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Role of Myeloperoxidase, Paraoxonase, and Nitric Oxide System in the Blood and Pericardial Fluid of Patients with Ischemic Heart Disease after Direct Myocardial Revascularization

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Abstract—To study the role of paraoxonase, myeloperoxidase, arginase, asymmetric dimethylarginine, and nitric oxide in the mechanisms of the pathogenesis of postpericardiotomy syndrome (PPCS), 76 patients with ischemic heart disease (IHD) who underwent coronary artery bypass grafting were examined. Patients were divided into two groups: Group 1, IHD patients who were not diagnosed with PPCS as a result of clinical studies, and Group 2, IHD patients who were diagnosed with PPCS. The results indicate that the postoperative period after coronary artery bypass grafting is associated with the inhibition of paraoxonase, the activation of myeloperoxidase, enhanced arginase activity, increased nitrite/nitrate and asymmetric dimethylarginine levels; it may also be accompanied by the development of endothelial dysfunction and increased systemic inflammatory response. In the present work, inverse correlations were found between the paraoxonase aryl esterase activity and myeloperoxidase activity in plasma, as well as the paraoxonase aryl esterase activity in blood plasma and arginase activity in erythrocytes in patients of both groups. Tests to predict the development of postpericardiotomy syndrome were developed based on the ratio of activity of the studied enzymes.

Keywords: coronary artery bypass grafting, systemic inflammatory response, postpericardiotomy syndrome, paraoxonase, myeloperoxidase, arginase, asymmetric dimethylarginine, nitric oxide

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INTRODUCTION

Ischemic heart disease (IHD) is one of the most important age-related diseases. Despite the almost nearly two hundred years of research on its history, the search for and improvement of methods for the treatment of this disease remain a priority [4]. The methods of direct myocardial revascularization, in particular, coronary artery bypass grafting (CABG), have recently become most relevant. According to numerous studies, CABG is significantly superior to drug therapy in efficiency and is indispensable for multiple lesions of the coronary vessels [8, 14]. Despite its obvious advantages, cardiac surgery is often associated with surgical trauma, hemodynamic changes, and the development of systemic inflammatory response and endothelial dysfunction. Myeloperoxidase (MPO) is a key enzyme linking inflammation and oxidative stress in cardiovascular pathologies. As a result of MPO activation, high-density lipoproteins (HDLs) are oxidized by highly reactive hypochlorites, which leads to lipoprotein dysfunction and a change in lipoprotein properties to pro-inflammatory [18].

It is known that MPO is able to reduce the bioavailability of nitric oxide ($NO^{\cdot}$) and thereby contribute to the development of endothelial dysfunction. The involvement of MPO in the pathogenesis of cardiovascular diseases is closely related to the functioning of another group of enzymes, paraoxonases (PONs), which have antioxidant properties and protect HDLs from oxidation [6]. Endothelial dysfunction is associated with impaired relaxation and antiaggregation properties, increased cell growth, the proliferation of smooth muscle cells, and abnormal vascular permeability [30]. $NO^{\cdot}$ deficiency, which is the leading humoral factor in vascular relaxation, is considered to be one of the most important causes of the development of endothelial dysfunction [24]. $NO^{\cdot}$ is normally synthesized in small amounts by endothelial NO synthase (*eNOS*). The lack of $NO^{\cdot}$ in the endothelium and a decrease in its bioavailability is promoted, on the one hand, by cytokine overproduction, and, on the other hand, by increased arginase activity, which competes with *eNOS* for a common substrate, *L*-arginine. In addition, asymmetric dimethylarginine (ADMA) can directly inhibit endothelial NO synthase and

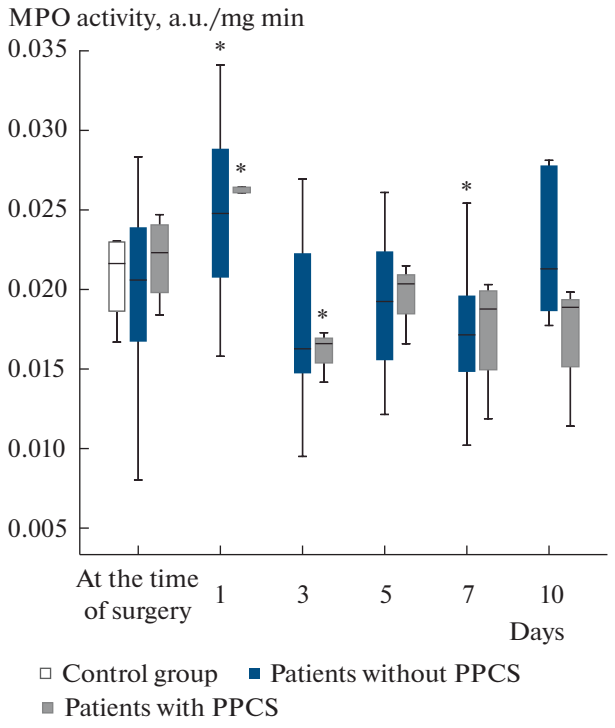

Fig. 1. MPO activity in the blood plasma of IHD patients with and without PPCS after CABG. * Statistically significant differences compared with the control group, $p < 0.05$.

cause a relative NO˙ deficiency [26]. It is known that an increase in arginase activity at a high level of ADMA stimulates eNOS-uncoupling and the intensification of cardiovascular inflammation [32].

