УДК 616.132.2-004.6
https://doi.org/10.20538/1682-0363-2025-2-14-27

Coronary Calcium Associated with Changes in Instrumental and Humoral Markers of Sympathetic Activity in Patients with Non-Obstructive Coronary Atherosclerosis

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Abstract

Aim. To study the associations between sequential factors of the 10-year coronary heart disease (CHD) risk index MESA, heart rate variability (HRV), molecular markers of sympathetic activity and the presence or absence of calcium in the coronary arteries (CA) in patients with non-occlusive coronary atherosclerosis.

Materials and methods. A total of 30 patients with suspected CHD, as a result of which at least one CA stenosis < 70% with a left ventricular ejection fraction ≥ 50% according to transthoracic echocardiography was identified using coronary computed tomography angiography. HRV was studied by means of daily monitoring of electrocardiograms, analyzing the parameters of time and spectral analysis. All patients had blood samples taken to measure copeptin, catestatin, high-sensitivity C-reactive protein (hsCRP) and amino-terminal pro-brain natriuretic peptide (NT-proBNP). Statistical analysis was performed after dividing the distribution into two subgroups depending on the value of the coronary calcium index (coronary calcium Agatston score; CCI): group 1 (CCI 0, $n = 11$) and group 2 (CCI > 0, $n = 19$).

Results. Statistically significant ($p < 0.05$) correlations of CCI with lipid damage indices were established regarding total cholesterol and low-density lipoprotein cholesterol (LDL-C) ($r = –0.36$ and $r = –0.40$, respectively), coronary artery age ($r = 0.77$), 10-year coronary heart disease risk index MESA ($r = 0.78$) and 10-year prognosis of adverse cardiovascular events ($r = 0.39$). Multivariate regression analysis showed that the presence of coronary artery indices (CCI > 0) in patients with non-obstructive coronary artery lesions is independently associated with a family history of coronary heart disease [odds ratio (OR) 1.92, $p = 0.0011$]; HRV indices [NN (OR 1.75, $p = 0.0001$); SDANN (OR 1.43, $p = 0.0136$); pNN50 (OR 1.34; $p = 0.0153$); rMSSD (OR 1.88; $p = 0.0793$)] and high-density lipoprotein cholesterol (OR 1.09; $p = 0.0111$) were determined. The study determined threshold values of LDL-C (≤ 1.82 mmol/L; AUC = 0.72; $p = 0.002$) and copeptin (≤ 0.485 ngm/L; AUS = 0.672; $p = 0.021$) and hsCRP with catestatin (hsCRP ≤ 1.21 g/L and catestatin ≤ 138.1 μg/ml; AUC = 0.674; sensitivity 56.2%; $p = 0.021$), which in such patients can be used as markers associated with the presence of coronary calcium.

Conclusion. The presence of calcium in the coronary arteries in patients with non-obstructive lesions of the coronary arteries associated with an aggravated family history of CHD, disintegration of the autonomic heart regulation, which is expressed in the suppression of the activity of the parasympathetic division of the autonomic nervous system and the levels of reduction of LDL-C.

Keywords: coronary calcium, non-obstructive coronary atherosclerosis, heart rate variability, markers of sympathetic activity, myocardial blood flow reserve; microvascular dysfunction

Conflict of interest. The authors declare no obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The study was conducted as part of the applied scientific research "New integrative high-tech methods of diagnosis and treatment of ischemic heart disease" No. 123051500131-6.

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Conformity with the principles of ethics. All patients signed a voluntary informed consent to participate in the study. The study was approved by the Committee on Biomedical Ethics of Cardiology Research Institute of the Tomsk National Research Medical Center (Protocol No. 177 of 30.10.2018).

For citation: Grakova E.V., Kopeva K.V., Maltseva A.N., Dasheeva A., Zavadovsky K.V., Gusakova A.M., Svarovskaya A.V., Vorozhtsova I.N., Antsifirova E.L., Shadrina Yu.L. Coronary Calcium Associated with Changes in Instrumental and Humoral Markers of Sympathetic Activity in Patients with Non-Obstructive Coronary Atherosclerosis. *Bulletin of Siberian Medicine.* 2025;24(2):14–27. https://doi.org/10.20538/1682-0363-2025-2-14-27.

Наличие коронарного кальция ассоциировано с изменением инструментальных и гуморальных маркеров симпатической активности у больных с неокклюзирующим коронарным атеросклерозом

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РЕЗЮМЕ

Цель. Изучить наличие ассоциаций между традиционными факторами 10-летнего индекса риска ишемической болезни сердца (ИБС) MESA, вариабельностью ритма сердца (ВРС), молекулярными маркерами симпатической активности и наличием или отсутствием кальция в коронарных артериях (КА) у пациентов с неокклюзирующим коронарным атеросклерозом.

Материалы и методы. В настоящее исследование включены 30 пациентов с подозрением на ИБС, которым посредством коронарной компьютерной томографической ангиографии был идентифицирован как минимум один стеноз КА менее 70% с фракцией выброса левого желудочка ≥ 50% по данным трансторакальной эхокардиографии. Вариабельность ритма сердца исследовали посредством суточного мониторирования электрокардиограммы, анализируя показатели временного и спектрального анализа. У всех пациентов были взяты образцы крови для измерения копептина, катестатина, высокочувствительного С-реактивного белка (вчСРБ) и аминоконцевого промозгового натрийуретического пептида (NT-proBNP). Статистический анализ проводился после разделения исследуемой популяции на две подгруппы в зависимости от величины индекса коронарного кальция (coronary calcium (Agatston) score; ИКК): 1-я группа (ИКК 0, $n = 11$) и 2-я группа (ИКК >0, $n = 19$).

