Semenova P. A., Nevzorova V. A., Plekhova N. G., Chernenko I. N., Potapova E. S., Ivanchuk U. S.
Pacific State Medical University, Vladivostok, Russia

Markers of redox potential of blood leukocytes in acute coronary syndrome, depending on the presence of type 2 diabetes mellitus

Aim	Evaluating the redox potential of white blood cells (WBC) in acute coronary syndrome (ACS) depending on the presence or absence of type 2 diabetes mellitus (DM2).
Material and Methods	The study included 100 men and women aged 35 to 65 years who were managed for ACS at the Primary Vascular Department (PVD) of the Vladivostok Clinical Hospital #1. The control group consisted of 30 healthy volunteers matched with ACS patients in major anthropometric characteristics. Examinations were performed according to clinical recommendations. Blood was withdrawn for measuring cell activity of enzymes (superoxide dismutase, SOD; succinate dehydrogenase, SDH; and glutathione reductase, GR) and serum concentration of malonic dialdehyde (MDA). Based on the ACS type, all patients were divided into 3 main ACS groups, and then the groups were subdivided into subgroups based on the presence of DM2.
Results	Development of ACS was associated with changes in WBC redox potential. These changes were characterized by a significant decrease in SDH activity in all ACS patients, irrespective of their ACS type, and a moderate decease in GR in patients with myocardial infarction compared to patients with unstable angina and healthy volunteers. At the same time, the SOD activity and MDA concentration were practically unchanged compared to the control group. There were practically no significant differences in the enzyme activities between the ACS subgroups with or without DM2.
Conclusion	The WBC activities of SDH and GR on day 1 of ACS can be considered as the indicators for early diagnosis of mitochondrial dysfunction resulting from the cardiovascular catastrophe as well as the markers for impaired primary cell defense. MDA and SOD values are not informative for determining the intensity of oxidative stress and further damage of the antioxidant system.

Keywords	Acute coronary syndrome; ST-segment elevation myocardial infarction; non-ST-segment elevation myocardial infarction; unstable angina; mitochondrial dysfunction; type 2 diabetes mellitus
For citations	Semenova P.A., Nevzorova V.A., Plekhova N.G., Chernenko I.N., Potapova E.S., Ivanchuk U.S. Markers of redox potential of blood leukocytes in acute coronary syndrome, depending on the presence of type 2 diabetes mellitus. Kardiologiia. 2023;63(5):33–39. [Russian: Семенова П.А., Невзорова В.А., Плехова Н.Г., Черненко И.Н., Потапова Е.С., Иванчук Ю.С. Маркеры окислительно-восстановительного потенциала лейкоцитов крови при остром коронарном синдроме в зависимости от наличия сахарного диабета 2-го типа. Кардиология. 2023;63(5):33–39].

Corresponding Author	Semenova P. A. E-mail: polina.selyukova@gmail.com

Introduction

Circulatory system diseases (CSDs) continue to lead among causes of death of the population and do not up give their leading positions even during the COVID-19 pandemic. Through the active implementation of organizational measures intended for prompt diagnosis, routing, early application of invasive interventions, and compliance with recommended approaches to treatment and secondary prevention, the mortality of patients with acute coronary syndrome (ACS) was stabilized in the Russian Federation over the past ten years [1]. At the same time, ACS remains the most common type of the onset of coronary artery disease (CAD) in the Russian Federation, as in the rest of the world, and subsequently contributes the most to cardiovascular remodeling, early vascular aging, and heart failure. The combination of CSD and type 2 diabetes mellitus (DM) is a hallmark of the modern adult population, and it considerably accelerates the processes of atherosclerosis and cardiovascular dysfunction [2]. Among the existing models for predicting the outcomes of CAD in combination with type 2 DM, attention is drawn to the state of mitochondria, violated biology of which contribute significantly to the reduction and loss of energy potential of the cells and can be considered the ground zero of premature cardiovascular aging [3, 4]. Among the available and informative markers of the state of mitochondrial biogenesis, of active interest is the evaluation of the levels of intracellular enzymes dependent on the processes of ischemia and reperfusion in ACS.

