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MYELOPEROXIDASE ACTIVITY AFFECTS THE HIGH-DENSITY LIPOPROTEIN CHOLESTEROL LEVEL AND THE COURSE OF CHRONIC CORONARY HEART DISEASE IN PATIENTS WITH ARTERIAL HYPERTENSION

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BACKGROUND: Coronary heart disease is one of the leading causes of death and disability worldwide. Myeloperoxidase plays the key role in its pathogenesis. Oxidative modification of high-density lipoprotein particles by myeloperoxidase followed by impaired reverse cholesterol transport and the decrease of high-density lipoprotein cholesterol level results in atherosclerosis progression. We studied the effect of myeloperoxidase on reverse cholesterol transport among patients with arterial hypertension and different clinical forms of chronic coronary heart disease, judging by findings in blood plasma.

AIM: The ultimate goal was to establish whether that effect is associated with the total amount of myeloperoxidase or its activity.

METHODS: 93 patients were recruited (65.4 ± 10.1 years old in average; men — 30 (32%)) with arterial hypertension and different clinical forms of chronic coronary heart disease. Depending on the diagnosis established, all participants were divided into 3 groups. Group I (control) contained patients with arterial hypertension, but without chronic coronary heart disease ($n = 46$). Group II ($n = 26$) included patients with initially stable coronary syndromes of chronic coronary heart disease (stable angina and/or scheduled surgical interventions for stable coronary heart disease), who never experienced acute adverse cardiac events. Group III ($n = 21$) contained patients with acute coronary syndrome (acute myocardial infarction) in the past 6 months or earlier. The total myeloperoxidase content (MPO-T) was assayed by enzyme-linked immunosorbent assay (ELISA). Home-modified specific immune-extraction followed by enzymatic detection (SIEFED) test was used to measure the active myeloperoxidase (MPO-A). Then, the coefficient of myeloperoxidase activity (MPO-CA) and the ratio of coefficient of myeloperoxidase activity to high-density lipoprotein cholesterol (MPO-CA/HDL-C) were calculated.

RESULTS: The level of MPO-A was higher in patients from group III with complicated form of chronic coronary heart disease, as compared with group II ($p < 0.05$). MPO-CA in patients of group III also was higher in comparison with group II ($p = 0.001$). Weak positive correlation was found between MPO-T and MPO-A in the whole cohort under investigation ($r = 0.26$; $p < 0.05$), and the relationship was stronger in the group III ($r = 0.59$; $p < 0.05$). In addition, negative correlation between MPO-A and HDL-C was found in group III ($r = –0.46$; $p < 0.05$). The MPO-CA/HDL-C ratio was higher in patients with anamnestic acute coronary syndrome, as compared with patients manifesting non-complicated stable coronary heart disease ($p < 0.001$) and with patients of group I who had no coronary heart disease ($p < 0.001$). To determine diagnostic value of the MPO-CA/HDL-C the receiver operating characteristic curve (ROC-curve) was plotted. The calculated area under curve (AUC) was 0.8 which indicates a high predictive value of the MPO-CA/HDL-C ratio for different forms of chronic coronary heart disease.

CONCLUSION: The results of our study demonstrate that in patients with preceding history of acute coronary syndrome, as compared with those having a stable course of chronic coronary heart disease, the effect of myeloperoxidase on reverse cholesterol transport depends on its activity rather than concentration. MPO-CA/HDL-C ratio mirrors the complicated chronic coronary heart disease and might serve as an additional indicator of residual risk.

Keywords: myeloperoxidase; high-density lipoprotein cholesterol; coronary heart disease; reverse cholesterol transport; ELISA; SIEFED.

List of abbreviations

AH, arterial hypertension; AUC, area under curve; BBS, borate buffered saline; BSA, bovine serum albumin; CHD, coronary heart disease; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; ESR, erythrocyte sedimentation rate; HDL-C, high-density lipoprotein cholesterol; HDL-P, high-density lipoprotein particles; LDL, low-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; mox-LDL, low-density lipoprotein oxidized by myeloperoxidase; MPO, myeloperoxidase; MPO-A, active myeloperoxidase; MPO-CA, coefficient of myeloperoxidase activity; MPO-T, total myeloperoxidase; PBS, phosphate buffered saline; RCT, reverse cholesterol transport; ROC, receiver operating characteristic; ROS, reactive oxygen species; SIEFED, specific immune-extraction followed by enzymatic detection; TC, total cholesterol; TG, triglycerides.

ВЛИЯНИЕ АКТИВНОЙ МИЕЛОПЕРОКСИДАЗЫ НА УРОВЕНЬ ХОЛЕСТЕРИНА ЛИПОПРОТЕИНОВ ВЫСОКОЙ ПЛОТНОСТИ И ТЕЧЕНИЕ ИШЕМИЧЕСКОЙ БОЛЕЗНИ СЕРДЦА У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ

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Обоснование. Ишемическая болезнь сердца — одна из ведущих причин инвалидности и смертности во всем мире, а миелопероксидаза играет ключевую роль в ее патогенезе. Окислительная модификация липопротеинов высокой плотности под воздействием миелопероксидазы с последующим угнетением обратного транспорта холестерина и снижением концентрации холестерина липопротеинов высокой плотности приводит к прогрессированию атеросклероза. Мы изучали влияние миелопероксидазы на обратный транспорт холестерина, основываясь на показателях, определяемых в плазме крови у пациентов с артериальной гипертензией и разными клиническими формами хронической ишемической болезни сердца.