Результаты. Установлены статистически значимые ($p < 0,05$) корреляции ИКК с показателями липидного спектра: общим холестерином и холестерином липопротеидов низкой плотности (ХС ЛПНП) ($r = –0,36$ и $r = –0,40$ соответственно), возрастом коронарных артерий ($r = 0,77$), индексом 10-летнего риска ИБС MESA ($r = 0,78$) и с 10-летней вероятностью наступления неблагоприятных сердечно-сосудистых событий ($r = 0,39$). Многофакторный регрессионный анализ позволил установить, что наличие кальция в коронарных артериях (ИКК > 0) у пациентов с необструктивным поражением КА независимо связано с отягощенным семейным анамнезом ИБС [отношение шансов (ОШ) 1,92, $p = 0,0011$]; показателями ВРС [NN (ОШ 1,75, $p = 0,0001$); SDANN (ОШ 1,43, $p = 0,0136$); pNN50 (ОШ 1,34; $p = 0,0153$); rMSSD (ОШ 1,88; $p = 0,0793$)] и холестерина липопротеидов высокой плотности (ОШ 1,09; $p = 0,0111$). Определены пороговые значения ХС ЛПНП (≤1,82 ммоль/л; AUC = 0,72; $p = 0,002$) и копептина (≤0,485 нгм/л; AUC = 0,672; $p = 0,021$) и комбинации вчСРБ с катестатином (вчСРБ ≤ 1,21 г/л и катестатин ≤ 138,1 нг/мл; AUC = 0,674; чувствительность 56,2%; специфичность 82,2%; $p = 0,021$), которые у таких пациентов могут использоваться в качестве маркеров, ассоциированных с наличием коронарного кальция.

Заключение. Наличие кальция в коронарных артериях у пациентов с необструктивным поражением КА ассоциировано с отягощенным семейным анамнезом преждевременной ИБС, дезинтеграцией вегетативной регуляции работы сердца, выражающейся в подавлении активности парасимпатического отдела вегетативной нервной системы, и снижением уровней ХС ЛПНП.

Ключевые слова: коронарный кальций, неокклюзирующий коронарный атеросклероз, вариабельность ритма сердца, маркеры симпатической активности, резерв миокардиального кровотока, микроваскулярная дисфункция

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Исследование выполнено в рамках прикладного научного исследования «Новые интегративные высокотехнологичные методы диагностики и лечения ишемической болезни сердца» № 123051500131-6.

Соответствие принципам этики. Все пациенты подписали добровольное информированное согласие на участие в исследовании. Исследование одобрено комитетом по биомедицинской этике НИИ кардиологии Томского НИМЦ (протокол № 177 от 30.10.2018).

Для цитирования: Гракова Е.В., Копьева К.В., Мальцева А.Н., Дашеева А., Завадовский К.В., Гусакова А.М., Сваровская А.В., Ворожцова И.Н., Анцифирова Е.Л., Шадрина Ю.Л. Наличие коронарного кальция ассоциировано с изменением инструментальных и гуморальных маркеров симпатической активности у больных с неокклюзирующим коронарным атеросклерозом. *Бюллетень сибирской медицины.* 2025;24(2):14–27. https://doi.org/10.20538/1682-0363-2025-2-14-27.

INTRODUCTION

In the age of personalized medicine, the timely detection of cardiovascular risk in people is the decisive factor for ensuring adequate prevention of cardiovascular pathology, which is the leading cause of mortality and morbidity among the working-age population. It is interesting that the absolute risk is often significantly lower than the risk predicted, for example, by the Framingham risk score for non-fatal myocardial infarction or cardiac death in the next 10 years [1–4]. Undoubtedly, the problem of early risk assessment and risk stratification tools is highly relevant in the Russian Federation, since high mortality among people of working age who do not have proven cardiovascular diseases (CVD) remains quite high.

Certain progress has been made in this direction, in particular, Boitsov et al. [1] provide information that the National Medical Research Center for Therapy and Preventive Medicine developed a Russian scale to assess the risk of fatal cardiovascular complications over the next 10 years, based on the SCORE system and designed for the first time for the Russian population; researchers from Saratov State Medical University proposed an automated system for non-invasive monitoring of the degree of risk of developing CVD and its complications [5]. Researchers from Siberia (Barnaul and Tyumen) also made certain advances in this area [5, 6].

As one of the risk modifiers in assessing the risk of CVD, according to the 2018 ESC guidelines for the diagnosis and treatment of chronic coronary syndromes with certain assumptions (no data on the impact on prognosis, unreasonable costs for coronary computed tomography angiography and functional imaging tests to examine asymptomatic patients at low risk, without diabetes mellitus, with no family history of early coronary heart disease (CHD) or smoking history), it was proposed to consider the coronary calcium index (coronary calcium index, CCI), since it provides a 66% improvement in reclassification compared to traditional risk factors [3, 7].

There is another point of view on the appropriateness of using CCI [8]. Thus, in contrast to the 2018 ESC and 2019/2018 AHA/ACC guidelines, experts from the US Preventive Services Task Force (USPSTF) provide data that, compared with non-traditional CVD risk factors, taking into account CCI leads to an unreliable increase in the quality of reclassification. Despite this, it should not be denied that the assessment of coronary calcium of the heart contributes greatly to the reclassification of risk for a particular patient. In particular, according to R.A. Groen et al. (2024), patients' knowledge of their calcium level correlates with improved compliance with the treatment regimen and more effective lifestyle modification [9].

In recent years, there has been some evidence that high atherosclerotic load is closely associated with cardiac vegetative dysfunction through the innervation of vascular walls (endothelial dysfunction), which is mediated by the autonomic nervous system (ANS), the activity of its sympathetic and parasympathetic branches [10]. There is very little evidence of a dose-dependent effect of statins on baroreceptor sensitivity, sympathetic activity, and regulation of cardiovascular reflexes [11]. However, the pathways that mediate the effect of the autonomic nervous system on the structure and function of blood vessels and are complex and poorly understood, as evidenced by scarce data in the scientific literature of recent years.