Malondialdehyde (MDA) is a well-studied indicator of oxidative stress (OS) and lipid peroxidation products

(LPP) of cell membranes [5]. Excessively accumulated MDA has an active mutagenic potential, which can be inverted by enzymes of effective intracellular antioxidant protection (AOP) [6]. Specifically, glutathione reductase (GR) is one of the main AOP enzymes that protect from the damaging effect of hydrogen peroxide in OS [7]. GR restores the disulfide bond of oxidized glutathione with the participation of nicotinamide adenine dinucleotide phosphate (NADPH) [8]. Superoxide dismutase (SOD) is an equally important protective enzyme acting against the damaging effects of reactive oxygen species (ROS). SOD catalyzes the dismutation of oxygen superoxide into oxygen and hydrogen peroxide, inhibits the LPP process, protecting the vascular endothelium and reducing the atherogenic effect of ROS [9, 10]. Succinate dehydrogenase (SDH) another significant element in maintaining mitochondrial balance of the cell in ischemia. It which belongs to the protein complex of the mitochondrial inner membrane and is engaged in the Krebs cycle and respiratory electron transport chain [11].

Evaluating the redox potential of white blood cells (WBCs) in patients with ACS of various forms and with or without type 2 DM can be considered as a promising approach to the identification of the most significant prognostic markers of cell damage in ischemia for the subsequent construction of prognostic models for the course of ACS and the development of the best possible prevention measures.

Objective

Assess of the redox potential of WBCs in ACS depending on the presence and absence of type 2 DM.

Material and Methods

The study included 100 male and female patients from 35 to 65 years old who were treated in the Department of Vascular Surgery of Vladivostok Clinical Hospital No. 1 (Vladivostok, Russian Federation). Newly diagnosed ACS without ST segment elevation (NSTE-ACS) and/or with ST segment elevation (STE-ACS) with or without newly diagnosed type 2 DM with a less than 5-year history were the main inclusion criteria. More than 5-year history of type 2 DM, type 1 DM, a history of ACS, acute cerebrovascular accident, a history of coronary interventions, documented chronic kidney disease stage 4 and higher, peripheral arterial disease, cancer of any duration, and severe liver diseases were the exclusion criteria.

The control group consisted of 30 healthy individuals with anthropometric characteristics comparable to the main patient group. All subjects signed an informed consent form allowing the use of anonymously obtained data. The study was approved by the Ethics Committee of Pacific State Medical University (Vladivostok, Russian Federation; Minutes No. 17 dated March 15, 2021).

All patients underwent general clinical examinations used in the diagnosis of ACS, including invasive coronary angiography. Blood sampling for biochemical analysis was performed in the fasting state using standard laboratory methods. Blood lipid parameters were evaluated using Mindray kits on the Mindray BC-120 analyzer. Total cholesterol (TC) and triglycerides (TG) were measured by enzyme photometric methods, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol by direct methods; glucose by glucose oxidase method; alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by kinetic methods, creatinine and urea by colorimetric method, troponin I by chemiluminescent microparticle immunoassay.

The activity of cell mitochondrial enzymes and the content of MDA were assessed using blood samples collected in the fasting state from the cubital vein in tubes containing dry clot activator and ethylenediaminetetraacetic acid using vacuum systems on day 1 of the hospital treatment. WBCs were isolated by centrifugation for 30 min at 1800 rpm with the selection of the resulting cell layer, RBCs were removed using a lysis solution. The resulting cells were washed twice with versene solution, centrifuged at 1800 rpm, and adjusted to 2×10^6 cells/mL, after which they were lysed by freezing at –20°C. Enzymes providing WBC redox potential were isolated by centrifugation at 15000 g for 15 min, and the resulting precipitate was resuspended in cold HEPES buffer.

Serum MDA was determined by the reaction with thiobarbituric acid using the Lipid Peroxidation Assay Kit. The resulting product was determined by colorimetry (wavelength 532 nm). SOD was determined in WBC lysate using the Superoxide Dismutase Assay Kit; the enzyme's ability to process the superoxide produced by the reaction of hypoxanthine with xanthine oxidase was also assessed. Reduced tetrazolium salts were converted to formazan, the content of which was determined by colorimetry at a wavelength of 600 nm. SDH activity in cell lysate was detected using the Succinate Dehydrogenase Assay Kit and evaluated by the enzyme's ability to convert succinate to fumarate, as a result of which tetrazolium salts were reduced to formazan, the content of which was analyzed by colorimetry at a wavelength of 440 nm. GR was detected using the Glutathione Reductase Assay Kit, in which GR reduced oxidized glutathione reacting with 5,5' – dithiobis-2 nitrobenzoic acid to form a yellow compound, the activity of which was measure at a wavelength of 405 nm.