All of this leads to a high risk of postoperative complications, one of which is postpericardiotomy syndrome (PPCS). It should be noted that many of its pathogenetic aspects are still unclear, and no less important is the fact that the range of possible markers that can prevent the development of this syndrome has not been determined. The purpose of this work was to study the role of MPO, *PON*, and NO˙ system in the blood and pericardial fluid in patients with coronary artery disease who underwent direct myocardial revascularization and to assess the effectiveness of these indicators as predictors of PPCS.

MATERIALS AND METHODS

The study included 76 patients aged 41–75 (58 ± 1.5 years) with coronary artery disease who underwent CABG in the cardiac surgery department of the Rostov State Medical University. The inclusion criteria were the following: FC III–IV angina pectoris, stenosis of the left coronary artery trunk by 75% or more, severe stenosis of the near sections of the main arteries, and multiple lesions of the coronary vessels. Patients were divided into two groups: Group 1, IHD patients who were not diagnosed with PPCS as a result of clinical studies (PPCS–), and Group 2, IHD patients who were diagnosed with PPCS (PPCS+). The biochemical parameters were studied in the following dynamics: at the time of surgery and on days 1, 3, 5, 7, and 10 of the postoperative period. The blood of 20 practically healthy human donors of both sexes aged 46.2 ± 0.7 was used as the control.

The materials for biochemical studies were red blood cells, blood plasma, and pericardial fluid. Blood was collected in the morning on an empty stomach from the cubital vein. To obtain plasma, whole blood was centrifuged for 10 min at 3000 rpm. A 1%-erythrocyte hemolysate was obtained via lysing of the erythrocyte pellet with distilled water, followed by incubation at +37°C for 30 min. Pericardial fluid was taken during surgery and prior to analysis was centrifuged for 10 min at 3000 rpm.

The MPO activity was determined spectrophotometrically [3]. The *PON* aryl esterase activity was evaluated by the rate of phenylacetate hydrolysis [16]. The arginase activity was assessed by an increase in the content of urea, the product of catalyzed reaction. The urea content was assessed by reaction with diacetylmonoxime [2]. The ADMA level was determined by ELISA with a commercial kit (Immundiagnostik, Germany). The measurements were carried out on a StatFax 2100 microplate reader (Awareness Technology, USA). The NO˙ level was evaluated from measurements of the content of its stable metabolites and nitrite /nitrates (NOx) [1].

Statistical processing of the results was carried out with the Mann–Whitney *U* test and the Statistica 10.0 and SPSS Statistics 17.0 programs. The differences were considered significant at $p < 0.05$. The results were presented as a median (*Me*) with an interquartile range (25th–75th percentile). The nonparametric Spearman's rank correlation coefficient was used to determine the possible correlations. The integral diagnostic information content of laboratory tests was evaluated via the construction of characteristic curves (*ROC* analysis) [27].

RESULTS AND DISCUSSION

According to the results, we observed a 20–27% increase in MPO activity in the blood plasma of patients of both groups on day 1 after surgery as compared to control values. In Group 1, the enzyme activity was decreased by 16% on day 7 after CABG; in Group 2, the decrease was 22% already on day 3 (Fig. 1).

In the work of S.R. Alam et al., the plasma MPO level increased within 2 h after CABG [5]. It is known that an increased MPO concentration 3 h after cardiac surgery is a prognostic factor for postoperative complications [21].

It is important to emphasize that the key role in the development of the systemic inflammatory response

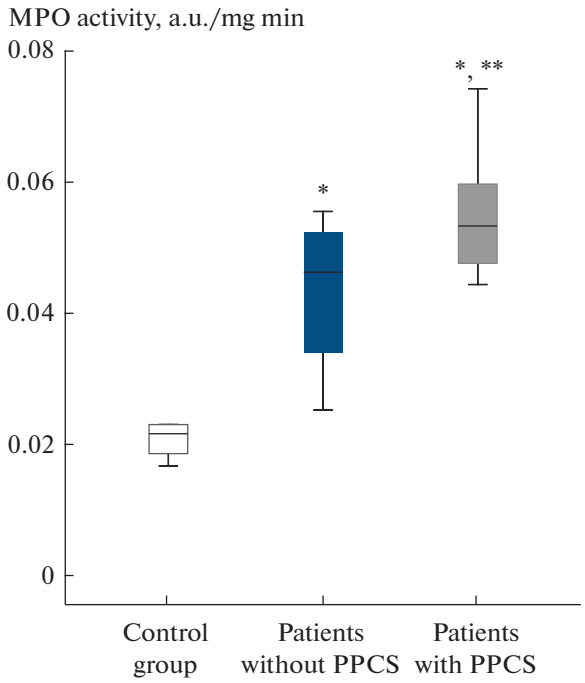

Fig. 2. MPO activity in pericardial fluid in IHD patients who underwent CABG at the time of surgery. The MPO activity values in donor plasma were used as control ones. * Statistically significant differences as compared with the control group, $p < 0.05$; ** statistically significant differences between patients of Group 1 and Group 2.