It is known that endothelial dysfunction, a pathological vascular phenotype of all systemic arteries characterized by the damaging effect of vasoconstrictor, pro-inflammatory and prothrombotic mediators, which can be assessed by the level of humoral biomarkers, on the endothelial vascular membrane and leads to a violation of the endothelium ability to recover, is reasonably considered an independent pathobiological driver of atherosclerosis and related pathogenetic pathways of cardiovascular diseases [12, 13]. Meanwhile, data on the presence of integrative pathophysiological cross-interactions of humoral biomarkers, branches of the autonomic nervous system in relation to the state of myocardial blood flow in the early stages of atherosclerosis development depending on its severity, assessed by the CCI, are clearly insufficient [2]. Interest in studying this problem is also easily explained from the point of view of its practical focus, bearing in mind the search for therapeutic targets and opportunities for effective lifestyle modification and patient adherence to treatment.

A aim of the study was to evaluate the presence of association between traditional factors of the 10-year MESA coronary heart disease risk index, heart rate variability (HRV), and humoral markers of sympathetic activity depending on the presence or absence of calcium in the coronary arteries (CA) in patients with non-occlusive coronary atherosclerosis.

MATERIALS AND METHODS

The prospective, single-center, non-randomized, clinically controlled study to assess the relationship between traditional risk factors, heart rate variability, and molecular and instrumental markers of sympathetic activity and cardiovascular risk and their contribution to the assessment of the 10-year MESA coronary heart disease risk index. Data from patients with suspected coronary heart disease (complaints of pain in the heart and/or shortness of breath during exercise) were collected and analyzed at Cardiology Research Institute, Tomsk National Research Medical Center, Russian Academy of Sciences (Tomsk, Russia) over the period from 2022 to 2023. The study was conducted in accordance with the principles of Declaration of Helsinki and was approved by the Ethics Committee, dated October 30, 2018. Written informed consent was obtained from all patients at the time of their inclusion in the study.

Exclusion criteria were as follows: age under 18 years, left ventricular ejection fraction (LVEF) < 50%, inflammatory myocardial diseases, storage diseases, the presence of congenital or acquired valvular pathology – diagnosed moderate to severe heart disease, history of myocardial revascularization, active infection or serious hematological, metabolic or endocrine dysfunction; chronic kidney disease stages 4–5 (glomerular filtration rate (CKD-EPI) < 30 ml/min/1.73 m^2), condition after pacemaker installation, hypertrophic or dilated cardiomyopathy, ventricular extrasystole grade III–IV (Lown grade), the presence of chronic heart failure (CHF) with preserved LVEF (symptoms and/or signs of CHF; LVEF ≥ 50%; NT-proBNP level more than 125 pg/ml; structural heart change (LV hypertrophy and/or left atrial enlargement) and/or diastolic dysfunction), stroke, transient ischemic attack, history of pulmonary embolism of any duration, acute condition at the time of the study (acute coronary syndrome, acute cerebrovascular accident, pulmonary embolism, acute myocarditis, acute pericarditis, dissecting aortic aneurysm, acute heart failure), obstructive atherosclerotic lesion of the coronary arteries (≥ 70%), identified according to multislice computed tomography coronary angiography (MCTCA), poor quality of MCTCA, the presence of objective signs of previous myocardial infarction, pregnancy, and breastfeeding. . Exclusion criteria from the study also included patient's refusal to further participate in the study.

All patients underwent a general examination, determination of the level of coronary calcium according to MCTCA, and assessment of markers of autonomic dysfunction.

The study included patients (n = 30) aged 59.7 [54.1; 67.2] years (63.3% men) with suspected coronary heart disease, with symptoms of stable angina pectoris and/or dyspnea, who were identified with at least one coronary artery stenosis <70% according to

MCTCA data, LVEF ≥ 50% according to transthoracic echocardiography. Group 1 included patients with CCI = 0, patients with CCI > 0 constituted group 2. There were no statistically significant differences in the number of individuals with cardiovascular risk (SCORE2 scale) in the categories of "low, moderate, high, and very high risk": in group 1 – 18.2, 18.2, 36.4 and 27.3%, in group 2 – 5, 15, 35 and 45%, respectively.

Biochemical studies of markers of autonomic dysfunction. Blood samples were collected, frozen and stored for further analysis of sympathetic activity and cardiovascular risk markers (natriuretic peptide, high-sensitivity C-reactive protein, catestatin, and copeptin).

Blood samples were obtained in the morning on an empty stomach after a 16-hour fast by venipuncture; adequate centrifuged serum samples were stored at -26 °C with one freeze-thaw cycle. Determination of serum biomarkers in vitro was performed by enzyme immunoassay (catestatin, RayBio, USA; copeptin (human), Phoenix Pharmaceutical, Inc., USA; high-sensitivity C-reactive protein, Biomedica immunoassays, Austria; NT-proBNP, Biomedica immunoassays, Austria). Photometric detection of the immunochemical reaction was performed on an Infinite F50 microplate reader (Tecan, Australia).

Heart rate variability (HRV) was analyzed using 24-hour electrocardiogram monitoring (24-hour ECG). At least 12 hours before and during 24-hour ECG, patients were prohibited from drinking caffeinated beverages, and 24 hours before 24-hour ECG, patients who received β-blockers were discontinued. Temporal (SDNN; SDANN; SDNNidx; RMSSD; NN50, 100, 200; pNN50, 100, 200) and spectral parameters of HRV (VLF; LF; HF; LF/HF) were assessed. A detailed description of the HRV parameters and their interpretation are presented in our other work [14].

