

## INTERACTION BETWEEN RISK FACTORS AND INDUCED BLOOD OXIDATION IN PATIENTS WITH STABLE CORONARY ARTERY DISEASE

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Exposure on key modified risk factors, mainly hypercholesterolemia, arterial hypertension and diabetes mellitus, is an essential component of successful management of patients with coronary artery disease (CAD). As far as the concept of cardiovascular continuum goes, the predisposing behavioral factors that contribute to the development of these abnormal conditions include smoking, hypodynamia and obesity. Oxidative stress is closely associated with atherogenesis at every stage of progression. An open non-randomized prospective study is conducted. An observational group includes 89 patients with stable CAD. Key risk factors of cardiovascular diseases and their correlation with the values of induced blood oxidation were analyzed. Statistically significant ( $p < 0.05$ ) positive correlation between hypercholesterolemia and coefficient of oxidative activity ( $r = 0.22$ ), smoking and initial rate of blood oxidation ( $r = 0.24$ ), maximum rate of blood oxidation ( $r = 0.25$ ), coefficient of oxidative activity ( $r = 0.24$ ), diabetes mellitus and time of the initiation period ( $r = 0.25$ ); negative correlation between smoking and time of the initiation period ( $r = -0.4$ ) were detected. The results obtained show there is a correlation between a lifestyle and oxidative status of patients with stable CAD. Thus, influence on behavioral risk factors is the most important task of management of patients with cardiovascular pathology.

**Key words:** coronary artery disease, lifestyle, atherosclerosis, oxidative stress

**Author contribution:** Shereshneva MV — review of up-to-date and foreign literature regarding the examined issue, formulation of the subject study, determining tasks and goals, laboratory research of induced blood oxidation values, mathematical and statistical treatment of data, making conclusions; Ilyin MV — development of research program, formulation of the subject study, determining tasks and goals, mathematical and statistical treatment of data, and making conclusions.

**Compliance with ethical standards:** the research underwent through an ethical expertise and was approved by the Ethics Committee of the Yaroslavl Medical University of the Ministry of Health of Russia. Prior to inclusion into research, patients received a detailed explanation of tasks and goals, and a voluntary informed consent was obtained.

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## ВЗАИМОСВЯЗЬ ФАКТОРОВ РИСКА И ПОКАЗАТЕЛЕЙ ИНДУЦИРОВАННОГО ОКИСЛЕНИЯ КРОВИ У БОЛЬНЫХ СТАБИЛЬНОЙ ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

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Неотъемлемым компонентом успешного ведения пациентов с ишемической болезнью сердца является воздействие на ключевые модифицируемые факторы риска, прежде всего гиперхолестеринемии, артериальную гипертензию, сахарный диабет. С позиции концепции сердечно-сосудистого континуума, предрасполагающими поведенческими факторами, способствующими развитию данных патологических состояний, являются курение, гиподинамия, ожирение. Окислительный стресс неразрывно связан с процессами атерогенеза на каждом этапе его прогрессирования. Проведено открытое нерандомизированное проспективное исследование. Группа наблюдения представлена 89 больными со стабильной ишемической болезнью сердца. Проанализированы ключевые факторы риска сердечно-сосудистых заболеваний и их взаимосвязь с показателями индуцированного окисления крови. Выявлены статистически значимые ( $p < 0,05$ ) положительные корреляционные связи гиперхолестеринемии и коэффициента окислительной активности ( $r = 0,22$ ), курения и инициальной скорости окисления крови ( $r = 0,24$ ), максимальной скорости окисления крови ( $r = 0,25$ ), коэффициента окислительной активности ( $r = 0,24$ ), сахарного диабета и времени периода инициации ( $r = 0,25$ ); отрицательная корреляционная связь курения и времени периода инициации ( $r = -0,4$ ). Полученные результаты свидетельствуют в пользу того, что существует связь между образом жизни и оксидативным статусом в популяции пациентов со стабильной ишемической болезнью сердца. Таким образом, одной из важнейших задач в ведении больных с сердечно-сосудистой патологией является влияние на поведенческие факторы риска.

**Ключевые слова:** ишемическая болезнь сердца, образ жизни, атеросклероз, окислительный стресс

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

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

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Cardiovascular pathology is still the leading reason for mortality and disability in developed countries including the Russian Federation as almost half of all cases of death occurs due to cardiovascular diseases [1]. In spite of achievements of modern pharmacotherapy, management of patients with high cardiovascular risk is still a non-trivial task in the practice of a clinician. In order for treatment of patients with coronary artery disease to be effective, lifestyle has to be essentially modified.

