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Effects of nitric oxide on sympathoadrenal system activity in patients with ischemic heart disease in coronary artery bypass grafting

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ABSTRACT

Aim. To investigate changes in laboratory parameters of sympathoadrenal system activity and β-adrenergic receptor reactivity of erythrocyte membranes (β-ARMe) in ischemic heart disease (IHD) patients with clinical forms of arterial hypertension of high cardiovascular risk during coronary artery bypass grafting with anesthetic management including nitric oxide.

Materials and methods. In this randomized study with parallel distribution, 36 patients (male – 66.7%; average age – 68 [63; 70] years) with IHD and clinical forms of arterial hypertension of high cardiovascular risk were enrolled. According to the indications, all patients underwent elective coronary artery bypass grafting (CABG) using extracorporeal circulation (ECC). Patients were randomly divided into the main and control groups. Patients of the main group intraoperatively received NO at the concentration of 80 ppm first in the breathing circuit and then in the ECC circuit. Patients of the control group underwent CABG with standard mechanical lung ventilation and ECC. Before connecting to the ECC, at the end of ECC, and 1 day after CABG, all patients underwent clinical, laboratory, and instrumental tests in accordance with the clinical standards, β-ARMe was assessed, and the concentration of norepinephrine and epinephrine in the blood plasma was determined by ELISA.

Results. At the presurgical stage and 1 day after CABG, the groups did not differ in clinical and biochemical parameters. At the presurgical stage, the median values of β-ARMe in the main and control groups slightly exceeded the upper limits of normal and did not differ significantly. CABG was not accompanied by changes in β-ARMe in the control group. Intrasurgical NO donation also did not affect the level of β-ARMe. One day after CABG, neither intergroup differences in β-ARMe nor significant changes in the parameter during follow-up in each group were noted. In both control and main groups, a significant increase in the levels of epinephrine and norepinephrine was detected 1 day after CABG compared to the baseline level. At the same time, there were no intergroup differences in the level of catecholamines either before ECC or 1 day after CABG.

Conclusion. In cardiac surgery with extracorporeal circulation, the use of NO for the purpose of organ protection does not affect the level of β-ARMe and changes in the mediator response of the sympathetic system to stress in patients with IHD and clinical forms of hypertension of high cardiovascular risk.

Keywords: nitric oxide, coronary artery bypass grafting, β-adrenergic receptor reactivity of erythrocyte membranes, epinephrine, norepinephrine

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study protocol was approved by the Bioethics Committee at the Cardiology Research Institute of Tomsk NRMC (Minutes No. 208 dated January 20, 2021).

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Эффекты оксида азота на показатели активности симпато-адреналовой системы пациентов с ишемической болезнью сердца при операции коронарного шунтирования

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РЕЗЮМЕ

Цель. Изучить динамику лабораторных показателей активности симпатоадреналовой системы и показателя β-адренореактивности мембран эритроцитов у больных ишемической болезнью сердца (ИБС) с клиническими формами артериальной гипертонии (АГ) высокого кардиоваскулярного риска на этапах выполнения операции коронарного шунтирования с анестезиологическим обеспечением, включающим применение оксида азота.

Материалы и методы. В рандомизированное исследование с параллельным распределением были включены 36 пациентов (из них 66,7% – мужчины; средний возраст 68 [63; 70] лет) с диагнозом ИБС с клиническими формами АГ высокого кардиоваскулярного риска. Согласно показаниям пациентам были выполнены плановые операции коронарного шунтирования (КШ) в условиях искусственного кровообращения (ИК). Пациенты были рандомизированы в основную и контрольную группы. Пациенты основной группы интраоперационно получали NO в концентрации 80 ppm первоначально в ингаляционный контур, а затем в контур ИК. Пациентам контрольной группы операция КШ была выполнена в условиях стандартной искусственной вентиляции легких и ИК. Всем пациентам перед подключением ИК, в конце ИК и через 1 сут после операции КШ выполняли комплекс клинических и лабораторно-инструментальных исследований согласно стандартам медицинской практики, оценивали β-адренореактивность мембран эритроцитов (β-АРМэ) и определяли концентрацию в плазме крови норадреналина и адреналина методом ИФА.