Echocardiography (EchoCG) was performed in all patients according to the standard protocol using the EPIQ device (Philips Ultrasound, Inc., USA). The cardiac structures were visualized using B- and M-scanning according to the generally accepted method. All studies were performed by a highly qualified specialist.

MCTCA and quantitative assessment of coronary artery calcification. All patients underwent MCTCA on a 64-row tomograph Revolution Evo tomograph (GE HealthCare, USA). The day before MCTCA of the heart, patients were advised to exclude caffeinated beverages, metformin, sildenafil, and painkillers from their diet. To determine the CCI, non-contrast computed tomography of the heart region was performed with prospective ECG synchronization and subsequent reconstruction in 75% of the R-R phase of the cardiac cycle interval. Recording was performed from the level of the tracheal bifurcation to the diaphragm with breath holding (6–8 s) in a step-by-step mode with a slice thickness of 2.5 mm and a tube rotation time of 0.4 s. The voltage in the tube was 120 kV, the current was 200–435 mA. The CI analysis was performed using the Agatston method on the Advantage Workstations 4.7 workstation (GE Healthcare, Milwaukee, WI, USA) in the SmartScore 4.0 software (in Agatston units) [15].

As a result of processing, data were obtained on coronary artery calcification by vascular regions (left coronary artery trunk, anterior descending artery, circumflex artery, and right coronary artery) and in total for the coronary bed [16]. Additionally, based on the MCTCA data, the 10-year risk of coronary heart disease according to MESA and the age of the coronary arteries were estimated using the corresponding calculators developed, tested, and described by Robyn et al. (2015) and Blaha et al. (2021) [17, 18].

To perform MCTCA, patients were administered 70–90 ml of non-ionized, low-osmolar radiopaque contrast agent Iopromide (Ultravis 370) at a rate of 5 ml/s, followed by the introduction of 40 ml of normal saline at the same rate. The recording was made in a spiral ECG (prospective or retrospective) synchronized mode with an X-ray tube rotation speed of 0.35 m and a slice thickness of 0.625 mm. The voltage in the tube was 120 kV, the current was 450–550 mA. CardIQ Xpress 2.0 software was used to plot and analyze the coronary arteries. The analysis collected data on the presence of atherosclerotic plaques and the degree of coronary artery stenosis. The criterion for obstructive lesion was a narrowing of ≥ 70%.

Dynamic single-photon emission computed tomography (SPECT) of the heart and myocardial perfusion scintigraphy (MPS). The study was performed using a 2-day rest/exercise protocol using 99mTc-methoxy-isobutyl-isonitrile; adenosine triphosphate (160 μg/kg/min) was administered as a stress agent during the exercise test. Myocardial perfusion and blood flow parameters were analyzed using 4DM Reserve v.2015 and Corridor 4DM SPECT software (INVIA, Ann Arbor, USA). The standard MPS data were used to assess global indices (SSS, SRS, SDS), and the dynamic SPECT data were used for quantitative global indices such as stress and rest myocardial blood flow (sMBF, rMBF), and myocardial blood flow reserve (MBFR).

Statistical data processing, as in our previous work, was performed using the Statistica 10.0 (StatSoft, Inc., USA). The distribution of features was assessed using the Shapiro–Wilk test, and the homogeneity of general variances was assessed using Levene's test. Quantitative data were presented as median and interquartile range *Me* [Q_{25}; Q_{75}]. The Mann–Whitney *U* test was used to test statistical hypotheses when comparing two independent groups. Correlation analysis was used with the calculation of Spearman's rank correlation coefficients to measure association between variables. When analyzing qualitative features, we analyzed contingency tables using the Pearson's $\chi 2$ test or Fisher's exact test when the mathematical expectation of values in any of the table cells with the specified boundaries was below 10. To assess the sensitivity and specificity of the models and select the cutoff threshold, we used ROC analysis with the construction of characteristic curves and calculation of the area under the curve (AUC, area under curve). The AUC value exceeding 0.70 was considered significant. To identify factors that have a significant impact on the course and prognosis of the disease, we calculated the odds ratio (OR) with a 95% confidence interval (CI). The critical significance level *p* for all statistical analysis procedures used was 0.05.

RESULTS

The clinical baseline characteristics of the study population are shown in Table 1.

Table 1

Basic Clinical and Laboratory Characteristics of Patients with Non-Obstructive Coronary Atherosclerosis

