯГМУ Минздрава России. До включения в исследование пациентам были подробно разъяснены его цели и задачи, было получено добровольное информированное согласие.

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Cardiac surgery is a serious step of a patient's life. Its outcomes mainly depend on a psychological attitude, awareness and behavior at an early stage of rehabilitation. There are known associations between psychological factors and the intensity of pain during the postoperative period, quality of life, and surgical outcomes [1]. Although compliance with the rules of medical ethics has always been part of cardiac surgery practice, ethical suggestions have recently become its essential

component. Informed consent, conflict of interests, professional self-regulation, and many other issues increasingly attract attention of cardiologists and cardiac surgeons [2].

In exceptional cases a doctor has to take decisions, which contradict the principles of classical medical ethics, due to high achievements of biological and medical science and introduction of novel medical technologies. Great attention to personality rights, including the right of a patient, has provided

new insights into relationship between a doctor and a patient, which became a prerequisite for occurrence and development of biomedical ethics, which is a combination of biological knowledge and human values [3].

One of the key points determining the course of post-operative period and prognosis include compliance to treatment and the patient's awareness of the risk of possible complications. In this regard, discussing the issues of drug support and determining the risk of surgical intervention at the stage of preparation to surgery will allow him to decide on consent to the operation, and the correction of psycho-emotional stress will provide an opportunity to manage the psycho-emotional state, increase adherence and improve the prognosis [4].

Previous studies show a significant decrease in severity of anxious, hypochondriacal and sensitive types of attitude towards the disease, as well as a decrease in the severity of unproductive coping strategies and a decrease in the level of depression in patients after coronary artery bypass surgery against the background of perioperative psychological support and an early start of physical rehabilitation [5]. According to available data, it is the predominance of productive copying strategies, that is associated with better adherence to therapy in patients with CAD undergoing coronary artery bypass surgery, while unproductive coping is typical for patients with low compliance [6].

Nowadays the number of non-urgent interventions for myocardial revascularization in patients with CAD is increasingly growing. Despite improvements in the technique of performing coronary artery bypass grafting and an increase in the number of operations without cardiopulmonary bypass, there remains a high risk of development of perioperative complications [7]. Prediction and quantitative assessment of adverse events probability during coronary artery bypass grafting becomes an important element of the patient's psychological preparation for surgery.

The purpose of the study is to determine the predictors of unfavorable events during CABG in the context of increasing the patient's psychological readiness for surgery.

## PATIENTS AND METHODS

The study was conducted at the Yaroslavl Regional Clinical Hospital (the city of Yaroslavl). The work was included into the program of scientific studies of the Yaroslavl State Medical University of the Ministry of Health of Russia and went through ethical review procedures. 89 patients with stable CAD aged  $58.1 \pm 8.3$ , including 70 men aged  $57.8 \pm 8.2$  years and 19

women aged  $63.9 \pm 6.9$  years were examined. The control group consisted of 24 relatively healthy donors, including 9 (37.5%) men and 15 (62.5%) women aged  $50.0 \pm 9.0$  years. CAD was confirmed by the results of a clinical examination, stress tests and coronary angiography data. Medical management complied with up-to-date clinical recommendations.

Induced blood oxidation parameters were assessed using a YSI 5300 biological oxygen monitor (Yellow Springs Instrument Company, YSI Inc., USA). Free radical oxidation of blood components was induced by the water-soluble inducer AAPH (2,2'-azobis (2-amidino-propane) dihydrochloride). The rate of blood oxidation ( $V_{ox}$ ),  $10^{-8}$  mol/L·s; time of initiation period (T), min; initial rate of blood oxidation ( $V_{init}$ ),  $10^{-8}$  mol/L·s; maximum rate of blood oxidation ( $V_{max}$ ),  $10^{-8}$  mol/L·s; terminal rate of oxidation  $V_{term}$ ,  $10^{-8}$  mol/L·s; and coefficient of oxidative activity ( $K_A$ ), % were determined from the slope of the oxygen concentration curve in the sample;

The Mini Mental State Examination (MMSE) assay (Folstein M. F. et al, 1975) was used to screen and assess the severity of post-operative cognitive dysfunction. Cognitive functions were assessed after the effects of anesthesia had subsided.

Statistical analysis of the data was performed using STATISTICA 10.0 (StatSoft Inc., CLLJA). The normality of the distribution of variables was checked using the Kolmogorov-Smirnov tests with the Lilliefors and Shapiro-Wilk correction. To study the relationship between two characteristics, Spearman correlation analysis was used. The study of the type of dependence of a trait on one or more other traits was carried out on the basis of logistic regression analysis. The critical value of statistical significance level was 5.0%.

## STUDY RESULTS

The results of comparative analysis of induced blood oxidation parameters in patients with CAD are shown in table 1.