Результаты. На дооперационном этапе и спустя 1 сут после операции КШ сформированные группы не различались по клиническим и биохимическим показателям. На дооперационном этапе медианы показателей β-АРМэ в основной и контрольных группах незначительно превышали верхнюю границу нормы и значимо не различались. Выполнение КШ не сопровождалось изменениями показателя β-АРМэ у пациентов в контрольной группе. Интраоперационная донация NO также не отразилась на уровне β-АРМэ. Через 1 сут после операции КШ не отмечено как межгрупповых различий β-АРМэ, так и значимых изменений показателя на сроках наблюдения в отдельно взятой группе. У пациентов контрольной и основной групп выявлено значимое повышение уровня адреналина и норадреналина спустя 1 сут после операции КШ по сравнению с исходным уровнем. В то же время не получено межгрупповых различий по уровню катехоламинов как до ИК, так и через сутки после операции КШ.

Заключение. Использование NO с целью органопротекции не влияет на уровень β-АРМэ и динамику медиаторного ответа симпатической системы на стресс у больных ИБС, имеющих клинические формы АГ высокого кардиоваскулярного риска, при кардиохирургических операциях с использованием искусственного кровообращения.

Ключевые слова: оксид азота, коронарное шунтирование, адренореактивность эритроцитов, адреналин, норадреналин

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Соответствие принципам этики. Все пациенты подписали информированное согласие на включение в исследование. Исследование одобрено комитетом по биомедицинской этике НИИ кардиологии Томского НИМЦ (протокол № 208 от 20.01.2021).

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INTRODUCTION

The use of extracorporeal circulation (ECC) has significantly expanded the possibilities of invasive heart interventions. However, applying ECC increases the risk of damage to other vital organs [1, 2]. To a large extent, this is due to the formation of reactive oxygen species, which lead to the alteration of the membrane structures of the endothelium and cellular components of the blood [3, 4]. ECC, along with other negative factors accompanying extensive surgical interventions, causes the development of perioperative stress in the patient body. It is well known that the sympathoadrenal system (SAS) is activated in the body during a stress response [5, 6]. The majority of patients who require surgical intervention using ECC have a chronic form of ischemic heart disease (IHD) combined with hypertension. It has been shown that such patients are characterized by predominance of sympathetic regulation over parasympathetic one. This results in consistently high levels of catecholamines in the blood of patients. Hypersympathicotonia, along with changes in the lipid bilayer of cell membranes in conditions of chronic vascular pathology, triggers remodeling of transmembrane and cell surface proteins. Previous studies have shown that beta-adrenergic receptor reactivity of erythrocyte membranes (β-ARMe) quite fully reflects not only the state of β-adrenergic receptors (β-AR) of erythrocytes but also the general β-adrenergic receptor reactivity of the body and its changes during the treatment of the prior disease [7, 8].

The use of nitric oxide (NO) is one of the novel approaches to organ protection during cardiac surgery requiring ECC. It consists in introducing NO donors, NO synthase inducers, or gaseous NO into the breathing circuit. Depending of the concentration used, NO can have a damaging or protective effect [9]. Despite the publications over the past decade [10–12], the fundamental pathophysiological mechanisms of organ-protective effects and the safety of exogenous NO supply during ECC remain under study.

The aim of the study was to investigate changes in laboratory parameters of SAS activity and β-ARMe in IHD patients with clinical forms of arterial hypertension of high cardiovascular risk during coronary artery bypass grafting with anesthetic management including nitric oxide.

MATERIALS AND METHODS

This randomized study with parallel distribution enrolled 36 patients. Of these, 24 (66.7%) were men. The average age in the sample was 68 [63; 70] years. All patients were diagnosed with IHD with a clinical form of hypertension of high cardiovascular risk.

The inclusion criteria were the following: diagnosis of IHD with a clinical form of hypertension of high cardiovascular risk, elective coronary artery bypass grafting (CABG), bypass surgery of 2–4 vessels using ECC, age over 18 years, a signed voluntary informed consent.

The exclusion criteria were the following: absence of a patient's voluntary informed consent; a history of cancer; critical condition before CABG; taking norepinephrine, epinephrine or dopamine 3 days before CABG; left ventricular ejection fraction < 30%; blood transfusion in the last 4 months before CABG;

methemoglobinemia (congenital and acquired); bleeding diathesis; intracranial hemorrhage; severe left ventricular failure (NYHA functional class III and IV).