Parameters	Group 1, *n* = 11 CCI = 0	Group 2, *n* = 19 CCI > 0	*p*
Age, years, *Me* [Q_{25}; Q_{75}]	57.1 [40.9; 68.8]	62.9 [48.1; 76.5]	0.1853
Female, *n* (%)	4 (36.4)	7 (36.8)	0.7162
Diabetes mellitus, *n* (%)	0 (0)	2 (10.5%)	0.1379
Atrial fibrillation, *n* (%)	1 (9.1)	5 (26.3)	0.1577
Arterial hypertension, *n* (%)	11 (100.0)	19 (100.0)	1.0000
Current smoking, *n* (%)	1 (9.09)	8 (42.11)	0.0142
Family history of premature CHD, *n* (%)	11 (100)	12 (63.16)	0.0021
Systolic blood pressure, mm Hg, *Me* [Q_{25}; Q_{75}]	125.0 [120.0; 130.0]	125.0 [120.0; 130.0]	0.9178
Diastolic blood pressure, mm Hg, *Me* [Q_{25}; Q_{75}]	80.0 [72.0; 90.0]	80.0 [70.0; 85.0]	0.6623
Heart rate, beats per minute, *Me* [Q_{25}; Q_{75}]	73.0 [70.0; 77.0]	68.0 [65.0; 72.0]	0.0048
Glucose, mmol/L, *Me* [Q_{25}; Q_{75}]	5.65 [4.47; 6.54]	5.40 [4.12; 5.90]	0.6484
Cathestatin, μg/ml, *Me* [Q_{25}; Q_{75}]	222.23 [136.7; 294.1]	172.40 [100.2; 210.4]	0.1467
Copeptin, ng/mL, *Me* [Q_{25}; Q_{75}]	0.439 [0.334; 0.689]	0.441 [0.374; 0.485]	0.5801
hsCRP, g/L, *Me* [Q_{25}; Q_{75}]	2,50 [1,20; 4,70]	3,1 [1,70; 11,90]	0,0491
Total cholesterol, mmol/l, *Me* [Q_{25}; Q_{75}]	5,18 [4.10; 6.12]	4.3 [3.41; 5.52]	0.0292
HDL-C, mmol/L, *Me* [Q_{25}; Q_{75}]	1.3 [1.02; 1.59]	1.20 [1.03; 1.59]	0.4910
LDL-C, mmol/L, *Me* [Q_{25}; Q_{75}]	2.81 [2.11; 3.9]	1.82 [1.49; 2.50]	0.0014
Achievement of target LDL-C levels, n (%)	1 (9.09%)	4 (21.05%)	0.2760
Therapy, *n* (%)			
Statins	7 (63.64%)	15 (78.94%)	0.1116
Beta-blockers	5 (45.45%)	10 (52.63%)	0.4114
ACE inhibitors	2 (18.18%)	8 (42.11%)	0.1063
Angiotensin II receptor blockers	3 (27.27%)	4 (21.05%)	0.4175
Calcium channel antagonists	2 (18.18%)	6 (31.58%)	0.3784
Diuretic	3 (27.27%)	4 (21.05%)	0.4175

Note. Here and in Table 5:NT-proBNP – N-terminal propeptide of natriuretic hormone (B-type); ACE – angiotensin-converting enzyme; hsCRP – high-sensitivity C-reactive protein; CCI – coronary calcium index; CHD – coronary heart disease; HDL-C – high-density lipoprotein cholesterol; LDL-C – low-density lipoprotein cholesterol.

A total of 30 patients with an average age of 59.7 years [54.1; 67.2] were included in the cohort. Two-thirds of the examined patients were men (men 63.3%, *n* = 19). All patients were taking antihypertensive drugs and had a history of arterial hypertension, and dyslipidemia was diagnosed in 100% of cases, for which three out of four patients were taking statins. At the same time, judging by the number of patients

who achieved target LDL-C levels, the drug doses were clearly not optimal. Another predominant cardiovascular risk factor (76.7%, n = 23) was a family history of premature coronary heart disease. Significantly less common among other risk factors were smoking (30%), atrial fibrillation (20%), and type 2 diabetes mellitus (6.7%). According to MSCT-CAG data, all patients were found to have stenosis of up to 70% of the vessel lumen in at least one coronary artery, with stenosis of 50–70% in almost half of those examined (46.7%, n = 14).

The patients were divided into groups depending on the CCI value: group 1 (CCI 0, n = 11) and group 2 (CCI > 0, n = 19). Family history of premature coronary heart disease was found in all patients of group 1 and significantly less frequently (63.2%, p = 0.0021) in group 2. Moreover, among patients with CCI > 0 there were more (p = 0.0142) smokers, they were diagnosed with 50–70% coronary artery stenosis and damage to more than one epicardial artery twice more often (p = 0.0077). The catestatin level in patients with CCI > 0 was 22.4% (p = 0.1467) lower than in individuals with CCI = 0, but the hsCRP content, on the contrary, was higher in those examined in group 2 (2.50 vs. 3.1; p = 0.049).

The levels of cholesterol and LDL-C in patients with CCI = 0 were higher than similar indicators in individuals with CCI > 0, while the frequency of achieving the target level of LDL-C in group 1 was clearly lower than in group 2, despite a comparable number of patients taking statins.

The MESA 10-year coronary heart disease risk index, taking into account coronary calcium in patients of group 2, was 2.5 (p < 0.0343) times higher than the same indicator in group 1 (Fig. 1). Statistically significant differences also concerned such an indicator as the difference between coronary age and chronological age taking into account the CCI, in particular, such in the group of patients with CCI > 0 was 2.5 times higher than the same indicator in patients of group 1 (CCI = 0).

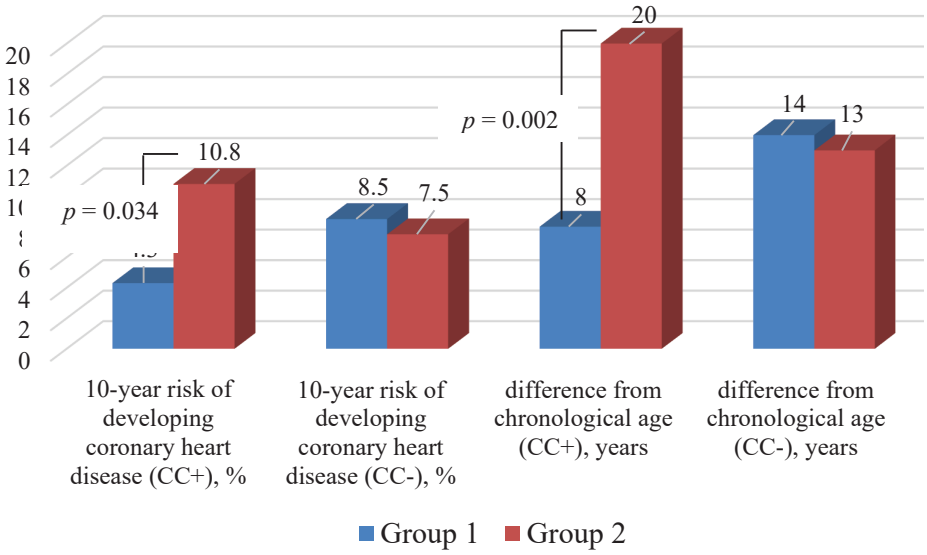


Fig. 1. The risk index for developing coronary heart disease over 10 years and the difference between coronary age and chronological age in groups of patients with non-occlusive coronary atherosclerosis depending on the presence or absence of coronary calcium

The analysis of global myocardial SPECT data is presented in Table 2. Standard parameters of SCF, myocardial blood flow reserve, and myocardial blood flow parameters at rest and under stress test conditions did not differ between the groups. At the same time, statistically significant (p < 0.05) differences were observed in the number of coronary arteries with atherosclerotic plaques and the number of patients with 50–70% stenosis.