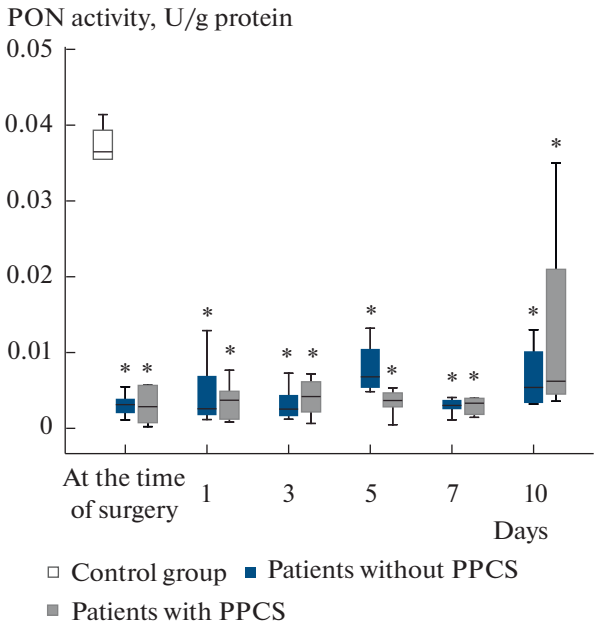

Fig. 3. PON aryl esterase activity in blood plasma in IHD patients who underwent CABG. * Statistically significant differences compared with the control group, $p < 0.05$.

that develops with PPCS belongs to the MPO released from activated neutrophils. The MPO secretion and the subsequent formation of active chlorine forms may be due to the recruitment and activation of neutrophils during inflammation, the transformation of monocytes into macrophages in vascular intimae induced by modified low-density lipoproteins (LDLs), and the association of neutrophils with damaged areas of the endothelium. MPO initially binds to the vascular endothelium and then penetrates into the subendothelial matrix of the cell [25]. The products of the MPO-catalyzed reaction lead to the oxidation of LDLs, which contribute to the development of atherogenesis due to the accumulation of cholesterol and the conversion of macrophages into foam cells.

During surgery, the MPO activity in the pericardial fluid in patients of both groups significantly exceeded that in the control group: by 98% in Group 1 and by 171% in Group 2; moreover, the MPO activity was 37% higher in Group 2 than in Group 1 (Fig. 2).

B. Butts et al. noted a more significant increase in MPO activity in the pericardial fluid in patients undergoing CABG as compared with that in blood plasma within 48 h after surgery [9]. Excessive MPO activity in the pericardial fluid in patients with PPCS may indicate a morphological and biochemical rearrangement of neutrophils, their adhesion, degranulation, and the formation of neutrophilic traps. As a rule, such changes are accompanied by the activation of NADPH oxidase, which indirectly increases the concentration of substrate (H_2O_2) for MPO [15].

In the work, we found a direct correlation between MPO activity in plasma and pericardial fluid in patients without PPCS ($R = 0.9$, $p < 0.05$), as well as with PPCS ($R = 0.71$, $p < 0.05$).

The results indicate that the *PON* aryl esterase activity in the blood plasma of patients of both groups was significantly decreased as compared with the norm over the entire observation period: by 74–80% in Group 1 and by 61–85% in Group 2 (Fig. 3). The studied indicator reached the minimal values in both groups on the first postoperative day.

The *PON* aryl esterase activity in the pericardial fluid was decreased relative to the control parameters by 52% in Group 1 and by 76% in Group 2 (Fig. 4). The *PON* aryl esterase activity in Group 1 was 49% lower than that in Group 1.

Paraoxonases belong to the class of aryl esterases that hydrolyze organophosphorus compounds and possess antioxidant and antiatherogenic properties. Due to esterase and lipolactonase activity, *PON*s prevent the accumulation of lipid peroxides from oxidized LDLs, stimulate HDL-mediated activation of $NO^{\bullet}$ synthase, and increase the release of cholesterol from cholesterol-overloaded macrophages [10].