The data obtained were processed using StatTech v. 2.7.1. Categorical data were expressed by the absolute values and percentages, quantitative variables were

ISSN 0022-9040. Kardiologiia. 2023;63(5). DOI: 10.18087/cardio.2023.5.n2389

presented using the medians (Me) and the lower and upper quartiles [Q1; Q3]. Quantitative variables were compared between two groups using the Mann-Whitney U-test. The direction and tightness of the correlations between two quantitative variables were evaluated using the Spearman's rank coefficient of correlation (ρ). The critical value of significance (p) was set to 0.05.

Results

The clinical and laboratory findings in ACS and control patients are presented in Table 1.

The presented data show that ACS and control patients were not significantly different in age, sex composition, and BMI (p>0.05). The analysis the findings in patients with ACS showed that patients with type 2 DM were older (p<0.001), and there were more female patients among (55.1% versus 13.7%; p < 0.001).

All patients with ACS had significantly higher SBP compared to the control group, however, it not exceed the recommended values in most cases. At hospitalization, 35 patients had elevated SBP within the range of arterial hypertension (AH) grade 1, blood pressure normalized during hospital treatment. Moreover, DBP was higher (<90 mm Hg in all cases) in the general group of ACS patients and in the subgroup of patients without DM than in the control group. Higher levels of urea and creatinine were established further in several patients with ACS compared to the control group, which were within the range of recommended values. Glucose levels determined at hospitalization were also higher irrespective of food intake in ACS compared to the control group, but they were within the range of recommended values for patients without type 2 DM. Glucose levels were predictably statistically significantly higher in patients with type 2 DM. AST was higher in the ACS group than in the control group irrespective of the presence and absence of type 2 DM, and was also not beyond the recommended values. TC, LDL cholesterol, and TG were predictably higher in all patients with ACS than in the control group, which is associated with instable course of atherosclerosis.

Depending on the clinical form of ACS, all patients were divided into 3 subgroups: patients with unstable angina (UA), patients with non-ST-segment elevation myocardial infarction (NSTEMI), and patients with ST-segment elevation myocardial infarction (STEMI). According to the results presented in Table 2, a statistically significant

Table 1. Clinical and laboratory findings in ACS and control patients

Parameter	Control group (n = 30)	General group of ACS patients		
		All patients (n = 100)	Patients with DM type 2 (n = 49)	Patients without DM type 2 (n = 51)
Age, years	58 [43; 62]	61 [53; 64]	63 [56; 64] p_2<0,001	58 [51; 63]
Female, %	50	31.8	55.1 p_2 < 0.001	13.7 p_3 < 0.001
BMI, kg/m^2	24 [23; 27]	25 [23; 27]	25 [23; 32]	24 [23; 26]
SBP, mm Hg	115 [110; 124]	130 [120; 140] p_1 < 0.001	130 [125; 140] p_2<0,001	135 [116; 144] p_3<0,001
DBP, mm Hg	70 [65; 75]	75 [70; 85] p_1 = 0.019	75 [70; 80]	78 [70; 85] p_3 = 0.032
HR, bpm	66 [60; 74]	68 [64; 72]	69 [62; 76]	66 [62; 70]
Creatinine, μmol/L	82 [71.02; 96.0]	75 [70.0; 79.75] p_1 = 0.006	84 [70.0; 97.0] p_2 = 0.032	79.5 [70.5; 93.75] p_3 = 0.032
Urea, mmol/L	2.85 [2.52; 3.55]	6.50 [5.40; 8.30] p_1 < 0.001	7.40 [5.95; 9.0] p_2 < 0.001; p_4 = 0.018	6.15 [4.90; 7.15] p_3<0,001
Glycemia, mmol/L	5.35 [4.53; 5.78]	6.10 [5.50; 7.70] p_1 < 0.001	8.1 [5.8; 10.8] p_2 < 0.001; p_4 < 0.001	5.8 [5.30; 6.57] p_3 = 0.008
ALT, U/L	30 [27; 33]	27 [18; 39]	28 [18; 41]	27 [18; 39]
AST, U/L	20 [19; 23]	27 [20; 38] p_1 < 0.001	28 [20; 38] p_2<0,001	27 [20; 36] p_3 < 0.001
TC, mmol/L	3.47 [2.31; 4.30]	5.20 [4.30; 5.47] p_1 < 0.001	6.10 [4.78; 7.22] p_2 < 0.001	5.62 [4.71; 6.58] p_3 = 0.006
LDL cholesterol, mmol/L	3.47 [2.31; 4.30]	2.75 [2.40; 3.0] p_1 < 0.001	3.5 [2.14; 4.45] p_2 = 0.038	3.42 [2.56; 4.18] p_3 = 0.038
TG, mmol/L	0.95 [0.88; 1.08]	1.38 [1.10; 1.90] p_1 < 0.001	1.59 [1.16; 1.94] p_2<0,001	1.29 [1.09; 1.77] p_3 < 0.001
Troponin I, ng/mL	–	2.30 [0.01; 7.60]	2.8 [0.01; 10.10]	1.9 [0.01; 6.2]