Цель — установить, связано ли это влияние с общей концентрацией миелопероксидазы или ее активностью.

Материалы и методы. В исследование были включены 93 пациента (средний возраст 65,4±10,1, 30 (32%) мужчин) с артериальной гипертензией и разными клиническими формами хронической ишемической болезни сердца. В зависимости от установленного диагноза все пациенты были разделены на 3 группы. Пациенты с артериальной гипертензией, но без хронической ишемической болезни сердца вошли в контрольную группу I (n=46). В группу II (n=26) были включены пациенты с изначально стабильными коронарными синдромами хронической ишемической болезни сердца (стабильная стенокардия и/или выполненное оперативное вмешательство по поводу стабильной ишемической болезни сердца), которые никогда не переносили острый коронарный синдром. В группу III (n=21) вошли пациенты, которые перенесли острый коронарный синдром (острый инфаркт миокарда) 6 мес. назад или ранее. Для определения общей миелопероксидазы (MPO-T) проводили иммуноферментный анализ (ELISA). Для измерения активной миелопероксидазы (MPO-A) была применена модифицированная нами версия детекции активности фермента после его специфической иммуносорбции (SIEFED). Затем были рассчитаны коэффициент активности миелопероксидазы (MPO-CA) и отношение коэффициента активности миелопероксидазы к холестерину липопротеинов высокой плотности (MPO-CA/HDL-C).

Результаты. У пациентов из группы III с осложненной формой хронической ишемической болезни сердца был выше уровень MPO-A по сравнению с группой II (p <0,05). MPO-CA у пациентов группы III также был выше по сравнению с группой II (p=0,001). Во всей изучаемой когорте между MPO-A и MPO-T была выявлена слабая положительная корреляция (r=0,26; p <0,05), и она была сильнее в группе III (r=0,59; p <0,05). В дополнение, отрицательная корреляция между MPO-A и HDL-C была найдена в группе III (r=–0,46; p <0,05). Значение отношения MPO-CA/HDL-C было выше у пациентов, перенесших острый коронарный синдром в анамнезе, по сравнению с пациентами, у которых было стабильное неосложненное течение хронической ишемической болезни сердца (p <0,001), и с пациентами из группы I, у которых ишемической болезни сердца не было (p <0,001). Для определения диагностической значимости отношения MPO-CA/HDL-C был проведен анализ чувствительности и специфичности (ROC-анализ) и построена ROC-кривая. Рассчитанная площадь под кривой (AUC) составила 0,8, что показывает высокое прогностическое значение отношения MPO-CA/HDL-C для разных форм хронической ишемической болезни сердца.

Заключение. Результаты нашего исследования показывают, что у пациентов с перенесенным острым коронарным синдромом по сравнению с пациентами, у которых характер течения хронической ишемической болезни сердца был стабильным, влияние миелопероксидазы на обратный транспорт холестерина зависит от ее активности, а не от концентрации. Отношение MPO-CA/HDL-C выявляет осложненную форму ишемической болезни сердца и может служить дополнительным фактором резидуального риска.

Ключевые слова: миелопероксидаза; холестерин липопротеинов высокой плотности; ишемическая болезнь сердца; обратный транспорт холестерина; ELISA; SIEFED.

Background

Cardiovascular diseases associated with atherosclerosis are the leading cause of death and disability all over the world [1], therefore the problem of early diagnosis and stratification of the risk of an adverse outcome remains relevant.

In recent years, new data have been published showing the key role of myeloperoxidase (MPO) in pathogenesis of coronary heart disease (CHD). On the one hand, progression of coronary atherosclerosis is strongly dependent on the ability of MPO to oxidize low-density lipoprotein (mox-LDL). Oxidation of low-density lipoprotein (LDL) is associated with formation of a growing atherosclerotic plaque and the subsequent acute cardiovascular

event, especially when the plaque is ruptured [2–7]. On the other hand, MPO causes oxidative modification of high-density lipoprotein particles (HDL-P) followed by impaired reverse cholesterol transport (RCT), which is the natural secure mechanism providing the efflux of cholesterol from foam cells in the arterial wall and its subsequent delivery to the liver for elimination via bile [8–14]. Besides, experimental data revealed the involvement of MPO in the development and progression of endothelial dysfunction [5, 15, 16]. The latter also leads to arterial hypertension (AH) and atherosclerosis. Thus, it seems important to study MPO as a diagnostic and/or prognostic biomarker of different clinical forms and adverse outcomes of CHD [17–22] or as a guide for treatment response [23, 24].

However, despite sufficient evidence in favor of MPO participation in atherosclerosis progression, there are unaddressed problems preventing wide acceptance of this enzyme as a biomarker of chronic CHD.

Firstly, MPO is the major constituent of the azurophilic granules of neutrophils, and its involvement in the pathogenesis of infectious and noninfectious diseases provides an immune response [25–27].

Secondly, multiple effects of MPO discredit it as the biomarker of a particular disease. This enzyme participates in the organism's nonspecific defense, but can also be a severe damaging factor, catalyzing the production of reactive oxygen species (ROS) in the halogenating cycle, which usually causes oxidation of amino acids, proteins, lipids, proteoglycans, and nucleic acids [25, 27, 28]. Besides, the heme-containing cationic MPO is able to bind with negatively charged amino acid residues of lipoproteins, proteoglycans, and cell surface membrane proteins [29–31].

Thirdly, MPO activity is modulated by several natural inhibitors, such as ceruloplasmin [32–34], paraoxonase-1 [35], or hypochlorous acid produced in the MPO-catalyzed reaction [36]. Hence, the total amount of MPO does not always mirror its real deleterious effect in the course of atherogenesis.