Table 3 presents the temporal parameters of HRV, but the spectral indicators did not have significant differences and are not presented in the table.

When analyzing the results of the HRV study, signs of disintegration of the autonomic regulation of cardiac function were revealed, expressed in the suppression of the activity of the parasympathetic division of the autonomic nervous system, which reflects one of the HRV indicators – rMSSD [19]. In particular, compared with group 1, in patients with CCI > 0, rMSSD was 1.6 times lower (p = 0.044).

Analysis of the ROC curve characteristics showed that copeptin levels ≤0.485 ng/ml allow identification of patients whose CCI exceeds zero, although they showed low but statistically significant discriminatory ability of the model (AUC = 0.672; sensitivity 88%, specificity 60%; p = 0.021) (Fig. 2, *a*).

Table 2

Data of MCTCA and Dynamic SPECT in Patients with Non-Obstructive Coronary Atherosclerosis

Parameters	Group 1, n = 11 CCI = 0	Group 2, n = 19 CCI > 0	p
Calcium index, Agatston units, *Me* [Q_{25}; Q_{75}]	0 [0.0; 0.0]	191.00 [68.0; 367.0]	0.000
CA stenosis 50–70%, n (%)	3 (27.27)	11 (57.90)	0.008
Number of CA with plaques, n (%)	1.0 [1.0; 2.0]	3.0 [2.0; 3.0]	0.000
Standard semiquantitative indices of myocardial perfusion impairment, Me [Q_{25}; Q_{75}]			
SSS	2.0 [0.0; 3,0]	2.0 [0.0; 3.0]	0.450
SRS	0.0 [0.0; 0.0]	0.0 [0.0; 0.0]	0.568
SDS	2.0 [0.0; 3.0]	2.0 [0.0; 2.0]	0.217
Dynamic SPECT parameters, Me [Q_{25}; Q_{75}]			
sMBF, ml/min/g	1.33 [0.81; 1.79]	1.29 [0.98; 1.75]	0.840
rMBF, ml/min/g	0.94 [0.59; 1.23]	0.76 [0.56; 1.08]	0.367
MBFR	1.41 [1.22; 1.61]	1.47 [1.23; 2.09]	0.429

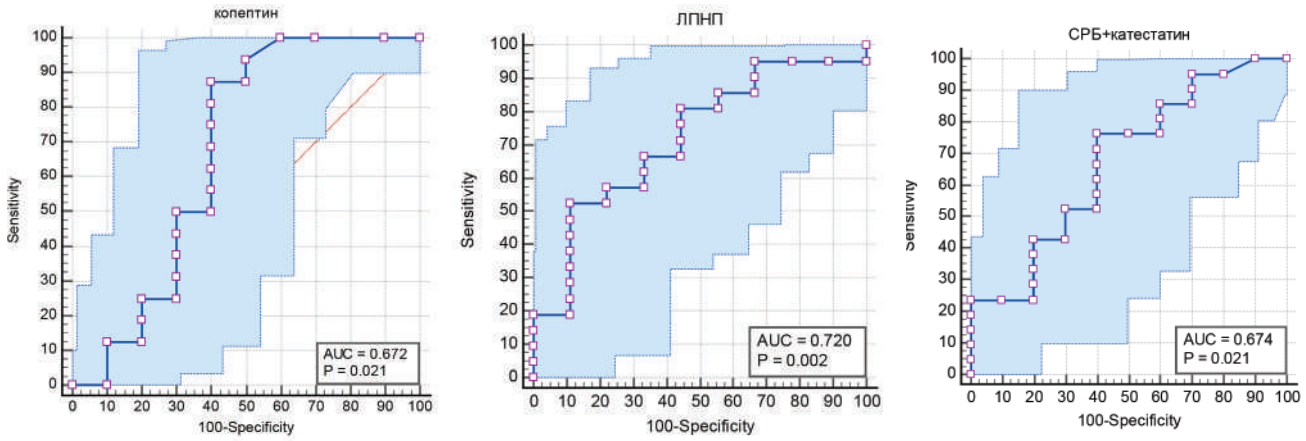
Note. Here and in Table 4: SDS – stress-rest difference; SRS – rest score; SSS – stress score; CA – coronary artery; MCTCA – multislice computed tomography coronary angiography; SPECT – single photon emission computed tomography; rMBF – rest myocardial blood flow; MBFR – myocardial blood flow reserve; sMBF – stress myocardial blood flow.