BMI, body mass index; p_1 – general group of ACS patients versus the control group; p_2 – ACS patients with DM type 2 versus the control group; p_3 – ACS patients without DM type 2 versus the control group; p_4 – ACS patients with DM type 2 versus ACS patients without DM type 2.

Table 2. WBC enzyme activity and MDA levels in ACS and control patients

Parameter	Control group (n = 30)	General group (n = 100)	UA (n = 36)	STEMI (n = 37)	NSTEMI (n = 27)
SDH, μmol/L	8.89 [8.6; 11.08]	1.2 [1.0; 1.3] $p_1 < 0.001$	1.2 [1.07; 1.4] $p_2 < 0.001$	1.13 [0.99; 1.3] $p_3 < 0.001$	1.13 [0.99; 1.3] $p_4 < 0.001$
GR, μmol/L	3.60 [2.8; 3.9]	2.78 [2.3; 2.9] $p_1 = 0.003$	2.86 [2.7; 3.2]	2.73 [2.09; 2.8] $p_3 = 0.004$	2.75 [2.4; 2.9] $p_4 = 0.020$
SOD, μmol/L	56.21 [21.7; 75.8]	24.36 [15.4; 58.3]	24.3 [17.9; 58.3]	20.5 [15.4; 58.3]	33.02 [16.9; 58.3]
MDA, μmol/L	278.1 [155.1; 502.6]	261.5 [253.3; 310.5]	217.0 [165.3; 719.8]	278.6 [150.7; 393.8]	312 [161.9; 474.8]

p_1 – general group of ACS patients versus the control group; p_2 – patients with UA versus the control group;
p_3 – STEMI patients without versus the control group; p_4 – NSTEMI patients versus the control group.

decrease in the SDH levels was found in both the general ACS group and in all three subgroups compared to the control group. Reduced SDH is indicative of abnormal oxidative cell metabolism in ischemia due to the excessive need for the activation of respiratory electron transport chain.

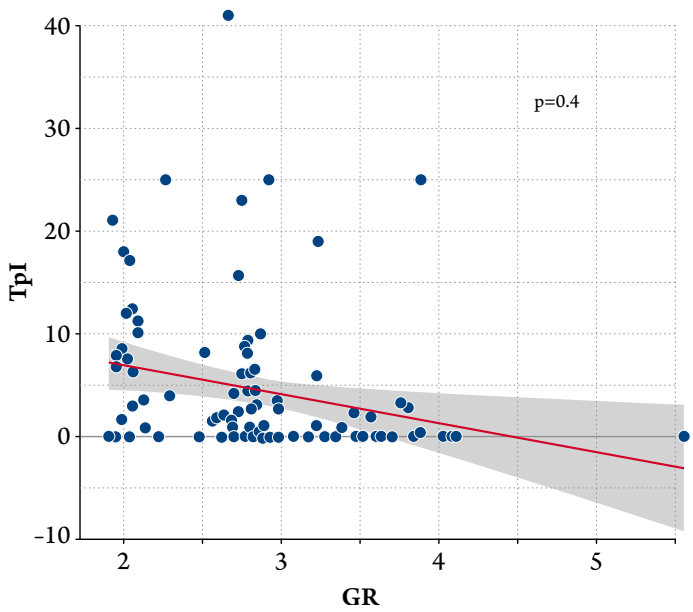
Moreover, a significant decrease in GR was found patients with NSTEMI and STEMI and the general ACS group compared to the control group (p=0.003; p=0.004, and p=0.020, respectively). This is obviously due to the accumulation of ROS in WBCs as a result of the damaging effects of oxidized glutathione being the main substrate for GR activity. At the same time, the activity of GR did not differ in patients with UA and without myocardial necrosis from the control group. According to the results obtained, MDA and SOD activity did not differ between different ACS subgroups and the control group.