Fourthly, it is worth noting that MPO release from degranulated neutrophils, its interaction with LDL, and mox-LDL storage by macrophages in course of atherosclerotic plaque formation occur in the arterial wall [6, 37, 38]. It is far more intricate to take a sample of tissue from the atherosclerotic plaque compared with blood sampling during routine follow-up procedures. While sampling of atherosclerotic plaques for analysis is not under consideration, mox-LDL monitoring so far has not many chances in routine clinical practice. From this viewpoint, investigating MPO effects on HDL-P and RCT with concomitant high-density lipoprotein cholesterol (HDL-C) level decrease appears as the right choice, since the markers of this process can be determined in a blood sample.

And fifthly, there are difficulties in comparing and interpreting the data from different studies due to the lack of a generally accepted approach to the pre-analytical phase and to measuring MPO concentration and activity.

On account of the problems described, the divergent results of multiple studies testing only amount of MPO as the biomarker, should not surprise. New solutions are needed for clinical implementation of MPO measurement. A number of investigations indicated the need to determine not only MPO concentration, but also its enzymatic activity [22, 39–41]. Considering the ratio between MPO and associated parameters, i.e. paraoxonase-1 inhibitor [42], HDL-P [43] or HDL-C [44] seems to be informative.

We studied the effect of MPO on RCT, judging by analysis findings in blood plasma among patients with AH and different clinical forms of chronic CHD. The ultimate **aim** was to establish whether that effect is associated with the total amount of MPO or its activity.

Methods

Clinical characteristics of study groups. In trial were recruited patients from the Clinical cardiology department of the Institute of Experimental Medicine who have previously been diagnosed with AH and different clinical forms of chronic CHD. Mean age of study population was 65,4 ± 10,1, men — 30 (32%), women — 63 (68%). Before enrollment in trial all participants signed the informed consent form.

All data including diagnosis, conducted examination, medical treatment, and surgical intervention, if any, were collected from the primary medical documentation. According to the indications, patients received the following drug classes, i.e. angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, diuretics, mineralocorticoid receptor antagonists, beta-blockers, statins, antithrombotic therapy, if needed.

Patients who have had acute coronary syndrome (acute myocardial infarction) and/or surgical intervention for CHD less than 6 months ago were not included in the study. Besides, we did not include patients with acute exacerbations of chronic inflammatory diseases or malignancy, unless it has been cured prior to the enrollment.

Depending on the established diagnosis all participants were divided into 3 groups. Patients with AH but without chronic CHD formed the control group I ($n = 46$). Group II ($n = 26$) included patients with initially stable coronary syndromes of chronic CHD (stable angina and/or scheduled surgical interventions for stable CHD), who never experienced

acute adverse cardiac events. Group III ($n = 21$) contained patients who had acute coronary syndrome (acute myocardial infarction) 6 months ago and earlier. Median and interquartile range of disease duration after acute event were 3 (2; 13) years.

Pre-analytical phase. Blood samples were collected into vacutainers with K3EDTA from patients at admission. After that, within 2 hrs the samples were centrifuged at 600×g for 15 min. Thus obtained, plasma was aliquoted, frozen and stored at –80°C. In samples obtained simultaneously lipid profile (total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), HDL-C), complete blood count with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were determined using standard methods.

Active MPO (MPO-A) assay. MPO-A measurement was accomplished with modified by us version of the specific immune-extraction followed by enzymatic detection (SIEFED) test. For MPO-A estimation we used monoclonal anti-MPO antibodies derived from immunized mice as reported earlier [45]. 100 μL of antibodies (2F7 clone) in borate buffered saline (BBS) with a concentration of 5 mg/L were added to the wells of a standard 96-well polystyrene plate for immobilizing it on a solid surface. For that purpose, the plate was incubated at 37°C and continuous stirring 300 r.p.m. throughout the time of 2 hrs or at 4°C for 8 hrs without stirring. After incubation the plate was washed three times with BBS containing 0.05% Tween-20. After that, into each well we added 100 μL blocking buffer containing 3% milk solution in phosphate buffered saline (PBS) with 0.05% Tween-20 and incubated it in 1 hr at 37°C and continuous stirring 300 r.p.m. Then, into the wells with blocking buffer we added 10 μL evaluated plasma samples or 10 μL standard MPO solutions in 3% milk with a concentration between 200 ng/mL and 3.125 ng/mL obtained by two-fold serial dilutions. Next, we incubated the plate again at 37°C and continuous stirring 300 r.p.m. in 1 hr and washed three times with BBS containing 0.05% Tween-20. For MPO-A concentration measurement we added into the wells developing buffered solution containing 20 mM NaBr, 200 mM $(NH_4)_2SO_4$, 24 mM Na-citrate buffer, pH 6.0, 1 μM 10-acetyl-3,7-dihydroxyphenoxazine, and 10 μM H_2O_2. In a time of 30 min the plate was incubated at 37°C and continuous stirring 300 r.p.m. After that, we measured the fluorescence intensity of resorufin formed as a result of the reaction using the multimodal plate reader CLARIOstar (BMG Labtech, Germany) at a wavelength of 580–620 nm (excitation at 535–555 nm). For MPO-A concentration calculation we made use of calibration curve constructed in MARS software (BMG Labtech, Germany) by standard solution concentration measurement. Results were expressed as ng/mL.