A. Wysocka et al. proved the possibility of using *PON*1 activity as a prognostic marker to prevent the development of postoperative complications in patients undergoing CABG [31]. A decrease in PON

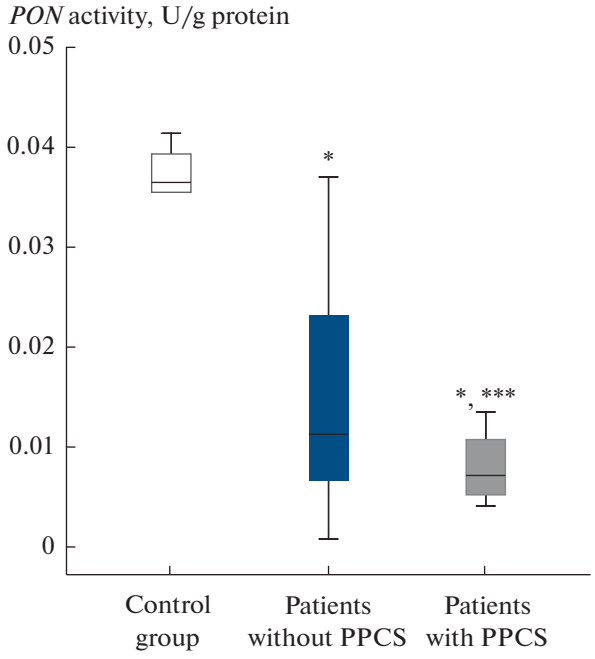

Fig. 4. PON aryl esterase activity in pericardial fluid in IHD patients who underwent CABG at the time of surgery. The PON aryl esterase activity values in donor plasma were used as the control. * Statistically significant differences as compared with the control group, $p < 0.05$; ** statistically significant differences between patients with postpericardiotomy syndrome and patients without it.

activity in pericardial fluid is a risk factor for the development of cardiopathology [12]. In our study, we determined the correlation of *PON* aryl esterase activity in plasma and pericardial fluid in patients without PPCS ($R = 0.8$, $p < 0.05$) and with PPCS ($R = 0.87$, $p < 0.05$).

The obtained data indicated the activation of MPO and the implementation of its proinflammatory properties in the early postoperative period after CABG. In pathophysiological conditions, MPO is able to inhibit the anti-inflammatory and antioxidant *PON* enzyme, both directly and indirectly through active forms of chlorine [13]. As a result, an increase in MPO activity on day 1 after surgery is accompanied by a decrease in *PON* aryl esterase activity. It is known that the ratio of MPO and *PON* concentrations can be used as a predictor of the development of atherosclerosis and acute coronary syndrome [10]. The results showed a high inverse correlation between the activity of MPO and *PON* enzymes in blood plasma; the Spearman's rank correlation coefficient was -0.83 ($p < 0.05$). In the course of the study, we calculated a coefficient for blood plasma, which characterizes the ratio of the MPO peroxidase activity to the *PON* aryl esterase activity on the first postoperative day. It was found that, if this ratio exceeds 5.19 on day 1 of the postoperative period, then the development of PPCS after myocardial revascularization is possible with a 70% probability. For pericardial fluid, this ratio is equal to 4.27. If the MPO / *PON* activity ratio in the patient's pericardial fluid is higher than 4.27, then the probability of developing PPCS will be 71.4%. For the studied ratio of enzyme activity in IHD patients who underwent CABG, a high direct correlation dependence of plasma (first postoperative day) and pericardial fluid (time of surgery) was found; the Spearman's rank correlation coefficient was 0.71 ($p < 0.05$). The *ROC* curves were constructed to assess the efficiency of prognostic methods (Fig. 5). The sensitivity of the described method for plasma is 87.5%, the specificity is 75%, and the overall accuracy is 80%. For pericardial fluid, the test criteria are 71.4, 80, and 71.4%, respectively. The Area Under the *ROC* curve (*AUC*) of the test was 0.875 (95% CI 0.76–0.951) for plasma and 0.779 (95% CI 0.505–0.951) for pericardial fluid. The found AUC values indicate that the described diagnostic method has a high quality [27].

The arginase activity in blood erythrocytes increased by 48–174% in patients of Group 1 and by 70–220% in Group 2 over the entire observation period as compared to the control values (Fig. 6). The enzyme activity reached the maximal values on day 7 of the postoperative period in Group 1 and on day 1 in Group 2. The arginase activity was 27% higher in patients of Group 2 than those in Group 1 at the time of surgery, 71% higher on day 1 after surgery, and 25% higher on day 3. The activation of arginase is associated with the ischemia/reperfusion mechanism, which is a trigger factor in the development of a systemic inflammatory response. During ischemia, there is a violation of sarcolemmal integrity, which leads to the release of intracellular molecules, including enhancer RNAs that activate a sheddase (*TACE*) and thereby mediate the secretion of *TNF*-α; this, in turn, enhances arginase expression and activity [25].