The study was approved by the local Ethics Committee of the Cardiology Research Institute of Tomsk NRMC (Minutes No. 208 dated January 20, 2021). All patients signed an informed consent to participate in the study. According to the indications, all patients underwent CABG using ECC. The patients were randomly divided into 2 groups: study group and control group. Patients of the study group received NO intraoperatively: first in the breathing circuit, then in the ECC circuit. For patients of the control group, CABG was performed using standard mechanical ventilation and ECC.

Baseline clinical and demographic characteristics of the study and control groups did not differ (Table 1).

Table 1

Baseline Clinical and Demographic Characteristics of Patients

Characteristics	Study group, *n* = 18	Control group, *n* = 18	*p*
Age, years, *Me* [25; 75]	68 [36; 70]	68 [61; 70]	0.849
Men, *n* (%)	12 (66.7 %)	12 (66.7%)	1
Women, *n* (%)	6 (33.3%)	6 (33.3%)	1
BMI, kg / m^2, *M* ± *SD*	31.7 ± 4.8	30.7 ± 5.3	0.555
LVEF, %, *Me* [25; 75]	60 [46; 65]	56 [45; 65]	0.924
CRD, *n* (%)	4 (22.2 %)	7 (38.9 %)	0.471
AF, *n* (%)	4 (22.2 %)	3 (16.7 %)	1
Grade I AP, *n* (%)	1 (5.6 %)	1 (5.6 %)	0.850
Grade II AP, *n* (%)	6 (33.3 %)	4 (22.2 %)	0.850
Grade III AP, *n* (%)	11 (61.1 %)	13 (72.2 %)	0.850
PICS, *n* (%)	11 (61.1 %)	13 (72.2 %)	0.725
Grade 3 hypertension, *n* (%)	18 (100 %)	18 (100 %)	1
NYHA FC I CHF, *n* (%)	2 (11.1 %)	2 (11.1 %)	0.510
NYHA FC II CHF, *n* (%)	7 (38.9 %)	11 (61.1 %)	0.510
NYHA FC III CHF, *n* (%)	8 (44.4 %)	5 (27.8 %)	0.510
NYHA FC IV CHF, *n* (%)	1 (5.6 %)	0 (0.0 %)	0.510
DM, *n* (%)	7 (38.9 %)	5 (27.8 %)	0.725
Class 1 CKD, *n* (%)	1 (5.6 %)	3 (16.7 %)	0.139
Class 2 CKD, *n* (%)	7 (38.9 %)	12 (66.7 %)	0.139
Class 3a CKD, *n* (%)	9 (50.0 %)	3 (16.7 %)	0.139
Class 4 CKD, *n* (%)	1 (5.6 %)	0 (0.0%)	0.139
GFR, ml / min / 1.73 m^2	79.8 ± 13.2	62.2 ± 13.9	0.0004
Smoking, *n* (%)	11 (61.1 %)	7 (38.9 %)	0.318

Note. BMI – body mass index; LVEF – left ventricular ejection fraction; CRD – cardiac rhythm disorder; AF – atrial fibrillation; AP – angina pectoris; PICS – postinfarction cardiosclerosis; CHF – chronic heart failure; FC – functional class; DM – diabetes mellitus; CKD – chronic kidney disease; GFR – glomerular filtration rate.

Anesthetic management prior to CABG included premedication with narcotic analgesics, benzodiazepines, and antihistamines. Fentanyl (3.0–5.0 μg / kg) and propofol (1.5 μg / kg) were used to induce anesthesia. Pipecuronium bromide (0.1 μg / kg) was used for neuromuscular blockade. Anesthesia was maintained by inhalation of sevoflurane (2–3 vol.%) and infusion of fentanyl (3.0–5.0 μg / kg / h). Mechanical ventilation was performed using the Drager Primus apparatus (Drager AG, Germany) along a semi-closed breathing circuit in the Controlled Mandatory Ventilation mode with controlled volume of FiO_2 = 0.3 and higher, depending on the clinical situation. To measure central venous pressure and conduct infusion and transfusion therapy, central venous catheterization was performed. Blood pressure monitoring and arterial blood sampling for acid – base balance and gas monitoring were carried out through catheters inserted in the right and left radial arteries. To maintain anesthesia during ECC, propofol infusion (4 mg / kg / h) and fentanyl infusion (3.0–5.0 μg / kg / h) were performed via the infusion pump.