There were no differences in the activity of SDH, GR, SOD, and MDA between subgroups of ACS patients with and without type 2 DM. Based on the data obtained, we were interested in assessing the relationships between the indicators of GR activity and the troponin I (TpI) levels (Figure 1). Significant inverse correlation was established between higher levels of TpI and reduced GR. A 2.8 ng/mL increase in the TpI levels is a predictor of a 1 μmol/mL decrease of GR in WBCs (ρ=0.4; p<0.001). Hence, a decrease in the GR activity can be used as an additional marker of myocardial necrosis in the differential diagnosis of AU and MI.

We also analyzed correlation between the SDH activity and the levels of TpI (Figure 2). According to the data obtained, a 0.4 ng/mL increase in the TpI levels is a predictor of a 1 μmol/mL decrease of SDH in WBCs (ρ=0.45; p<0.001). The indicators of reduced activity of SDH do not allow differentiating forms of ACS but can be used as a general marker of unstable course of CAD.

No statistically significant correlation was found between the TpI levels and the MDA and SOD indicators (ρ=0.046; p>0.05 and ρ=0.166; p>0.05). Hence, the indicators of WBC redox potential dysfunction in tissue ischemia are differentially associated with the development of ACS. First, the activity of the main enzymes of mitochondrial respiratory chain, which is engaged in the process of oxidative phosphorylation, changes. Oxidoreductase enzyme GR catalyzes NADPH-dependent reduction of oxidized glutathione, protects the cell from toxic free radicals, and determines the cytoplasm redox potential. GR activity is engaged in the body's defense mechanisms against ROS products, specifically hydrogen peroxide and organic peroxides. Reduced GR activity turned out to be a more specific marker of necrosis. At the same time, a decrease in the SDH activity should be considered as an indicator of ischemia irrespective of the ACS form. SOD activity and MDA levels on day 1 of ACS does not differ from the control group, which may show the balance between OS and AOP, on the one hand, and, on the other hand, necessitate their estimation in other terms of the disease course, possibly earlier after the onset of ACS.

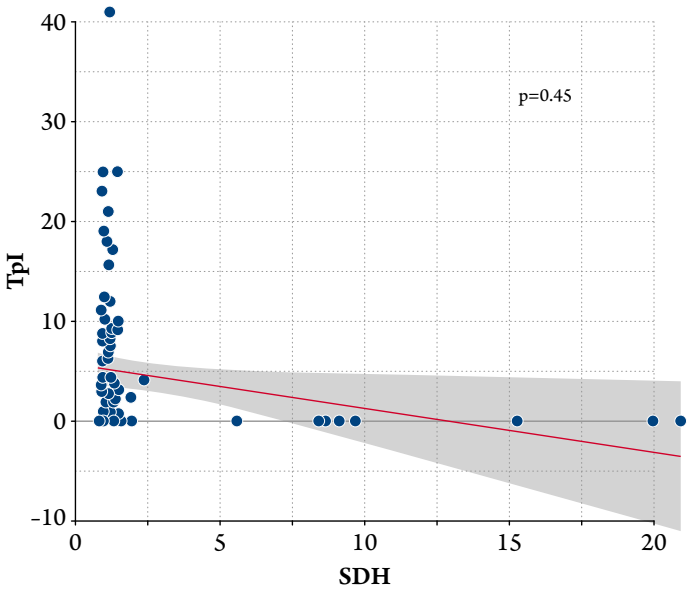
Figure 1. Regression function graph characterizing the dependence of TpI levels in ng/mL (Y axis) on the levels of GR in μmol/mL (X axis) in patients with MI



GR, glutathione reductase

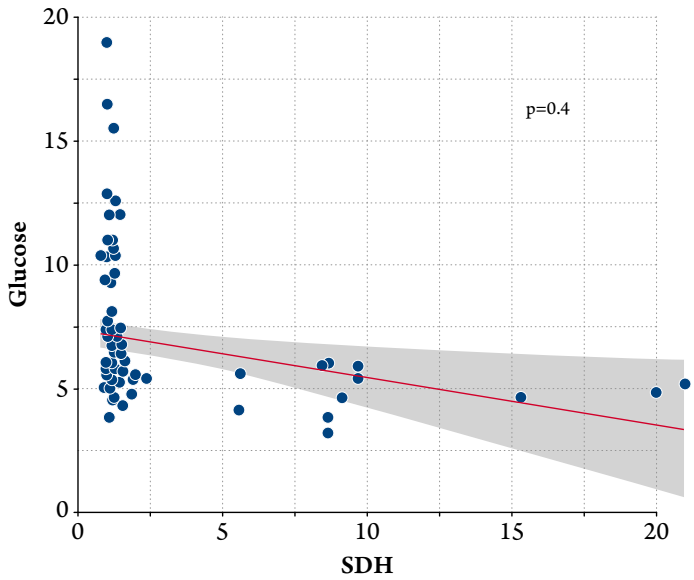
ISSN 0022-9040. Kardiologiia. 2023;63(5). DOI: 10.18087/cardio.2023.5.n2389