It is known that arginase is involved in endothelial NO synthase "uncoupling," which leads to a decrease in the $NO^{\cdot}$ level, the formation of highly reactive peroxynitrite, and the oxidation of HDLs and LDLs [33]. An inverse correlation exists between the $NO^{\cdot}$ concentration and the content of oxidized LDLs [11]. Oxidized LDLs and lipid peroxidation products (in particular, 4-hydroxynonenal) inhibit *PON* aryl esterase activity [19]. In our work, a high inverse correlation was found between the aryl esterase activity of *PON* and arginase; the Spearman's rank correlation coefficient was -0.93 ($p < 0.01$). During the study, we calculated the coefficient characterizing the ratio of arginase activity to *PON* aryl esterase activity on day 1 after CABG. It was found that, if this coefficient exceeds 0.39 on day 1 of the postoperative period, then the development of PPCS after myocardial revascularization is possible with a probability of 67%. The *ROC* curve was constructed to evaluate the effectiveness of the prognostic method (Fig. 7). The sensitivity of the described method for the prediction of PPCS is

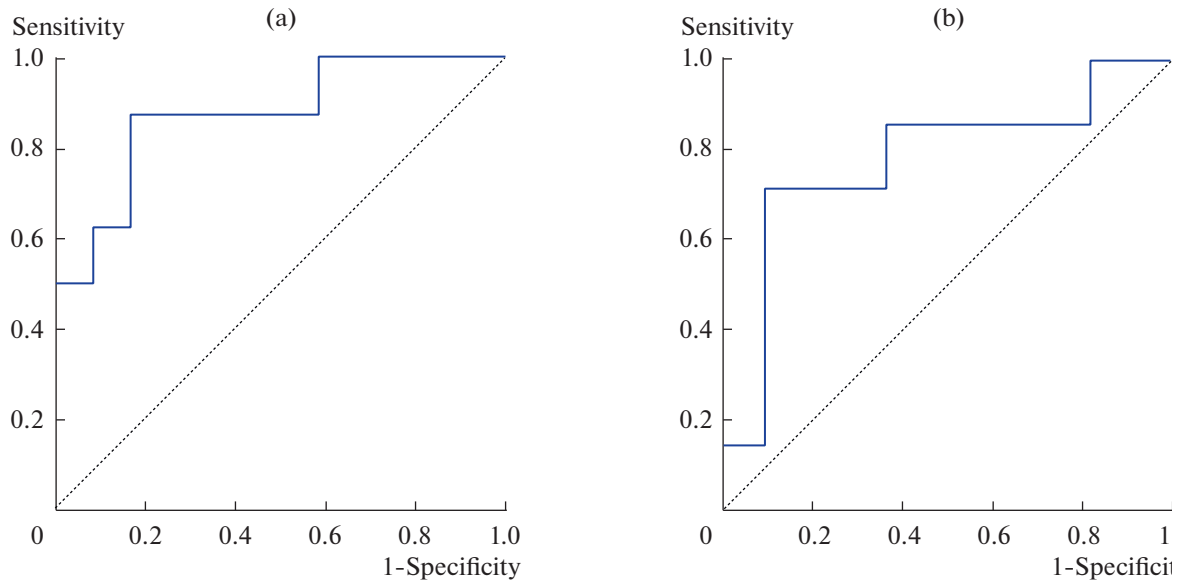

Fig. 5. ROC curve of a test designed to predict postpericardiotomy syndrome in (a) blood plasma and (b) pericardial fluid.

75%, the specificity is 69.2%, and the overall accuracy is 75%. The area under the *ROC* curve was 0.779 (95% CI 0.579–0.981), which indicates that the described method is of high quality.

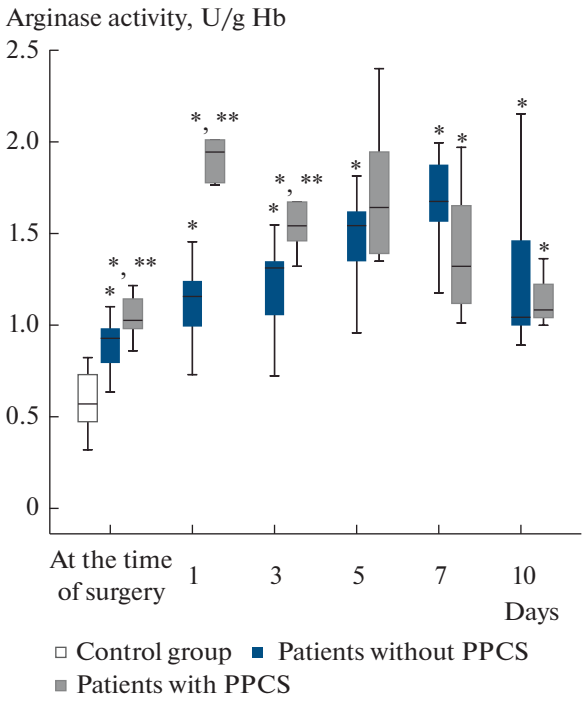

Fig. 6. Arginase activity in the blood erythrocytes of IHD patients after CABG. * Statistically significant differences compared with the control group, $p < 0.05$; ** statistically significant differences between patients with postpericardiotomy syndrome and patients without it.

The level of ADMA in the blood plasma of patients without PPCS was found to have increased by 24, 27, and 67% on days 1, 3, and 5 after surgery as compared with the control group (Fig. 8). The ADMA content was markedly increased in the blood plasma of PPCS patients at the time of surgery and on days 3 and 5 after surgery; it was 54, 39, and 76% higher than the control values. In Group 2, the studied indicator was 26% higher at the time of surgery and 9% higher on day 3 after surgery as compared to Group 1. It is suggested that CABG can trigger ADMA accumulation.