During CABG, we carried out extensive intraoperative monitoring of the patient's condition, which included: continuous ECG analysis, capnometry, capnography for invasive blood pressure measurement, pulse oximetry, diuresis measurement, thermometry with a sensor in the oropharynx, monitoring of the NO/NO_2 ratio. To assess the adequacy of anesthesia and ECC, acid – base balance, hematocrit, hemoglobin, and lactate were monitored using the STAT PROFILE Critical Care Xpress analyzer (NOVA Biomedical, USA).

ECC was performed using the Stockert apparatus (Stockert GmbH, Germany) in the nonpulsatile mode. The perfusion index was 2.5 l / min / m^2. Connection to the ECC circuit was carried out in a standard manner via the aorta – right atrium. To ensure hypocoagulation, heparin was administered before ECC at a dose of 3 mg / kg, maintaining activated coagulation time > 480 s. During ECC, the temperature in the oropharynx was maintained at 35.5–36.6 °C, the hemoglobin level ≥ 80 g / l, and the mean arterial pressure at 50–80 mm Hg. Myocardial protection was achieved by perfusion of the ascending aorta or coronary artery (in case of aortic regurgitation) with a cold (5–8 °C) crystalloid solution (Custodiol HTK-Bretschneider; Dr Franz Köhle rChemie GmbH, Bensheim, Germany) at a dose of 3 ml / kg for 6–8 minutes according to the manufacturer's instruction. Local hypothermia with ice slurry was used. After the end of ECC, heparin was inactivated with protamine in a 1:1 ratio.

Patients of the study group, immediately after tracheal intubation, received NO intraoperatively

at a concentration of 80 ppm in the breathing circuit and then, after the start of ECC, to the ECC circuit. After disconnection from the ECC, NO delivery was resumed in the anesthesia machine circuit at the concentration of 80 ppm until the end of surgery. Delivery and monitoring of NO/NO_2 were carried out using plasma-chemical NO synthesis AIT-NO-01 system (Tianox, RFNC-VNIIEF, enterprise of Rosatom State Atomic Energy Corporation, Sarov, Russia). The maximum permissible NO_2 concentration in the study group was 2 ppm.

All patients underwent a complex of clinical, laboratory, and instrumental tests in accordance with clinical standards at the following stages of surgery: before connecting to ECC, at the end of ECC, 1 day after CABG. In the meantime, we assessed body β-ARMe measurements using the Beta-ARM Agat kit (Agat-Med LLC, Russia, https://www.agat.ru/documents/instructions/4994/). This method is based on inhibition of hemolysis of erythrocytes placed in hypoosmotic medium in the presence of a selective β-blocker. According to the manufacturer's protocol, β-ARMe values in 93% of apparently healthy individuals are in the range of 2.0–20.0%, which reflects an increase in osmotic fragility of erythrocytes following binding of the adrenergic blocker to β-ARs. Higher values of β-ARMe reflect reduced osmotic fragility of erythrocytes and, therefore, weaker binding of the adrenergic blocker to β-ARs due to a decrease in the number of receptors on the cell membrane or their desensitization.

To assess the activity of SAS, before connecting to the ECC and 1 day after CABG, the concentrations of norepinephrine and epinephrine in the blood plasma of the patients of both groups were determined using ELISA kits for the quantitative determination of catecholamines (IBL CatCombi ELISA, Germany).

Statistical processing of the obtained data was carried out using the Statistica 10.0 software package. Normality of data distribution was checked using the Shapiro – Wilk test, since the number of patients in the study sample was less than 50. Normally distributed variables were presented as the mean and standard deviation $M \pm SD$. When the distribution was not normal, the data were presented as the median and the interquartile range *Me* [25; 75]. Qualitative data were presented as absolute and relative values – *n* (%). Quantitative variables of independent samples were compared by the *t*-test for normally distributed values or the Mann – Whitney *U*-test for non-normally distributed variables. Quantitative variables in dependent samples were compared using the *t*-test for normally distributed values or the Wilcoxon test for non-normally distributed variables. To compare qualitative variables in two samples, the Fisher's exact test was used. The differences were considered to be statistically significant at $p < 0.05$.