Total MPO (MPO-T) assay. For MPO-T estimation the enzyme-linked immunosorbent assay (ELISA) was performed using monoclonal anti-MPO antibodies (F18 clone) gotten from immunized mice as described earlier [45]. For antibodies immobilization we added into the wells of a standard 96-well polystyrene plate 100 μL antibodies solution in BBS with a concentration of 5 mg/L and incubated at 37°C and continuous stirring 300 r.p.m. throughout the time of 2 hrs or at 4°C for 8 hrs without stirring. After incubation the plate was washed three times with BBS containing 0.05% Tween-20. Then, into the wells we added 100 μL blocking buffer containing bovine serum albumin (BSA) in 200 mM $(NH_4)_2SO_4$ and 24 mM Na-citrate buffer, pH 6.0, and incubated it within 1 hr at 37°C and continuous stirring 300 r.p.m. After that, into the wells we added 10 μL evaluated plasma samples or 10 μL standard MPO solutions in 3% milk with a concentration between 200 ng/mL and 3.125 ng/mL obtained by two-fold serial dilutions and incubated it in a time of 2 hrs at the same conditions. Next, the plate was washed three times again with BBS containing 0.05% Tween-20. After that, into each well we added 100 μL anti-MPO antibodies 2F7 labeled with horseradish peroxidase in BBS containing 0.05% Tween-20 and incubated in 1 hr at 37°C and continuous stirring 300 r.p.m. After three times washing with BBS containing 0.05% Tween-20 into each well we added 100 μL developer consisting of 0.4 mM 3,3',5,5'-tetramethylbenzidine and 4 mM H_2O_2 in 80 mM Na-acetate buffer, pH 5.5. In 15 min the reaction was terminated with 50 mL of 1M H_2SO_4. Substrate detection and MPO-T concentration estimation made use of the multimodal plate reader CLARIOstar (BMG Labtech, Germany) at a wavelength of 540 nm and constructed in MARS software (BMG Labtech, Germany) the calibration plot by standard solution concentration measurement.

Calculated parameters based on laboratory data. Based on the data obtained from laboratory tests some coefficients were calculated according to the following formulas.

Coefficient of MPO activity (MPO-CA) was calculated as the ratio between MPO-A and MPO-T: MPO-CA = MPO-A/MPO-T.

The ratio MPO-A/HDL-C and MPO-T/HDL-C were used as well.

Lastly, the ratio MPO-CA/HDL-C was calculated.

Statistical analysis. Continuous variables are represented as median, interquartile range [Q_1–Me–Q_3), minimum and maximum values [min–max]. The Shapiro–Wilk test was performed to verify the data obtained for normal distribution. Some variables' distribution differed from the normal type, therefore non-parametric tests were implemented. The Kruskal–Wallis H test was applied for multiple

comparisons between the groups. Next, the Mann–Whitney *U* test was performed for subsequent pairwise comparisons with Bonferroni *post hoc* correction to adjust *p*-values. Correlation was tested using *r* — Spearman's correlation coefficient. To examine the diagnostic value of our study, the logistic regression analysis of variables was performed (logit model). Then, receiver operating characteristic (ROC) curve was deduced and the area under the ROC curve (AUC) was calculated. Statistical significance was established at $p < 0.05$.

Results and discussion

The main clinical and laboratory characteristics of groups under study are displayed in Table 1.

Table 1 / Таблица 1

The main clinical and laboratory characteristics of the groups (Q_1–*Me*–Q_3 [min–max])
Основные клинические и лабораторные показатели групп (Q_1–*Me*–Q_3 [min–max])

Characteristics	Group I	Group II	Group III	All groups
n	46	26	21	93
Age (years)	55–63–70 [46–86]	63–68–73 [58–84]	58–69–75 [42–87]	58–66–73 [42–87]
Gender (M/F)	M 13; F 33	M 3; F 23	M 14; F 7	M 30; F 63
Total cholesterol (mmol/L)	4.87–5.79–6.37 [3.29–8.90]	4.59–5.24–6.10 [3.32–9.02]	3.60–4.47–5.29 [3.13–8.73]	4.50–5.33–6.10 [3.13–9.02]
Low-density lipoprotein cholesterol (mmol/L)	2.45–3.14–3.55 [1.39–5.51]	2.33–2.79–3.45 [1.48–5.03]	1.81–2.34–2.90 [1.38–5.0]	2.25–2.86–3.44 [1.38–5.51]
HDL-C (mmol/L)	1.27–1.48–1.77 [0.86–2.80]	1.21–1.48–1.63 [0.94–2.48]	0.97–1.17–1.35 [0.79–1.88]	1.18–1.40–1.62 [0.79–2.80]
Triglycerides (mmol/L)	0.88–1.20–1.55 [0.33–7.21]	1.13–1.27–1.62 [0.56–5.44]	0.86–1.39–2.02 [0.35–3.58]	0.88–1.23–1.66 [0.33–7.21]
MPO-T (ng/mL)	45.1–59.3–68.5 [25.9–82.9]	41.6–56.7–77.1 [34.5–146.9]	46.7–52.8–71.8 [25.6–93.3]	45.1–57.0–71.3 [25.6–146.9]
MPO-A (ng/mL)	12.1–19.6–27.8 [3.9–50.6]	11.5–13.8–27.6 [4.3–46.8]	19.4–23.1–30.6 [12–52.5]	12.4–19.5–27.7 [3.9–52.5]
MPO-CA	0.28–0.37–0.49 [0.05–0.81]	0.20–0.31–0.41 [0.05–1.12]	0.39–0.52–0.55 [0.18–0.66]	0.25–0.38–0.52 [0.05–1.12]
MPO-T/HDL-C	27.80–37.72–56.59 [12.93–76.54]	30.0–39.59–58.65 [14.03–93.67]	37.72–45.13–57.27 [16.81–92.28]	30.52–41.42–57.58 [12.93–93.67]
MPO-A/HDL-C	7.54–11.83–22.41 [2.64–50.10]	5.52–12.63–16.93 [2.83–46.40]	13.88–17.84–29.33 [8.0–59.37]	8.0–13.61–23.10 [2.64–59.37]
MPO-CA/HDL-C	0.148–0.240–0.348 [0.034–0.798]	0.102–0.207–0.308 [0.051–1.120]	0.280–0.426–0.542 [0.120–0.810]	0.161–0.264–0.363 [0.034–1.120]
Leucocytes ($\times 10^9$/L)	4.5–5.5–6.4 [3.1–9.9]	4.9–5.6–6.4 [3.9–8.5]	5.5–5.9–6.8 [4.1–8.7]	4.8–5.6–6.4 [3.1–9.9]
Neutrophils ($\times 10^9$/L)	2.31–3.09–3.63 [1.24–5.85]	2.70–3.30–3.95 [1.60–5.54]	3.19–3.53–3.82 [2.17–6.0]	2.62–3.25–3.74 [1.24–6.0]
Erythrocyte sedimentation rate (mm/hr)	8–16–26 [3–44]	13–19–23 [7–43]	13–19–22 [3–34]	12–17–23 [3–44]
C-reactive protein (mg/L)	1.4–2.6–4.7 [0.4–27.5]	1.9–3.7–4.5 [1.0–7.6]	1.9–2.1–7.6 [1.1–16.9]	1.9–2.6–4.7 [0.4–27.5]