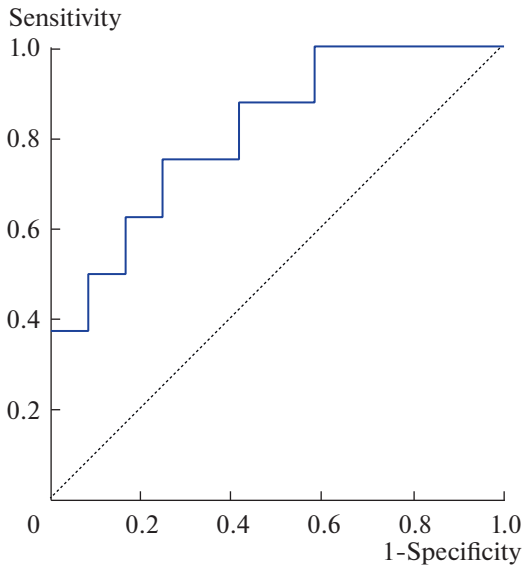

Fig. 7. *ROC* curve of a test designed to predict postpericardiotomy syndrome.

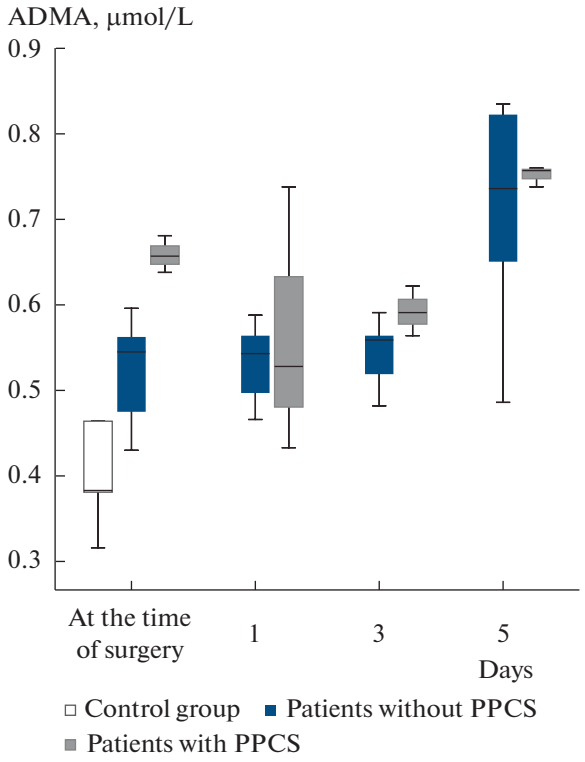

Fig. 8. ADMA content in the plasma of IHD patients after CABG. * Statistically significant differences compared with the control group, $p < 0.05$; ** statistically significant differences between patients with postpericardiotomy syndrome and patients without it.

Dimethylarginine dimethylaminohydrolases (DDAH) play the main role in its utilization. The development of oxidative stress that occurs in response to surgical trauma, the introduction of protamine, and anesthesia inhibit DDAH and lead to an increase in ADMA concentration [28, 29]. D. Plicner et al. in their study also noted an increase in the ADMA concentration in patients undergoing CABG from the time of surgery to day 7 after surgery [20]. It was proven that a high ADMA level can serve as a predictor of postoperative complications [20]. In the present study, a direct correlation was found between the arginase activity in erythrocytes and the ADMA content in the plasma of patients without PPCS ($R = 0.7$, $p < 0.05$). An inverse correlation was revealed between the arginase activity in red blood cells and the PON aryl esterase activity in blood plasma in Group 1 patients ($R = -0.87$, $p < 0.05$) and Group 2 ($R = -0.91$, $p < 0.05$). In a study by T. Bayrak et al., it was shown that an increase in the ADMA content was accompanied by a decrease in PON activity [7].

Despite the high arginase activity and an excessive ADMA level in IHD patients who underwent CABG, we observed in the present study an increase in the content of nitrites/nitrates in the blood plasma over the entire observation period. The NO*x* level was increased by 73–83% in the blood plasma of Group 1 patients; in Group 2, it exceeded the control values by 67–104% over the entire observation period. It reached the maximum values at the time of surgery in patients of both groups. The formation of an increased level of peroxynitrite, the enhancement of oxidative-nitrosyl stress, and an increased risk of cardiovascular complications occur against the background of excessive NO$^{\cdot}$ production [17]. Arginase is known to compete with *NOS* for *L*-arginine and is thus able to regulate NO$^{\cdot}$ production. However, the K_m of arginase is significantly higher (>1 mmol/L) than the K_m of *NOS* (from 2 to 20 μmol/L); therefore, direct competition for the substrate is unlikely in this case. However, the induced NO synthase is able to nitrosylate arginase-cysteine residues, reducing its K_m and increasing its competitiveness. L. Santhanam et al. showed that the inhibition of endothelial NO synthase and the development of endothelial dysfunction occur upon an increase in the activity of both enzymes [23]. Proinflammatory cytokines such as *IL*-1β and *TNF*-α stimulate the expression of induced *NOS* [22]. It is also known that the induced *NOS* isoform is less susceptible to inhibition by ADMA than endothelial and neuronal *NOS*. Therefore, it can be assumed that the induced NO synthase makes the main contribution to an increase in the NO$^{\cdot}$ level upon the development of a systemic inflammatory response [30].