Figure 2. Regression function graph characterizing the dependence of TpI levels in ng/mL (Y axis) on the SDH levels in μmol/mL (X axis) in patients with ACS



SDH, succinate dehydrogenase

Figure 3. Regression function graph characterizing the dependence of blood glucose levels in mmol/L (Y axis) on the SDH levels in μmol/mL (X axis) in patients with ACS



SDH, succinate dehydrogenase

Given the active involvement of glucose in the mitochondrial biogenesis, we studied the correlation between the glucose levels and WBC redox potential. Statistically significant inverse correlation was established between SDH activity and blood glucose levels (Figure 3).

Given the results obtained, a 1 μmol/mL decrease in SDH is a predictor of the need for a 0.2 mmol/L increase in glucose level (ρ=0.4; $p<0.001$). Thus, the adequate functioning of the mitochondrial respiratory chain controlled in ischemic conditions by the SDH activity requires higher glucose levels in ACS, which reflects violated energy conversion processes and can be further used as a predictor the disease outcome. Other intracellular enzymes of interest did not show statistically significant correlation with glucose levels: GR (ρ=0.221; $p>0.05$), SOD (ρ=0.192; $p>0.05$), MDA (ρ =0.197; $p>0.05$).

Discussion

The idea of a significant contribution of OS in the pathogenesis of ACS, and MI in particular, was formulated at the very end of the last century [12–15]. There are studies that prove that the progression of atherosclerosis directly depends on the increased production of ROS [16–19]. Excess of ROS in cell and tissue ischemia followed by reperfusion and reoxygenation may be associated with low antioxidant activity of the cells. It was of interest to assess the levels of enzymes of mitochondrial respiratory chain of WBCs on day 1 of ACS and monitor the dependence of AOP on the presence or absence of type 2 DM, the levels of myocardial damage markers and blood levels of glucose. The data obtained are partially consistent with the findings of other researchers showing close correlation between the activation of the production of LPP products in response to the development of ACS and reduced AOP of the body [20–22].

Among the indicators of enzymes involved in the regulation of WBC redox potential, the determination of SDH activity plays an important role due to the significant difference between its activity in healthy volunteers and patients with ACS. There was an almost 9 fold decrease in SDH activity in all patients with ACS, both in the general group and in all subgroups (UA, NSTEMI, and STEMI) compared to the control group. Given close inverse correlation between the levels of TpI and SDH activity, further research of the role of SDH in predicting ACS outcomes is expected.

The levels of GR activity were significantly lower in patients with MI than in healthy individuals. At the same time, GR did not differ between patients with UA and the control group. Hence, the activity of GR can be considered as a criterion for the diagnosis of myocardial necrosis as early as on day 1 of ACS. There was no difference between the activity of MDA and SOD in healthy individuals and patients with ACS. There are several studies that show an increase in the levels of MDA and a decrease in the SOD activity in patients with documented MI in the first hours after hospitalization compared to the control group and the correlation of their changes and some indicators included in the GRACE score (disease severity, smoking, and age over 45 years) [20]. The absence of differences in

the levels of MDA and SOD may be associated with blood sampling on day 1 of hospital treatment and the emergency interventions at the pre-hospital and early hospital stages. Uppal et al. [21] established the correlation in the changes in MDA and GR in ACS and the administration of acetylsalicylic acid, P2Y12 receptor antagonists, and enoxaparin before hospitalization.