Table 3

Data from Daily Holter ECG Monitoring (Indicators of Heart Rate Variability in Patient Groups), *Me* [Q_{25}; Q_{75}]

Parameters	Group 1, n = 11 CCI = 0	Group 2, n = 19 CCI > 0	p
SDNN, ms	123.5 [90.0; 169.0]	115.00 [99.0; 130.0]	0.5946
SDANN, ms	92.5 [70.0; 118.0]	93.00 [79.0; 102.0]	0.8801
SDNNidx, ms	63 [53.0; 73.0]	59 [53.0; 72.0]	0.3948
NN50, ms	4,132.5 [1,731.0; 12,890.0]	6,189.00 [3578.0; 16,397.0]	0.2049
NN100, ms	885.5 [369.0; 1,499.0]	438.00 [269.0; 6,363.0]	0.2049
pNN50, %	7.9 [4.0; 22.7]	5.75 [4.5; 18.0]	0.5946
rMSSD, %	57.0 [30.0; 72.0]	35.00 [27.0; 59.0]	0.0438

Note. Here and in Table 5: SDNN is the standard deviation of the full array of RR cardiointervals; SDANN is the standard deviation of the averaged normal R-R sinus intervals of all 5-minute periods for the entire observation period; SDNNidx is the average value of standard deviations of NN intervals calculated for 5-minute intervals in the specified recording period; rMSSD is the square root of the average sum of squares of differences between adjacent NN intervals; NN50 (100, 200) is the number of pairs of adjacent NN intervals that differ by more than 50 (100, 200) ms; pNN50 (100, 200)% is the NN50 (100, 200) value divided by the total number of NN intervals in the analyzed monitoring period (norm = 6.3 ± 0.8%); p is the statistical significance of intergroup differences.



a *b* *c*

Fig. 2. ROC curve characteristics of humoral biomarkers for optimal binary classification of the presence or absence of coronary calcium in patients with suspected CHD (ROC analysis): a) copeptin; b) LDL-C; c) hsCRP+catestatin. Note. The ordinate axis shows sensitivity (%), the abscissa axis shows 100 minus specificity (%). The rectangles show the sensitivity (Sensitivity) and specificity (Specificity) estimates for the corresponding decision rule threshold (Criterion), as well as the area under curve (AUC) values together with the significance level (p) estimates.

The best characteristics of the binary classification of the presence or absence of coronary calcium in patients with suspected coronary heart disease among humoral markers were shown by LDL-C ≤1.82 mmol/L (AUC = 0.72; sensitivity 52%, specificity 89%; $p = 0.002$) (Fig. 2B) and a combination of hsCRP with catestatin (hsCRP ≤ 1.21 g/L and catestatin ≤ 138.1 μg/ml; AUC=0.674; sensitivity 56.2%; specificity 82.2%; $p = 0.021$) (Fig. 2, *c*).

According to the correlation analysis, statistically significant (the *p* parameters for this analysis ranged from 0.001 to 0.02) relationships were established between the 10-year risk of developing coronary heart disease (taking into account the CCI) and the difference between coronary and chronological age with humoral biomarkers characterizing neurohumoral activation and reflecting the severity of endogenous neurohormonal stress, indices of myocardial perfusion impairment and indicators of myocardial blood flow and reserve (Table 4). In particular, the 10-year risk of developing coronary heart disease (taking into account the CCI) was directly associated with the volume of myocardial perfusion impairment at rest (SRS) ($r = 0.60$), and the myocardial blood flow indices at rest and under stress ($r = –0.45$ and $r = –0.35$, respectively) and the copeptin level ($r = –0.31$) were inversely associated. The difference between the coronary and chronological ages was negatively correlated with the levels of both biomarkers (copeptin – $r = –0.36$ and catestatin – $r = -0.44$) and was directly associated with SRS ($r = 0.66$). In turn, there was a moderate degree of association between the 10-year risk of developing coronary heart disease (taking into account the CCI) and the difference between the coronary and chronological ages ($r = 0.69$).

Table 4

"Heat Map" of Correlations between the Analyzed Biomarkers

Parameter	Copeptin	Cate-statin	sMBF	rMBF	MBFR	SRS	SDS	10-year risk	Difference from ChA
Copeptin		*				*		*	*
Catestatin	*								*
sMBF				*				*	
rMBF			*		*			*	
CFR				*		*	*		
SRS	*				*			*	*
SDS					*				
10-year risk	*		*	*		*			*
Difference from ChA	*	*				*		*	

Note. ChA – chronological age. * *p* for this correlation analysis were between 0.001 and 0.05.

Multivariate regression analysis revealed that the presence of coronary artery calcification (CCI = 0) in patients with non-obstructive coronary atherosclerosis was independently associated with the levels of lipid spectrum parameters, catestatin, and copeptin, a family history of coronary heart disease, smoking, diabetes mellitus, and the HRV parameter associated with the regulation of parasympathetic activity of the autonomic nervous system (rMSSD) (Table 5).

Table 5

Multivariable Linear Regression Model to Assess the Association between the Presence of Coronary Calcium and Clinical Characteristics, Heart Rate Variability Parameters, and Laboratory Biomarkers

Parameter	OR	95% CI
LDL-C decrease ≤ 1.82 mmol/L	10.83	2.13–23.12
Copeptin level decrease ≤ 0.485 ng/mL	2.67	1.09–5.89
Early heredity of coronary heart disease	1.15	1.01–2.98
rMSSD ≤ 42, ms	1.11	0.99–2.17
HDL-C increase ≥ 1.12 mmol/L	6.73	4.87–11.65
Total cholesterol, mmol/L	4.27	2.19–6.12
Type 2 diabetes mellitus	3.59	1.98–7.18
Catestatin concentration decrease ≤ 138.1 μg/mL	2.12	1.98–3.19

End of table 5

Parameter	OR	95% CI
Statin use	2.10	1.16–5.98
SDNNidx ≤ 60, ms	1.97	1.13–5.14
Smoking	1.10	0.98–3.09

Note. OR – odds ratio; CI – 95% confidence interval; $p < 0.0001$.

Other clinical, instrumental, including myocardial blood flow indicators, and laboratory parameters did not show statistical significance.