CONCLUSIONS

A close relationship between inflammation and endothelial dysfunction in IHD patients after direct myocardial revascularization has been revealed. It was shown that activation of the proinflammatory myeloperoxidase enzyme is accompanied by inhibition of the aryl esterase activity of the anti-inflammatory enzyme paraoxonase in plasma and pericardial fluid in patients with coronary artery disease undergoing CABG. The ratio of myeloperoxidase activity and paraoxonase aryl esterase activity in plasma and pericardial fluid is a predictor of the development of postpericardiotomy syndrome. An increase in the level and activity of mediators of endothelial dysfunction, asymmetric dimethylarginine, and arginase was found in blood plasma and red blood cells in IHD patients after CABG. The arginase activity and ADMA concentration are higher in red blood cells and blood plasma in patients with postpericardiotomy syndrome than in patients without it. An inverse correlation of arginase activity and aryl esterase activity of paraoxonase was revealed. The ratio of arginase to paraoxonase activity can be used to predict the development of postpericardiotomy syndrome. An increase in the concentration of stable metabolites of nitric oxide, nitrites, and nitrates in the blood plasma was found in patients of both groups, which may be associated with

excessive activation of inducible NO synthase due to the development of inflammation.

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COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests. The authors declare that they have no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants involved in the study.

REFERENCES

1. Golikov, P.P. and Nikolaeva, N.Yu., Determination of nitrite/nitrate (NOx) in blood serum, *Vopr. Biomed. Khim.*, 2004, no. 1, pp. 79–83.
2. Kolb, V.G. and Kamyshnikov, V.S., *Spravochnik po klinicheskoi khimii* (Handbook on Clinical Chemistry), Minsk: Belarus', 1982, pp. 290–292.
3. Saidov, M.Z. and Pinegin, B.V., Spectrophotometric determination of myeloperoxidase in phagocytic cells, *Lab. Delo*, 1991, no. 3, pp. 56–59.
4. Shumakov, K.V., Lefterova, N.P., Pak, N.L., et al., Coronary artery bypass in conditions of artificial blood circulation and on open heart: a comparative analysis of the immediate and long-term results and postoperative complications (cardiac arrhythmias, cognitive and neurological disorders, rheological features, and the state of the homeostasis system), *Kreativn. Kardiol.*, 2009, no. 1, pp. 28–50.
5. Alam, S.R., Lewis, S.C., Zamvar, V., et al., Perioperative elafin for ischaemia-reperfusion injury during coronary artery bypass graft surgery: a randomized-controlled trial, *Heart*, 2015, vol. 101, no. 20, pp. 1639–1645.
6. Aviram, M., Introduction to paraoxonases, *J. Lipids*, 2012, vol. 2012, pp. 1–2.
7. Bayrak, T., Bayrak, A., Işıldak, M., et al., Increased asymmetric dimethylarginine (ADMA) levels and decreased homocysteine thiolactonase/paraoxonase (HTLase/PONase) activities are related to the risk of cardiovascular disease in prediabetic/diabetic patients, *Turk. J. Biochem.*, 2014, vol. 39, no. 3, pp. 270–276.
8. Brener, S., Frequency and long-term impact of myonecrosis after coronary stenting, *Eur. Heart J.*, 2002, vol. 23, pp. 869–876.
9. Butts, B., Goeddel, L.A., George, D.J., et al., Increased inflammation in pericardial fluid persists 48 hours after cardiac surgery, *Circulation*, 2017, vol. 136, pp. 2284–2286.
10. Emami Razavi, E.A., Basati, G., Varshosaz, J., et al., Association between HDL particles size and myeloperoxidase/paraoxonase-1 (MPO/PON1) ratio in patients with acute coronary syndrome, *Acta Med. Iran.*, 2013, vol. 51, no. 6, pp. 365–371.
11. Gad, M.Z., Abdel-Maksoud, S.M., Hassanein, S.I., et al., Nitric oxide regulating proteins as biochemical and genetic markers of coronary artery disease, in *Biomarkers in Cardiovascular Disease,* Patel, V.B. and Preedy, V.R., Eds., Dordrecht: Springer-Verlag, 2016, pp. 1–27. https://doi.org/10.1007/978-94-007-7741-5_34-1
12. Hernandez, A.F., Pla, A., Valenzuela, A., et al., Paraoxonase activity in human pericardial fluid: its relationship to coronary artery disease, *Int. J. Leg. Med.*, 1993, vol. 105, pp. 321–324.
13. Huang, Y., Wu Z., Riwanto M., et al., Myeloperoxidase, paraoxonase-1, and HDL form a functional ternary complex, *J. Clin. Invest.*, 2013, vol. 123, no. 9, pp. 3815–3828.
14. Hueb, W., Lopes, N.H., Gersh, B.J., et al., Five-year follow-up of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease, *Circulation*, 2007, vol. 115, no. 9, pp. 1082–1089.
15. Keshari, R.S., Jyoti, A., Dubey, M., Kothari, N., et al., Cytokines induced neutrophil extracellular traps formation: implication for the inflammatory disease condition, *PLoS One*, 2012, no. 7, pp. 48111–48118.
16. Kilic, S.S., Aydin, S., Kilic, N. Serum arylesterase and paraoxonase activity in patients with chronic hepatitis, *World J. Gastroenterol.*, 2005, vol. 11, pp. 7351–7354.
17. Li, H. and Förstermann, U., Uncoupling of endothelial NO synthase in atherosclerosis and vascular disease, *Curr. Opin. Pharmacol.*, 2013, vol. 13, no. 2, pp. 161–167.
18. Loria, V., Dato, I., Graziani, F., et al., Myeloperoxidase: a new biomarker of inflammation in ischemic heart disease and acute coronary syndromes, *Mediators Inflammation*, 2008, vol. 2008, pp. 1–4.
19. Nguyen, S.D. and Sok, D.E., Oxidative inactivation of paraoxonase1, an antioxidant protein and its effect on antioxidant action, *Free Radical Res.*, 2003, vol. 37, no. 12, pp. 1319–1330.
20. Plicner, D., Mazura, P., Sadowski, J., et al., Asymmetric dimethylarginine and oxidative stress following coronary artery bypass grafting: associations with postoperative outcome, *Eur. J. Cardio-Thoracic Surg.*, 2014, vol. 45, pp. 1–6.
21. Preeshagul, I., Gharbaran, R., Jeong, K.H., et al., Potential biomarkers for predicting outcomes in CABG cardiothoracic surgeries, *J. Cardiothorac. Surg.*, 2013, vol. 8, no. 176, pp. 1–12.