Elevated glucose is required in response to the development of ischemia in ACS for the cell energy supply. According to our findings, SDH is the enzyme most sensitive to the intracellular energy state. At the same time, GR and SOD activity and MDA are not correlated with glucose levels. In the study by Deepa et al. [22], SOD and GR activity was lower in patients with MI and type 2 DM than in MI patients without type 2 DM. Unlike our findings, higher levels of TpI were observed in patients with type 2 DM. Established differences may be related to this fact, since according to our data, there GR and TpI levels are correlated. Hence, the AOP system tension, the marker of which is GR, depends on the levels of myocardial necrosis markers. Noteworthy is the established relation between lower activity of SDH and elevated glucose levels. More sensitive markers of mitochondrial dysfunction are obviously necessary for patients with ACS and DM. In our previous unpublished findings, there were sharp differences in the WBC mitochondrial potential in patients with ACS and type 2 DM and patients without DM.

Conclusion

After analyzing the state of enzymes involved in the regulation of WBC redox potential, two main enzymes were identified that are associated with the development of ACS. The activity of SDH decreases most irrespective of the clinical form of ACS. SDH plays a leading role in the regulation of intracellular redox potential, participates in the conversion of intracellular energy, and is the main regulator of the respiratory chain state and the Krebs cycle. The degree of a decrease in GR activity in WBCs as the main enzyme of cell protection against AOP and ROS in myocardial ischemia is less than that of SDH but is closely correlated with TpI levels. Hence, the determination of GH activity can be an additional criterion for the diagnosis of myocardial necrosis both as a result of the detection of this correlation and as a result of its significant decrease in documented infarction.

Thus, SDH and GH in WBCs within the first 24 hours of ACS can be considered as promising indicators for assessing the dysfunction of intracellular redox potential of WBCs. The activity of SOD, the main mitochondrial enzyme that prevents the dismutation of free oxygen species and inhibits the processes of AOP and proteins, does not differ significantly between ACS and control patients. Moreover, there is no difference in the levels of MDA in healthy individuals and patients with ACS, which can be explained by the time window between blood sampling (day 1, not within few hours) and therapeutic interventions at the pre-hospital and early hospital stages. According to the data obtained, there are no differences in the indicators of WBC redox potential in ACS patients with and without type 2 DM. This proves the universality of the response of WBC enzymes involved in the regulation of intracellular redox potential to the onset of ACS. Based on the literature and our preliminary findings, it is argued that it is necessary to study indicators directly related to the mechanisms of regulation of the energy potential of mitochondria in order to establish a hypothetical difference in the response to a vascular accident in the presence of DM.

Funding

No funding was received for this study.

No conflict of interest is reported.

The article was received on 10/12/2022

REFERENCES

1. Bogdanov D.Yu., Kondrashova E.A., Kulakova N.V., Shestakova N.V., Mokshina M.V., Martynenko I.M. Risk factors` characteristics of cardiovascular diseases in the population of Primorsk region residents depending on the status of smoking and age (according to the data of the epidemiological study of ESSE-RF). Pacific Medical Journal. 2017;4(70):45–50. [Russian: Богданов Д.Ю., Кондрашова Е.А., Кулакова Н.В., Шестакова Н.В., Мокшина М.В., Мартыненко И.М. Характеристика факторов риска сердечно-сосудистых заболеваний в популяции жителей Приморского края в зависимости от статуса курения и возраста (по данным эпидемиологического исследования ЭССЕ-РФ). Тихоокеанский Медицинский Журнал. 2017;4(70):45-50]. DOI: 10.17238/PmJ1609-1175.2017.4.45-50
2. Yuan M-J, Pan Y-S, Hu W-G, Lu Z-G, Zhang Q-Y, Huang D et al. A pilot study of prognostic value of non-invasive cardiac parameters for major adverse cardiac events in patients with acute coronary syndrome treated with percutaneous coronary intervention. International Journal of Clinical and Experimental Medicine. 2015;8(12):22440–9. PMID: 26885226
3. Giordano FJ. Oxygen, oxidative stress, hypoxia, and heart failure. Journal of Clinical Investigation. 2005;115(3):500–8. DOI: 10.1172/JCI200524408
4. Parekh AK, Barton MB. The Challenge of Multiple Comorbidity for the US Health Care System. JAMA. 2010;303(13):1303–4. DOI: 10.1001/jama.2010.381
5. Vanden Hoek TL, Li C, Shao Z, Schumacker PT, Becker LB. Significant Levels of Oxidants are Generated by Isolated Cardiomyocytes During Ischemia Prior to Reperfusion. Journal of Molecular and Cellular Cardiology. 1997;29(9):2571–83. DOI: 10.1006/jmcc.1997.0497
6. Gaschler MM, Stockwell BR. Lipid peroxidation in cell death. Biochemical and Biophysical Research Communications. 2017;482(3):419–25. DOI: 10.1016/j.bbrc.2016.10.086