N o t e. HDL-C, high-density lipoprotein cholesterol; MPO-T, total myeloperoxidase; MPO-A, active myeloperoxidase; MPO-CA, coefficient of myeloperoxidase activity; MPO-T/HDL-C; the ratio of total myeloperoxidase to high-density lipoprotein cholesterol; MPO-A/HDL-C, the ratio of active myeloperoxidase to high-density lipoprotein cholesterol; MPO-CA/HDL-C, the ratio of coefficient of myeloperoxidase activity to high-density lipoprotein cholesterol.
П р и м е ч а н и е. HDL-C — холестерин липопротеинов высокой плотности; MPO-T — общая миелопероксидаза; MPO-A — активная миелопероксидаза; MPO-CA — коэффициент активности миелопероксидазы; MPO-T/HDL-C — отношение общей миелопероксидазы к холестерину липопротеинов высокой плотности; MPO-A/HDL-C — отношение активной миелопероксидазы к холестерину липопротеинов высокой плотности; MPO-CA/HDL-C — отношение коэффициента активности миелопероксидазы к холестерину липопротеинов высокой плотности.

Table 2 / Таблица 2

P-value for comparing characteristics between groups
Значение p при сравнении показателей между группами

Characteristics	P-value for the Kruskal–Wallis H test	P-value for the Mann–Whitney U test comparing between groups II and III	P-value for the Mann–Whitney U test comparing between groups I and III	P-value for the Mann–Whitney U test comparing between groups I and II
MPO-T (ng/mL)	0.93	–	–	–
MPO-A (ng/mL)	0.04	0.01	0.08	0.30
MPO-CA	0.009	0.001	0.03	0.20
HDL-C (mmol/L)	0.004	0.008	<0.001	0.76
MPO-T/HDL-C	0.25	–	–	–
MPO-A/HDL-C	0.004	0.003	0.003	0.44
MPO-CA/HDL-C	<0.001	<0.001	<0.001	0.25
Leucocytes ($\times 10^9$/L)	0.10	–	–	–
Neutrophils ($\times 10^9$/L)	0.07	–	–	–
Erythrocyte sedimentation rate (mm/hr)	0.69	–	–	–
C-reactive protein (mg/L)	0.70	–	–	–

Note. MPO-T, total myeloperoxidase; MPO-A, active myeloperoxidase; MPO-CA, coefficient of myeloperoxidase activity; HDL-C, high-density lipoprotein cholesterol; MPO-T/HDL-C, the ratio of total myeloperoxidase to high-density lipoprotein cholesterol; MPO-A/HDL-C, the ratio of active myeloperoxidase to high-density lipoprotein cholesterol; MPO-CA/HDL-C, the ratio of coefficient of myeloperoxidase activity to high-density lipoprotein cholesterol.
Примечание. MPO-T — общая миелопероксидаза; MPO-A — активная миелопероксидаза; MPO-CA — коэффициент активности миелопероксидазы; HDL-C — холестерин липопротеинов высокой плотности; MPO-T/HDL-C — отношение общей миелопероксидазы к холестерину липопротеинов высокой плотности; MPO-A/HDL-C — отношение активной миелопероксидазы к холестерину липопротеинов высокой плотности; MPO-CA/HDL-C — отношение коэффициента активности миелопероксидазы к холестерину липопротеинов высокой плотности.

The chronic CHD presents as several dissimilar conditions with divergent clinical manifestations and outcomes. Non-complicated forms, such as stable *angina pectoris* with predictable symptoms differ from others by relatively benign course of the disease. In contrast, complicated forms, e.g. acute coronary syndrome, even after stabilization and migration to the chronic stage have less favourable prognosis due to the very high risk of recurrent acute cardiovascular events [46]. Thereby, evaluation of the underlying molecular mechanisms is needed for better understanding and more accurate prognosis of the adverse outcomes. It will help to identify the most vulnerable population groups and to implement preventive measures and specific treatment.