RESULTS

Table 2 demonstrates parameters characterizing the perioperative period. Procedure of NO donation into the breathing and then into the perfusion circuit led to an increase in the duration of the surgery, which did not reach statistical significance. The study and control groups did not differ in the ECC duration, the time of aorta clamping, or the volume of intraoperative blood loss. The groups were comparable in terms of blood pressure levels before and during ECC. There were also no intergroup differences in the acid – base balance, hematocrit, hemoglobin, and lactate levels at the stages of the surgery.

Table 3 demonstrates clinical and biochemical blood parameters in the study and control groups.

Table 2

Parameters of the Perioperative Period

Parameters	Study group, *n* = 18	Control group, *n* = 18	*p*
Surgery duration, min, *Me* [25; 75]	300 [260; 330]	270 [240; 300]	0.058
ECC duration, min, $M \pm SD$	95.50 ± 25.50	82.00 ± 15.04	0.062
Aorta clamping duration, min, $M \pm SD$	58.75 ± 18.67	48.50 ± 15.47	0.089
Mean BP before ECC, mm Hg, $M \pm SD$	104.59 ± 40.56	122.73 ± 36.83	0.128
Mean BP during ECC, mm Hg, $M \pm SD$	56.29 ± 6.89	53.35 ± 5.23	0.064
Blood loss during surgery, ml, *Me* [25; 75]	1,000 [800; 1,000]	1,000 [800; 1,000]	0.949
Homeostasis parameters during CABG			
Before ECC			
pH, *Me* [25; 75]	7.39 [7.37; 7.43]	7.40 [7.37; 7.41]	0.646
Lactate, mmol / l, *Me* [25; 75]	1.1 [0.9; 1.4]	1.1 [0.9; 1.4]	1

End of table 2

Parameters	Study group, *n* = 18	Control group, *n* = 18	*p*
Hb, g / l, *Me* [25; 75]	130 [123; 141]	132 [120; 137]	0.812
Hct, %, *M* ± *SD*	36.90 ± 3.75	38.44 ± 3.38	0.216
At the end of ECC			
pH, *Me* [25; 75]	7.41 [7.38; 7.40]	7.38 [7.37; 7.42]	0.223
Lactate, mmol / l, *Me* [25; 75]	1.50 [1.30; 2.10]	1.35 [1.00; 1.60]	0.064
Hb, g / l, *Me* [25; 75]	94.5 [85.0; 101.0]	95.0 [87.0; 101.0]	0.776
Hct, %, *M* ± *SD*	25.61 ± 3.18	27.00 ± 3.14	0.197
At the end of CABG			
pH, *Me* [25; 75]	7.35 [7.35; 7.40]	7.38 [7.37; 7.40]	0.448
Lactate, mmol / l, *Me* [25; 75]	1.5 [1.2; 2.1]	1.4 [1.1; 1.6]	0.107
Hb, g / l, *Me* [25; 75]	100.5 [92.0; 108.0]	103.5 [93.0; 112.0]	0.579
Hct, %, *M* ± *SD*	27.56 ± 3.22	28.89 ± 3.46	0.239
One day after CABG			
pH, *M* ± *SD*	7.42 [7.40; 7.44]	7.43 [7.38; 7.44]	0.591
Lactate, mmol / l, *M* ± *SD*	1.9 [1.5; 2.1]	1.8 [1.5; 2.3]	0.739
Hb, g / l, *M* ± *SD*	104 [92; 115]	106 [86; 119]	0.800
Hct, %, M ± SD	30.13 ± 3.99	29.57 ± 4.79	0.702

Note. ECC – extracorporeal circulation; BP – blood pressure; CABG – coronary artery bypass grafting; pH – hydrogen ion concentration or acid value; Hb – hemoglobin; Hct – hematocrit.