ISSN 0022-9040. Kardiologiia. 2023;63(5). DOI: 10.18087/cardio.2023.5.n2389

7. Zheng S-X, Sun C-H, Chen J. Cardioprotective effect of indirubin in experimentally induced myocardial infarction in wistar rats. International Journal of Clinical and Experimental Pathology. 2017;10(7):8082–90. PMID: 31966661
8. Bilan D.S., Shokhina A.G., Lukyanov S.A., Belousov V.V. The main redox pairs of the cell. Russian Journal of Bioorganic Chemistry. 2015;41(4):385–402. [Russian: Билан Д.С., Шохина А.Г., Лукьянов С.А., Белоусов В.В. Основные редокс-пары клетки. Биоорганическая химия. 2015;41(4):341-56]. DOI: 10.7868/S0132342315040041
9. Pytel E, Olszewska-Banaszczyk M, Koter-Michalak M, Broncel M. Increased oxidative stress and decreased membrane fluidity in erythrocytes of CAD patients. Biochemistry and Cell Biology. 2013;91(5):315–8. DOI: 10.1139/bcb-2013-0027
10. Qin Z, Reszka KJ, Fukai T, Weintraub NL. Extracellular superoxide dismutase (ecSOD) in vascular biology: an update on exogenous gene transfer and endogenous regulators of ecSOD. Translational Research. 2008;151(2):68–78. DOI: 10.1016/j.trsl.2007.10.003
11. Yang M, Pollard PJ. Succinate: A New Epigenetic Hacker. Cancer Cell. 2013;23(6):709–11. DOI: 10.1016/j.ccr.2013.05.015
12. Shlafer M, Kane PF, Wiggins VY, Kirsh MM. Possible role for cytotoxic oxygen metabolites in the pathogenesis of cardiac ischemic injury. Circulation. 1982;66(2 Pt 2):I85-92. PMID: 6282499
13. Epstein FH, McCord JM. Oxygen-Derived Free Radicals in Postischemic Tissue Injury. New England Journal of Medicine. 1985;312(3):159–63. DOI: 10.1056/NEJM198501173120305
14. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature. 1993;362(6423):801–9. DOI: 10.1038/362801a0
15. Alexander RW. Atherosclerosis as disease of redox-sensitive genes. Transactions of the American Clinical and Climatological Association. 1998;109:129–45. PMID: 9601133
16. Puddu P, Puddu GM, Cravero E, De Pascalis S, Muscari A. The emerging role of cardiovascular risk factor-induced mitochondrial dysfunction in atherogenesis. Journal of Biomedical Science. 2009;16(1):112. DOI: 10.1186/1423-0127-16-112
17. Ballinger SW, Patterson C, Knight-Lozano CA, Burow DL, Conklin CA, Hu Z et al. Mitochondrial Integrity and Function in Atherogenesis. Circulation. 2002;106(5):544–9. DOI: 10.1161/01.CIR.0000023921.93743.89
18. Ballinger SW. Mitochondrial dysfunction in cardiovascular disease. Free Radical Biology and Medicine. 2005;38(10):1278–95. DOI: 10.1016/j.freeradbiomed.2005.02.014
19. Madamanchi NR, Runge MS. Mitochondrial Dysfunction in Atherosclerosis. Circulation Research. 2007;100(4):460–73. DOI: 10.1161/01.RES.0000258450.44413.96
20. Shahzad S, Hasan A, Faizy AF, Mateen S, Fatima N, Moin S. Elevated DNA Damage, Oxidative Stress, and Impaired Response Defense System Inflicted in Patients With Myocardial Infarction. Clinical and Applied Thrombosis/Hemostasis. 2018;24(5):780–9. DOI: 10.1177/1076029617725602
21. Uppal N, Uppal V, Uppal P. Progression of Coronary Artery Disease (CAD) from Stable Angina (SA) Towards Myocardial Infarction (MI): Role of Oxidative Stress. Journal of clinical and diagnostic research. 2014;8(2):40–3. DOI: 10.7860/JCDR/2014/7966.4002
22. Deepa M, Pasupathi P, Sankar KBV, Rani P, Kumar SPS. Free radicals and antioxidant status in acute myocardial infarction patients with and without diabetes mellitus. Bangladesh Medical Research Council Bulletin. 2010;35(3):95–100. DOI: 10.3329/bmrcb.v35i3.2999