22. Rath, M., Müller, I., Kropf, P., et al., Metabolism via arginase or nitric oxide synthase: two competing arginine pathways in macrophages, *Front. Immunol.*, 2014, vol. 5, no. 532, pp. 1–10.

23. Santhanam, L., Lim, H.K., Lim, H. K., et al., Inducible NO synthase dependent S-nitrosylation and activation of arginase1 contribute to age-related endothelial dysfunction, *Circ. Res.*, 2007, vol. 101, pp. 692–702.

24. Schindhelm, R.K., Zwan, L.P., Teerlink, T., et al., Myeloperoxidase: a useful biomarker for cardiovascular disease risk stratification? *Clin. Chem.*, 2009, vol. 55, no. 8, pp. 1462–1470.

25. Schlüter, K.-D., Schulz, R., and Schreckenberg, R., Arginase induction and activation during ischemia and reperfusion and functional consequences for the heart, *Front. Physiol.*, 2015, vol. 6, no. 65, pp. 1–8.

26. Sibal, L., Agarwal, S.C., Home, P.D., et al., The role of asymmetric dimethylarginine (ADMA) in endothelial dysfunction and cardiovascular disease, *Curr. Cardiol. Rev.*, 2010, vol. 6, no. 2, pp. 82–90.

27. Simundic, A.M., Diagnostic accuracy—Part 1 Basic concepts: sensitivity and specificity, ROC analysis, STARD statement, *Point Care*, 2012, vol. 11, pp. 6–8.

28. Sydow, K. and Böger, R.H., Reloaded: ADMA and oxidative stress are responsible for endothelial dysfunction in hyperhomocyst(e)inaemia: effects of L-arginine and B vitamins, *Cardiovasc. Res.*, 2012, vol. 96, pp. 167–171.

29. Trocha, M., Merwid-Ląd, A., Szuba, A., et al., Effect of selected drugs on plasma asymmetric dimethylarginine (ADMA) levels, *Adv. Clin. Exp. Med.*, 2010, vol. 19, no. 2, pp. 233–243.

30. Vanhoutte, P.M., Shimokawa, H., and Tang, E.H.C., Endothelial dysfunction and vascular disease, *Acta Physiol.*, 2009, vol. 196, pp. 193–222.

31. Wysocka, A., Cybulski, M., Berbe, H., et al., Prognostic value of paraoxonase 1 in patients undergoing coronary artery bypass grafting surgery, *Med. Sci. Monit.*, 2014, vol. 11, no. 20, pp. 594–600.

32. Yang, Z. and Ming, X.-F., Arginase: the emerging therapeutic target for vascular oxidative stress and inflammation, *Front. Immunol.*, 2013, vol. 4, pp. 1–11.

33. Zhu, C., Yu, Y., Montani, J.-P., et al., Arginase-I enhances vascular endothelial inflammation and senescence through eNOS-uncoupling, *BMC Res. Notes*, 2017, vol. 10, no. 82, pp. 1–8.

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