Table 3

Changes in Clinical and Biochemical Blood Parameters at the Stages of the Study

Parameters	Study group, *n* = 18	Control group, *n* = 18	***p***
Before CABG			
Leukocytes, 10^9 / l, *M* ± SD	7.19 ± 1.76	7.52 ± 2.32	0.637
Platelets, 10^9 / l, *M* ± *SD*	240.78 ± 71.89	223.61 ± 50.25	0.412
ESR, mm / h, *Me* [25; 75]	6 [4; 15]	6 [5; 8]	0.832
CK, U / l, *Me* [25; 75]	73 [47; 120]	93 [76; 127]	0.223
CK-MB, U / l, *Me* [25; 75]	19 [16; 24]	20 [15; 24]	0.899
Glucose, mmol / l, *Me* [25; 75]	5.9 [5.3; 6.5]	7.2 [5.7; 7.9]	0.101
Urea, mmol / l, *Me* [25; 75]	5.7 [5.0; 6.7]	4.3 [4.2; 7.8]	0.250
Creatinine, µmol / l, *Me* [25; 75]	94 [87; 119]	82 [76; 88]	0.001
CRP, mg / l, *Me* [25; 75]	5.1 [1.2; 13.2]	3.5 [1.0; 12,4]	0.486
Total protein, g / l, *M* ± SD	70.29 ± 6.12	72.93 ± 9.08	0.399
ALT, U / l, *Me* [25; 75]	18.2 [16.0; 23.0]	21.8 [10.0; 42.6]	0.569
AST, U / l, *Me* [25; 75]	18.6 [13.0; 24.9]	22.4 [16.0; 26.0]	0.429
Total bilirubin, µmol / l, *Me* [25; 75]	12.8 [10.0; 18,7]	11.6 [9.7; 19.5]	0.857
One day after CABG			
Leukocytes, 10^9 / l, *M* ± *SD*	11.59 ± 3.01, *p** = 0.035	11.22 ± 2.99, *p** = 0.48	0.719
Platelets, 10^9 / l, *M* ± *SD*	183.44 ± 71.68, *p** = 0.678	165.89 ± 47.31, *p** = 0.834	0.392
CK, U / l, *Me* [25; 75]	754 [558; 993], *p** = 0.001	783 [569; 1,250], *p** = 0.001	0.564
CK-MB, U / l, *Me* [25; 75]	34 [32; 43], *p** = 0.001	35 [28; 42], *p** = 0.045	0.817
Glucose, mmol / l, *Me* [25; 75]	9.2 [7.6; 10.9], *p** = 0.036	9.7 [8.2; 11.6], *p** = 0.05	0.643
Urea, mmol / l, *Me* [25; 75]	7.1 [5.9; 8.3], *p** = 0.002	6.6 [5.8; 8.3], *p** = 0.449	0.607
Creatinine, µmol / l, *Me* [25; 75]	104.5 [84.0; 133.0], *p** = 1.0	94,0 [76.0; 116.0], *p** = 0.05	0.211
CRP, mg / l, *Me* [25; 75]	149 [128; 169], *p** = 0.000	139 [115; 160], *p** = 0.000	0.628
Total protein, g / l, *M* ± SD	53.67 ± 4.89, *p** = 0.001	53.33 ± 5.61, *p** = 0.013	0.875
ALT, U / l, *Me* [25; 75]	35 [27; 46], *p** = 0.009,	32 [15; 43], *p** = 0.239	0.646
AST, U / l, *Me* [25; 75]	57 [39; 68], *p** = 0.001	53 [43; 72], *p** = 0.002	0.962
Total bilirubin, µmol / l, *Me* [25; 75]	10.7 [8.6; 18.7], *p** = 0.802	12.1 [8.7; 27.7], *p** = 0.795	0.681

Note. ALT – alanine transaminase; AST – aspartate transaminase; CK – creatine kinase; CK-MB – creatine kinase, myocardial band.

In our study, the surgical intervention did not result in significant differences between the groups. At the same time, in both groups, there was a significant increase in CK, CK-MB, ALT, and AST and a decrease in total protein one day after CABG compared to the preoperative period. The increase in the activity of serum biomarkers of cell damage and the decrease in total protein in the postoperative period are certainly due to the large volume of surgical intervention on the tissues of the chest and heart. In the postoperative period, a significant increase in the concentration of urea in the blood plasma was noted only in the study group. However, this did not result in significant intergroup differences at this follow-up stage.

Table 4 demonstrates clinical parameters of the patients of the study and control groups, reflecting the features of their early postoperative period. According to the data presented, the use of NO during CABG did not lead to statistically significant differences between the groups. However, there were no intraoperative myocardial infarctions and oliguria / anuria in the study group. On the contrary, in the control group, the incidence of myocardial infarction and oliguria / anuria was 22.2% each. Due to a small sample size, intergroup differences did not reach a critical level of significance.