The well-established term 'risk factor' was introduced into practice during the Framingham Heart Study, the longest epidemiological study in medicine, in 1961. It laid the foundation of modern preventive cardiology and allowed to differentiate between the basic unfavourable factors producing a significant effect on the development of cardiovascular events [2]. The risk factors mainly include arterial hypertension, smoking, diabetes mellitus and hypercholesterolemia. It is important that they are modified.

Atherosclerosis and related oxidative stress represent key pathogenetic links of development and progression of coronary artery disease and cardiovascular events. Biochemical substrate of oxidative stress represents disturbed homeostasis of free radical oxidation and system of antioxidant defence [3–5].

Thus, effectiveness of therapy of cardiovascular diseases is closely associated not only with understanding the pathogenesis of atherosclerosis but also with activities aimed at the correction of modified risk factors [6–8].

## PATIENTS AND METHODS

The research was done at the State Budgetary Healthcare Institution of the Yaroslavl region 'Regional Clinical Hospital' (the city of Yaroslavl). The project is included into the program of scientific examination of the Yaroslavl State Medical University and underwent ethical expertise. 89 patients with stable coronary artery disease aged  $58.1 \pm 8.3$  were examined. They included 70 males aged  $57.8 \pm 8.2$  years and 19 females aged  $63.9 \pm 6.9$  years. The diagnosis of CAD was confirmed

by outcomes of a clinical research, load tests, coronary angiography data. Drug-induced therapy corresponded to updated clinical recommendations. Key modified factors of cardiovascular risk such as hypercholesterolemia in 38 patients, excessive weight or obesity in 75 patients, arterial hypertension in 81 patients, diabetes mellitus in 14 patients and 43 smokers were analyzed (table 1).

The values of induced blood oxidation were assessed using YSI 5300 Biological Oxygen Monitor (Yellow Springs Instrument Company, YSI Inc., USA). Free-radical oxidation of blood components was induced by AAPH water-soluble inducer (2,2-azobis (2-amidino-propane) dihydrochloride).

The oxygen concentration curve was used to determine as follows:

- 1) rate of blood oxidation ( $V_{ox}$ ),  $10^{-8}$  mole/L·s;
- 2) time of initiation period (T), min;
- 3) initial rate of blood oxidation ( $V_{init}$ ),  $10^{-8}$  mole/L·s;
- 4) maximum rate of blood oxidation ( $V_{max}$ ),  $10^{-8}$  mole/L·s;
- 5) ultimate rate of blood oxidation ( $V_{term}$ ),  $10^{-8}$  mole/L·s;
- 6) coefficient of oxidative activity (OA), %.

Statistical treatment of data was done with STATISTICA 10.0 (StatSoft Inc., USA). Testing for normal distribution of quantitative attributes was done using Kolmogorov-Smirnov's test with Lilliefors and Shapiro-Wilk amendment. To examine the correlation between two attributes, Spearman correlation analysis was used. The study of the type of dependence of an attribute on one or several other attributes was performed based on the logistic regression analysis. The critical value of statistical significance was equal to 5.0%.

## RESEARCH OUTCOMES

The results of correlation analysis of induced blood oxidation values and risk factors of cardiovascular complications are presented in table 2.

Among patients with CAD ( $n = 89$ ), there is a weak but statistically significant ( $p < 0.05$ ) positive correlation between

**Table 1.** Characteristics of patients with CAD

Parameters	Number of patients (%)
Total number of patients	89 (100,0)
Men	70 (78,65)
Women	19 (21,35)
age, years (M±SD)	58.1±8.3
men	57.8±8.2
women	63.9±6.9
Presence of modified risk factors of CAD	
Hypercholesterolemia	38 (42.7)
Excessive weight or obesity (BMI ≥ 25 kg/m <sup>2</sup> )	75 (84.3)
Arterial hypertension	81 (91.0)
Diabetes mellitus	14 (15.7)
Smoking	43 (48.3)