Patients with stable CAD had higher values of blood oxidation rate ( $2.07 > 1.9$ ;  $p = 0.049$ ), a shorter initiation period ( $0.97 < 1.91$ ;  $p = 0.001$ ), a higher initial rate of blood oxidation ( $3.29 > 2.11$ ;  $p = 0.0001$ ), a higher maximum rate of blood oxidation ( $3.5 > 2.54$ ;  $p = 0.001$ ), and a higher coefficient of oxidative activity ( $40.0 > 5.89$ ,  $p = 0.0001$ ) comparing to the control group.

The results of the analysis of the influence of induced blood oxidation rate values on the development of cognitive dysfunction in the early postoperative period are presented in Table 2.

**Table 1.** Comparative analysis of induced blood oxidation parameters in patients with CAD

Attribute	Control	CAD	p
Blood oxidation rate ( $V_{ox}$ ), $10^{-8}$ mol/l·s	1.90 (1.7; 2.2)	2.07 (1.8; 2.3)	0.049
Time of initiation period (T), min	1.91 (1.3; 2.5)	0.97 (0.67; 1.34)	0.001
Initial oxidation rate ( $V_{init}$ ), $10^{-8}$ mol/l·s	2.11 (1.6; 2.9)	3.29 (2.5; 4.83)	0.0001
Maximum oxidation rate ( $V_{max}$ ), $10^{-8}$ mol/L·s	2.54 (2.1; 3.1)	3.5 (2.76; 4.83)	0.001
Ultimate oxidation rate $V_{term}$ , $10^{-8}$ mol/L·s	1.86 (1.6; 2.2)	2.03 (1.76; 2.33)	0.28
Oxidation activity coefficient ( $K_A$ ), %	5.89 (-11.0; 22.7)	40 (15.65; 55.5)	0.0001

**Table 2.** Influence of blood oxidation rate ( $V_{ox}$ ) on development of cognitive dysfunction in patients with CAD during the postoperative period

	Multiple — R	Multiple — R2	Adjusted — R2	SS — Model	df — Model	MS — Model	F	p
Cognitive dysfunction	0.34	0.12	0.10	0.33	1	0.33	8.80	0.004

Logistic regression analysis proved the influence of blood oxidation rate on the development of cognitive dysfunction in the postoperative period of CABG ( $p=0.004$ ). Patients with high blood oxidation rate values represent a risk group for the development of cognitive dysfunction during coronary artery bypass grafting.

## DISCUSSION OF RESULTS

Oxidative stress is a component of the neuroinflammatory process, which is a common link in neurodegenerative diseases [8]. A number of large studies have proved the existence of a persistent relationship between oxidative stress and the development of neurodegenerative diseases, primarily Alzheimer's disease [9, 10]. Patients with depressive disorders have also been found to exhibit compromised oxidative status [11]. Low plasma antioxidant activity is associated with a larger focal area in patients with ischemic stroke [12]. Low plasma antioxidant activity is an independent predictor of delirium development in the postoperative period of coronary artery bypass grafting [13].

Current studies focus on the pathogenesis of neurodegenerative diseases associated with the development of dementia, such as Alzheimer's disease or Parkinson's disease. The mechanism underlying transient neurocognitive disorders after surgical interventions is poorly understood. Oxidative stress and disturbances of autophagy processes that occur during cardiac surgery as part of the ischemia-reperfusion phenomenon are integral pathogenetic links of systemic inflammation, which, probably, is in close connection with the development of neurocognitive disorders in the postoperative period. Together with the developing mitochondrial dysfunction, pathologic protein aggregation, impaired neurotransmitter metabolism, and inflammation, this leads to neuronal death [14].

The brain is extremely sensitive to oxidative stress, mainly due to high metabolic activity and relatively weak endogenous antioxidant defenses. Another important fact is the effect of

oxidative stress on the  $Ca^{2+}$  current that control bidirectional synaptic transmission. The intracellular  $Ca^{2+}$  accumulation can indirectly lead to inhibition of mitochondrial respiration and the accumulation of free radicals that damage cellular structures [15].

Thus, transitory disturbances of oxidative status during cardiac surgery lead to temporary neurocognitive disturbances by acting on the nervous system which is sensitive to homeostatic disruption. In this case, the effect of oxidative stress is not long enough to obtain a stable degenerative process.

Thus, transient disturbances in oxidative status observed during cardiac surgery, affecting the nervous system, which is sensitive to homeostasis disturbances, lead to temporary neurocognitive disorders. In this case, the effect of oxidative stress is not long enough for a persistent degenerative process to occur.

## CONCLUSIONS

High blood oxidation rate is an independent predictor of the development of cognitive dysfunction in the early postoperative period during coronary artery bypass grafting.

Determination of blood oxidation rate is one of the tools for risk management during cardiac surgery, starting from the preoperative preparation stage, which seems to be optimal for the implementation of a safe strategy, including psychological and medication support of the patient aimed at preventing the development of cognitive impairment.

The emergence of new medical technologies contributes to the development of ethical thought in the world, when the original main moral principle of medicine, the preservation of human life, is joined by others related to the right of a person to dispose of this life, as well as to have full information not only about the state of health, but also about the prognosis of the disease, which, among other things, is related to the safety of cardiac surgery and the prediction of the development of adverse events.

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