Table 4

Characteristics of the Early Postoperative Period

Characteristics	Study group, *n* = 18	Control group, *n* = 18	*p*
Reoperation, *n* (%)	0 (0.0%)	1 (5.6%)	1
Intraoperative complications, *n* (%)	1 (5.6%)	1 (5.6%)	1
Mechanical ventilation duration, min, *Me* [25; 75]	550 [395; 1,040]	480 [390; 625]	0.517
Tracheostomy, n (%)	1 (5.6%)	1 (5.6%)	1
Pneumonia, *n* (%)	4 (22.2%)	6 (33.3%)	0.711
RF (need for oxygen support), *n* (%)	3 (16.7%)	4 (22.2%)	1
Diuresis 1 day after CABG (ml), *Me* [25; 75]	3,275 [2,350; 3,900]	3,550 [2,400; 3,900]	0.874
Oliguria / anuria (< 0.5 ml / kg / h), *n* (%)	0 (0.0%)	4 (22.2%)	0.104
AMI, *n* (%)	0 (0.0%)	4 (22.2%)	0.104
AF in the postoperative period, *n* (%)	3 (16.7%)	7 (38.9%)	0.264
Delirium, *n* (%)	3 (16.7%)	3 (16.7%)	1
Stroke, *n* (%)	1 (5.6%)	2 (11.1%)	1
Stool (days after CABG), *Me* [25; 75]	4 [3; 4]	4 [3; 5]	0.319
Bed days in ICU, *Me* [25; 75]	1 [1; 6]	1 [1; 6]	1
Bed days in the in-patient department, *Me* [25; 75]	17.5 [16.0; 26.0]	19.5 [16.0; 31.0]	0.527

Note. RF – respiratory failure; AMI – acute myocardial infarction; AF – atrial fibrillation; ICU – intensive care unit.

The results of assessing catecholamine concentrations in the blood of patients are shown in Fig.1. In our study, in patients of the study and control groups, epinephrine concentration significantly increased 1 day after CABG compared to the level before ECC ($p = 0.005$ and $p = 0.003$, respectively) (Fig. 1, *a*). At the same time, the median concentrations of epinephrine in the study group before CABG and 1 day after it were higher compared to the control group. However, these differences did not reach statistical significance ($p = 0.063$ and $p = 0.095$, respectively).

Changes in the norepinephrine levels were similar in both the control ($p < 0.001$) and study groups ($p = 0.006$) (Fig. 1, *b*) without significant intergroup

Table 5

Beta-ARMe in Patients with Nitric Oxide Donation during CABG, *Me* [25; 75]

Stages of observation	Study group, *n* = 18	Control group, *n* = 18	*p*
β-ARMe before CABG	21.9 [14.3; 26.1]	21.2 [13.3; 26.2]	0.972
β-ARMe at the end of CABG	18.6 [13.5; 34.2]	20.8 [15.3; 27.5]	0.851
β-ARMe 1 day after CABG	25.3 [18.8; 42.7] p^* = 0.169	21.0 [14.3; 30.9] p^* = 0.838	0.187

Note. CABG – coronary artery bypass grafting; β-ARMe – β-adrenergic reactivity of erythrocyte membranes; *p* – significance level of differences between the groups. p^* – significance level of intragroup differences before CABG and 1 day after CABG.