**Table 2.** Matrix of correlation: risk factors of cardiovascular complications

Value	$V_{ox}$ , $10^{-8}$ mol/L·s	$V_{init}$ , $10^{-8}$ mol/L·s	T, min	$V_{term}$ , $10^{-8}$ mol/L·s	$V_{max}$ , $10^{-8}$ mol/L·s	oA, %
BMI	-0.04	0.11	0.01	0.15	0.14	0.01
Smoking	-0.09	0.24	-0.40	-0.04	0.25	0.24
AH	-0.2	-0.12	0.13	-0.01	-0.11	-0.18
DM	-0.11	-0.21	0.25	-0.02	-0.19	-0.19
Hypercholesterolemia	0.01	0.17	-0.20	-0.04	0.11	0.22

hypercholesteremia and oxidative activity coefficient ( $r = 0.22$ ); a weak positive correlation between smoking and initial rate of blood oxidation ( $r = 0.24$ ), moderate negative correlation with the time of initiation period ( $r = -0.4$ ), weak positive correlation with the maximum rate of blood oxidation ( $r = 0.25$ ) and coefficient of oxidative activity ( $r = 0.24$ ); weak positive correlation between diabetes mellitus and time of initiation period  $r = 0.25$ ).

## DISCUSSION OF RESULTS

Smoking is one of the key behavioral factors that determine the risk of development of unfavorable cardiovascular events. Tobacco smoke contains numerous components, which can result in oxidative damage of cellular structures: reactive oxygen species (ROS) are formed during tobacco incineration and in the process of biotransformation of numerous components forming part of the smoke stream [9]. It is established that smoking promotes decreased activity of the system of antioxidant protection. Smokers undergo through a significantly decreased activity of superoxide dismutase and glutathione peroxidase [10]. Arsenic, lead, cadmium and mercury presenting in the tobacco smoke decrease bioavailability of glutathione [11].

Development and progression of cardiovascular diseases are currently considered within the so-called cardiovascular continuum. The concept offered by Dzau V. and Braunwald E. in 1991 allows to treat a cardiovascular pathology as a continuous abnormal process starting from the effect of risk factors and until cardiac insufficiency and death are developed [12].

CAD substrate includes atherosclerosis which is a cascade of subsequent abnormal changes with oxidation of lipoproteins being an initial stage [13]. Within persisting unfavorable conditions, the basis of which is formed by such risk factors of cardiovascular diseases as arterial hypertension and dyslipidemia, ROS activate pro-inflammatory signaling pathways that promote oxidative modification of lipids and improve their atherogenicity [14, 15].

Hypercholesteremia is one of the most principal factors, which is essential in progression of atherosclerosis [16]. Close interaction between oxidative stress and dyslipidemia values was proven not only among patients with established atherosclerosis but also among those without the established

affection of the vascular bed [17–20]. So, one of the most important tasks, which allow to improve patient's quality of life and prognosis is to achieve target values of lipid profile depending on the rate of risk of cardiovascular complications.

Cardiovascular diseases constitute the main reason for death among patients with type 2 diabetes mellitus [21, 22]. Burden of diabetes mellitus is implemented not through progression of atherosclerosis only, but also through a specific complication such as diabetic cardiomyopathy [23]. It is assumed that its development is based on epithelial and mitochondrial dysfunction and glucotoxicity. In the presence of hyperglycemia, advanced glycation endproducts are accumulated within endothelial cells. The process is accompanied by increased production of ROS [24–26].

It is notable that tight glycaemic control is not associated with a decreased rate of cardiovascular events [27, 28], including in medicine of critical conditions [29, 30]. The results show that type 2 diabetes mellitus is a condition, which qualitatively differs from stable hyperglycemia as far as an abnormal effect on the cardiovascular system goes. Prevention of this disease is a pressing issue as well. Modification of lifestyle within the population can significantly reduce the risk of both cardiovascular and overall mortality [31].

## CONCLUSIONS

The main therapeutic task within the role of induced blood oxidation in the events of cardiovascular continuum is not so much an indirect effect on atherosclerosis, arterial hypertension or carbohydrate metabolism disorders among patients with stable CAD as it is the effect on primary behavioral risk factors such as smoking, improper feeding, excessive weight and hypodynamia.

Prevention issues are mainly associated with a patient's altered behavior. It depends on many social and mental factors, including the lifestyle of a family and immediate environment. Influence on these factors has a number of objective complications associated with mental and ethical aspects and formation of positive values. The issue of ethical management of real clinical practice needs to be discussed by the medical community in detail and implemented into educational programs for medical professionals.

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