In our study we distinguished patients with different clinical course of the chronic CHD in two separate groups and compared obtained data. Patients in our study were divided in two groups on the basis of different clinical course of the chronic CHD. The data obtained in each group were compared and (see Table 2).

Patients from group III with complicated form of the chronic CHD had higher level of MPO-A as compared with group II ($p < 0.05$), and MPO-T concentration was similar in both groups. The level of HDL-C level was expectedly lower among patients from group III in comparison with groups II ($p < 0.05$) and I ($p < 0.001$), in view that previous studies demonstrated association between low level of HDL-C and an increased risk of cardiovascular events in patients with stable CHD [47].

Measuring MPO-T and MPO-A allowed us calculating MPO-CA, which, on the one hand, reflects the percentage of metabolically active enzyme, and, on the other hand, can indicate the inhibition efficiency, i.e. the higher MPO-CA is, the lower is the effectiveness of inhibitors, the higher is the risk of the complicated CHD form and of adverse outcomes. MPO-CA among patients from group III was higher in comparison with group II ($p = 0.001$). Comparing other groups with group I revealed no statistically meaningful difference among them.

To assess the impact of MPO on RCT and HDL-C level in different clinical forms of chronic CHD, the relations MPO-T/HDL-C and MPO-A/HDL-C were calculated, as described earlier [48]. MPO-T/HDL-C ratio did not vary among the groups. Meanwhile, MPO-A/HDL-C ratio was higher among the patients in group III, who had experienced at least one acute coronary syndrome according to the anamnesis, as compared both with the patients of group II having non-complicated form of chronic CHD ($p < 0.05$) and those of group I without CHD ($p < 0.05$).

No significant differences between group II and group I were found as judged by manifestations under study. Thereby, among the patients suffering from stable CHD without acute events in the anamnesis and those without CHD whatsoever, the total amount of MPO, its enzymatic activity and it impact on the RCT were similar in properties and effects. Furthermore, no significant differences were found between the groups concerning other inflammatory markers, such as the total amount of leukocytes, neutrophils, ESR, and CRP.

Correlation analysis was performed to estimate the strength and direction of the relationships between the characteristics under study. Weak positive correlation was found between MPO-T and MPO-A in the whole cohort under investigation ($r = 0.26$; $p < 0.05$) (Fig. 1, *a*). Moreover, the relationship was stronger in the group III ($r = 0.59$; $p < 0.05$) (Fig. 1, *b*), but significant correlation lacked in other groups. This observation suggests that among the patients who have already experienced acute coronary syndrome (acute myocardial infarction) MPO is involved in the pathological process owing to the active fraction and, possibly, to poor efficacy of the natural inhibitory effect.

Positive correlation between the ratios MPO-T/HDL-C and MPO-A/HDL-C was detected in the whole cohort as well ($r = 0.49$; $p < 0.05$); it was