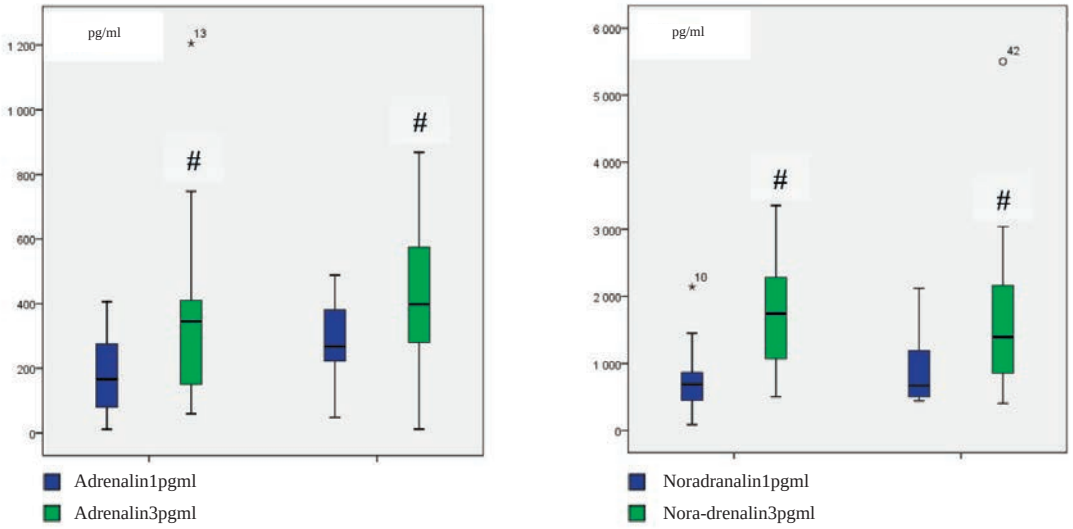

Fig. 1. Concentrations of epinephrine (*a*) and norepinephrine (*b*) in the study and control groups at the stages of CABG: # significant intragroup difference

– before ECC; – 1 day after CABG

differences both before ECC (p = 0.318) and 1 day after CABG (p = 0.0560).

Table 5 reflects baseline β-ARMe values and their subsequent changes. For both groups of patients, the baseline values of β-ARMe were at the upper range limit. CABG was not accompanied by significant changes in β-ARMe at the end of the surgery and 1 day after its completion. Intraoperative NO donation did not cause significant changes in this parameter in patients of the study group in perioperative and postoperative periods.

DISCUSSION

Connecting the patient's body to the ECC circuit is a crucial stage of CABG that increases the risk of vital organ damage [13, 14]. One of the novel approaches to organ protection is the use of NO. Effects of NO are dose-dependent, which results from the formation of physiologically active metabolites of NO and its interaction with various molecular targets [9, 10]. In particular, it has been shown for cardiomyocytes that activation of iNOS or NO donation suppresses function of ryanodine receptors through the cGMP-independent pathway [15]. This mechanism limits beta-adrenergic sensitivity of the myocardium and may be an important signaling pathway for the damaging effects of NO.

The absence of significant differences in baseline β-ARMe values in the study and control groups indicates the absence of functional overload in the SAS receptor pathway in patients with IHD and clinical forms of arterial hypertension of high cardiovascular risk enrolled in the study. In the postoperative period, the stability of β-ARMe in the study group was further evidence of NO application safety during CABG. It may be suggested that NO has no effects associated with a direct influence on the activity of the SAS receptor component. At the same time, it was shown that in both the study and control groups at the postoperative stage, the increase in the blood concentration of norepinephrine (by 1.5 and 2.0 times, respectively) and epinephrine (by 2.1 and 2.5 times, respectively) was revealed, which reflected the involvement of the SAS in maintaining the body homeostasis of operated patients. However, the absence of changes in β-ARMe both in the period of ECC disconnection and 1 day after CABG in patients of the control group speaks of adequate premedication. It could be concluded that intraoperative NO donation did not affect the parameters of SAS mediator metabolism, which also confirms the safety of the NO dose used.

CONCLUSION

In cardiac surgery with extracorporeal circulation, the use of NO for the purpose of organ protection does not affect the level of β-ARMe and changes in the mediator response of the sympathetic system to stress in patients with IHD and clinical forms of hypertension of high cardiovascular risk.

The limitation of the study was a small number of patients who were enrolled and completed the full course of examination.

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Rebrova T. Yu. – epinephrine / norepinephrine determination by ELISA, analysis and interpretation of the data, drafting of the manuscript. Churilina E.A. – collection, processing, and statistical analysis of clinical data. Podoksenov Yu. K. – study design, analysis and interpretation of clinical data, critical revision of the manuscript for important intellectual content. Korepanov V.A. – determination of beta-adrenergic reactivity of erythrocytes, statistical analysis of laboratory parameters. Kamenshchikov N.O. – development of inclusion / exclusion criteria, selection and inclusion of patients in the study according to the criteria, obtaining an informed consent from the patients. Muslimova E.F. – compilation of the database, analysis and interpretation of the data. Vorozhtsova I.N. – discussion of the results, final approval of the manuscript for publication. Afanasiev S.A. – conception and design of the study, final approval of the manuscript for publication.

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