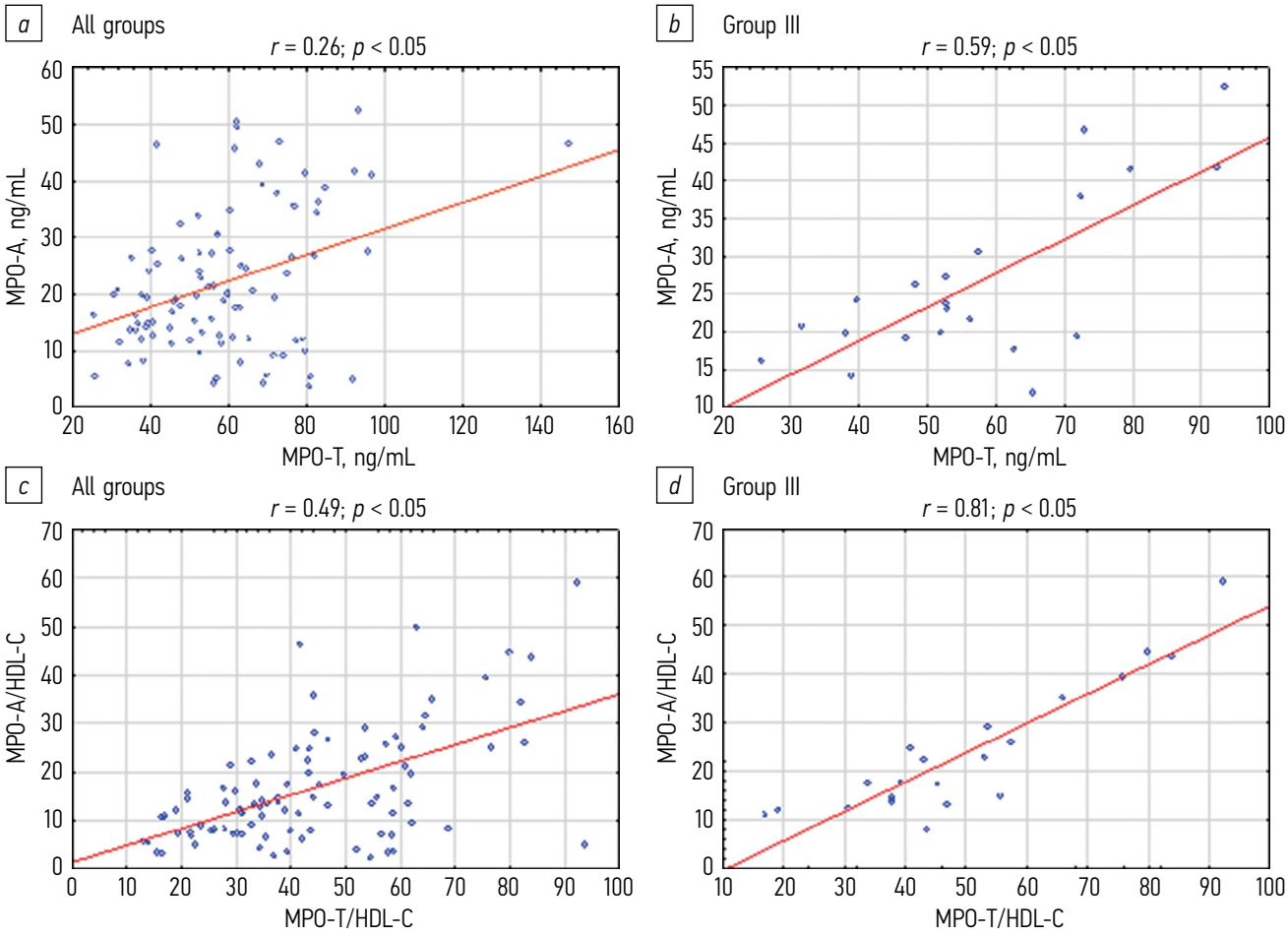

Fig. 1. Relationships between MPO-T, MPO-A and HDL-C. *a*, Scatter plot of correlation between MPO-T and MPO-A in all groups. *b*, Scatter plot of correlation between MPO-T and MPO-A in group III. *c*, Scatter plot of correlation between MPO-T/HDL-C ratio and MPO-A/HDL-C ratio in all groups. *d*, Scatter plot of correlation between MPO-T/HDL-C ratio and MPO-A/HDL-C ratio in group III. MPO-T, total myeloperoxidase; MPO-A, active myeloperoxidase; MPO-T/HDL-C, the ratio of total myeloperoxidase to high-density lipoprotein cholesterol; MPO-A/HDL-C, the ratio of active myeloperoxidase to high-density lipoprotein cholesterol.

Рис. 1. Взаимосвязь между показателями MPO-T, MPO-A и HDL-C: *a* — диаграмма рассеяния, демонстрирующая корреляцию между MPO-T и MPO-A во всех группах; *b* — диаграмма рассеяния, демонстрирующая корреляцию между MPO-T и MPO-A в группе III; *c* — диаграмма рассеяния, демонстрирующая корреляцию между отношением MPO-T/HDL-C и отношением MPO-A/HDL-C во всех группах; *d* — диаграмма рассеяния, демонстрирующая корреляцию между отношением MPO-T/HDL-C и отношением MPO-A/HDL-C в группе III. MPO-T — общая миелопероксидаза; MPO-A — активная миелопероксидаза; MPO-T/HDL-C — отношение общей миелопероксидазы к холестерину липопротеинов высокой плотности; MPO-A/HDL-C — отношение активной миелопероксидазы к холестерину липопротеинов высокой плотности.

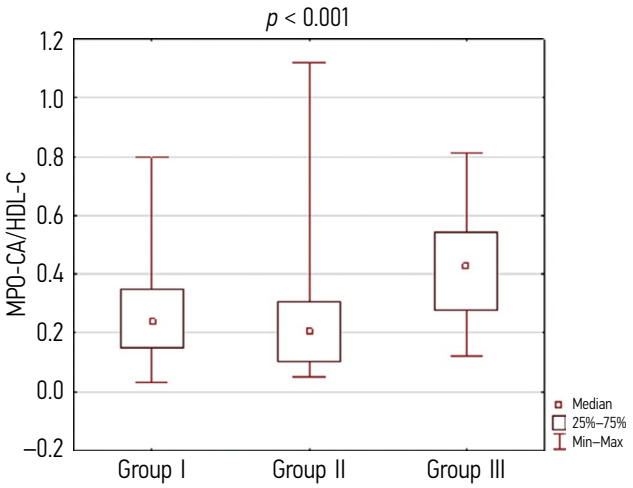

Fig. 2. Box plot of MPO-CA/HDL-C ratio comparison among the groups. The data are represented as median, interquartile range, minimum and maximum values. Statistical significance of the Kruskal–Wallis *H* test for multiple comparison, $p < 0.001$. MPO-CA/HDL-C, the ratio of coefficient of myeloperoxidase activity to high-density lipoprotein cholesterol.

Рис. 2. Диаграмма размаха для распределения отношения MPO-CA/HDL-C в группах. Данные представлены в виде медианы, межквартильного размаха, минимального и максимального значений. Статистическая значимость для *H*-критерия множественных сравнений Краскела–Уоллиса p <0,001. MPO-CA/HDL-C — отношение коэффициента активности миелопероксидазы к холестерину липопротеинов высокой плотности.

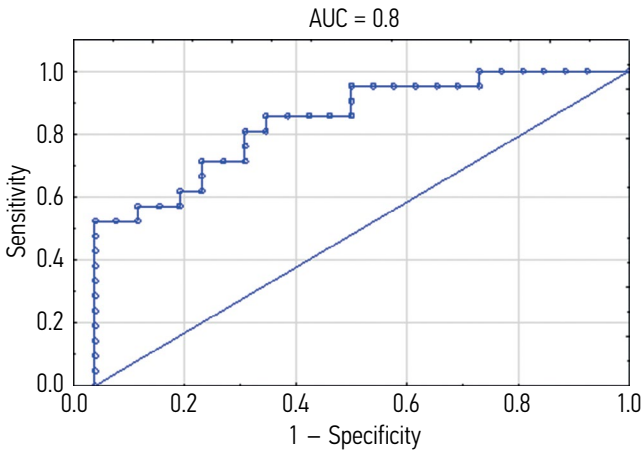

Fig. 3. The results of ROC-analysis of the MPO-CA/HDL-C ratio among the patients with different clinical forms of chronic coronary heart disease. ROC, receiver operating characteristic; AUC, area under curve; MPO-CA/HDL-C, the ratio of coefficient of myeloperoxidase activity to high-density lipoprotein cholesterol.

Рис. 3. Результаты ROC-анализа для отношения MPO-CA/HDL-C среди пациентов с разными клиническими формами хронической ишемической болезни сердца. ROC — рабочая характеристика приемника; AUC — площадь под кривой; MPO-CA/HDL-C — отношение коэффициента активности миелопероксидазы к холестерину липопротеинов высокой плотности.

stronger than MPO-T and MPO-A relationship. The strongest positive correlation was in the group III ($r = 0.81$; $p < 0.05$) (Fig. 1, *c*, *d*). The same observation was previously described for atherosclerotic plaque progression of the carotid arteries [49]. In addition, negative correlation between MPO-A and HDL-C was found in the group III ($r = –0.46$; $p < 0.05$). Thus, the impact of MPO activity on the RCT with concomitant HDL-C depletion was more significant among the patients with complicated form of chronic CHD than in other groups, and the principal issues of this study are interconnected.

Taking into account strong relationships between MPO-T, MPO-A and HDL-C, it is reasonable to estimate MPO activity and its impact on the RCT with allowance for HDL-C level. Multiple comparison test for obtained MPO-CA/HDL-C ratio revealed the differences between the groups (Fig. 2). Subsequent pairwise matching shows with high statistical significance that the MPO-CA/HDL-C ratio was higher among the patients who have had acute coronary syndrome in the anamnesis, as compared with the patients manifesting non-complicated stable CHD ($p < 0.001$) and with the patients from group I who had no CHD ($p < 0.001$). No significant difference between group II and group I was found.

Binary logistic regression (logit-model) was applied to determine diagnostic value of the MPO-CA/HDL-C ratio for different forms of chronic CHD (with or without previous history of acute coronary syndrome). Hence, ROC curve was constructed (Fig. 3). The calculated AUC was 0.8 which indicates a high predictive value of the MPO-CA/HDL-C ratio for different forms of chronic CHD. The cut-off value 0.351 with sensitivity 62% and specificity 81% was applied to predict possible adverse outcomes in this group of patients. The level of false positive results was relatively low i.e. 19%, which means that the MPO-CA/HDL-C ratio is acceptable for sifting out patients with relatively benign stable form of chronic CHD, not predisposed to acute cardiac events. Along with elucidation of the known risk factors, MPO-CA/HDL-C ratio can help to ascertain the patients with established cardiovascular disease. It also seems indicative of the residual risk of adverse outcomes, which combine lipidic and inflammatory components. Further research is needed to verify this hypothesis. Moreover, it seems promising to investigate natural MPO inhibitors as potential instruments in the therapy aimed at diminishing the risk of acute cardiovascular events and at better prognosis among the patients with chronic CHD.

Conclusions

The results of this study demonstrate that in patients with preceding history of acute coronary syndrome as compared with those having a stable

course of chronic CHD the effect of MPO on RCT depends on its activity rather than concentration. MPO-CA/HDL-C ratio mirrors the complicated chronic CHD and might serve as an additional indicator of residual risk. Studying the natural MPO inhibitors seems promising as it can help finding new approaches to a better prognosis for that group of patients.

Additional information

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Author contribution: All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

Personal contribution of each author: *I.A. Churashova:* conducting experiments, processing of the results, preparation of the manuscript; *A.V. Sokolov:* purification of myeloperoxidase, preparation of the manuscript; *V.A. Kostevich:* development of bromide version of SIEFED, preparation of labelled antibody, validation of ELISA and SIEFED results; *N.P. Gorbunov:* obtaining monoclonal antibodies against MPO, development of ELISA; *T.V. Baranova:* organization of samples storage and validation of MPO standards; *E.M. Firova:* coordination between clinic and scientific departments, concept development, research management; *M.Yu. Mandelshtam:* concept development, coordination between clinic and scientific departments; *V.B. Vasilyev:* concept development, research management, preparation of the manuscript.

Дополнительная информация

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Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов в финансовой или какой-либо другой сфере.

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Наибольший вклад распределен следующим образом: *И.А. Чурашова* — проведение эксперимента, обработка результатов, подготовка рукописи; *А.В. Соколов* — выделение и очистка миелопероксидазы, подготовка рукописи; *В.А. Костевич* — разработка варианта теста SIEFED с бромидом, получение меченых антител, валидация результатов тестов SIEFED и ELISA; *Н.П. Горбунов* — получение моноклональных антител к миелопероксидазе, разработка теста ELISA; *Т.В. Баранова* — организация накопления и хранения образцов, валидация стандартных образцов миелопероксидазы; *Э.М. Фирова* — взаимодействие между клиническим и научным отделами, разработка концепции, руководство клинической частью исследования; *М.Ю. Мандельштам* — разработка концепции, взаимодействие между клиническим и научным отделами; *В.Б. Васильев* — разработка концепции, общее руководство исследованием, подготовка рукописи.

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