DISCUSSION

An increasing number of evidence has shown that the coronary calcium index is more useful as a predictor of cardiovascular disease and a tool for cardiovascular risk stratification than the conventional Framingham risk score, C-reactive protein, or carotid intima-media thickness, especially in intermediate-risk cohort [2; 4, 20]. In a prospective cohort study of 6,814 people followed up for 3.8 years, compared with patients with a CCI of 0 ($p < 0.001$), the hazard ratios for developing a coronary event were 7.73 (CCI 101–300) and 9.67 (CCI > 300), and the AUC of the model was significantly higher (0.82 vs 0.77; $p < 0.001$) when CCI was added to standard risk factors [21].

Vonder et al. (2020) presented data that coronary calcium assessment may be of additional value in patients with stable chest pain to exclude CHD in case of a zero score or to stratify patients with increased risk who may require more intensive treatment [3]. Gottlieb et al. (2010) showed that in symptomatic patients referred for traditional coronary angiography, the absence of coronary calcification does not exclude obstructive CHD or the need for revascularization. [22]. Detection and characterization of coronary atherosclerosis using imaging tools are key key to determining the management of patients with known or suspected CHD [23].

According to the Consensus of the Quantitative Cardiovascular Imaging Study Group, among non-invasive diagnostic methods, MCTCA is the leading method for analyzing coronary atherosclerosis [24]. It has been demonstrated that the absence of coronary calcification is not a reliable indicator of the absence of functionally significant narrowing of the lumen of the coronary artery [21, 25]; in particular, in 3.5% of symptomatic patients, according to the CONFIRM study (n = 10,037), 50–70% coronary artery stenosis is detected [26].

In our study in patients with non-occlusive coronary atherosclerosis, depending on the presence or absence of calcium in the coronary arteries, we examined the presence of associations between traditional factors of the 10-year MESA coronary heart disease risk index, heart rate variability, and humoral markers of sympathetic activity. We showed that in patients with CCI > 0, the 10-year risk of developing coronary heart disease is 2.5 times higher ($p = 0.034$) compared to patients without coronary artery calcification. The coronary age in individuals of group 2 is also 2.5 times ($p = 0.02$) higher than the corresponding indicator in group 1. At the same time, the 10-year risk of developing coronary heart disease was associated with the sum of points at rest according to myocardial SPECT data and inversely correlated with myocardial blood flow indices at rest and under stress conditions. It is possible that the weak strength of the relationship is caused by both the small number of observations and the influence of a combination of clinical risk factors for CVD on the dynamics of myocardial blood flow and reserve indicators, which does not contradict the opinion of other researchers [27].

It was established that stenosis in at least one coronary artery of 50–70% was found in 27.3 and 57.9% of patients with CCI = 0 and CCI > 0, respectively, and all of them had moderate, high, or very high risk. At the same time, according to the data on the assessment of myocardial blood flow and perfusion, we did not obtain statistically significant differences. However, it is noteworthy that in the group of patients without coronary atherosclerosis, there was a tendency to decrease myocardial blood flow at rest, although stress MBF was practically at the same level. This caused a tendency to decrease the reserve of myocardial blood flow in this group compared to group 2. It should be noted that there is clearly insufficient data in the scientific literature on the assessment of myocardial ischemia in myocardial perfusion studies in patients with CCI = 0. Neves et al. (2017) presented the summary results of 8 studies (n = 3,717) that performed myocardial perfusion imaging under stress test conditions: on average, myocardial ischemia was detected in 7% of patients with CCI = 0 and in 13% of patients with CCI > 0 [25].

According to the correlation analysis of the associations of heart rate variability parameters with clinical and laboratory parameters and parameters of dynamic SPECT of the heart and MCTCA, no associations were found, but at the same time, a decrease in the rMSSD level was noted in patients with CCI > 0, which indicates the disintegration of the autonomic regulation of the heart, manifested in the suppression of the parasympathetic activity of the HRV, and is confirmed by the data of Hoshi et al. (2023), from which it follows that the presence of coronary artery calcification is associated with a worse cardiac vegetative profile [10; 28]. It should also be noted that, according to multivariate analysis, several HRV parameters characterizing the parameters of sympathetic activity in patients with non-occlusive atherosclerosis were associated with coronary calcification: rMSSD OR 1.105 (95% CI 0.99–2.17; $p < 0.000$) and SDNNidx OR 2.52 (95% CI 1.13–3.94; $p < 0.000$).

In addition to the listed indicators, the following clinical factors acted as independent markers of coronary calcification: the presence of diabetes mellitus OR 3.59 (95% CI 1.98–7.18; $p < 0.000$), a history of smoking OR 1.1 (95% CI 0.98–3.09; $p < 0.000$), and a family history of premature coronary heart disease OR 1.15 (95% CI 1.01–2.98; $p < 0.000$), the fact of taking statins OR 2.10 (95% CI 1.16–5.98; $p < 0.000$), as well as humoral biomarkers of sympathetic activity and CVD risk – catestatin OR 2.12 (95% CI 1.98–3.19; $p < 0.000$) and copeptin OR 2.67 (95% CI 1.09–5.89; $p < 0.000$), and lipid spectrum parameters – LDL-C OR 10.83 (95% CI 2.13–23.12; $p < 0.000$), HDL-C OR 6.73 (95% CI 4.87–11.65; $p < 0.000$), total cholesterol OR 4.27 (95% CI 2.19–6.12; $p < 0.000$).

When assessing the levels of lipid spectrum parameters, it was noted that in patients with CCI 0, the content of total cholesterol and LDL-C is clearly higher than in individuals with CCI > 0. However, the number of patients taking statins and, particularly, achieving target levels of LDL-C, in group 1 is lower (63.6 vs. 78.9% and 9.1 vs. 21.1%) compared to group 2. We did not obtain statistical significance for these parameters, but we should note a clear trend. This is not contradicted by the results of studies indicating that statin therapy increases coronary plaque calcification, and therefore researchers pay attention to the fact that when preventive therapy and effective treatment of risk factors begin, the degree of coronary calcification can increase, and the risk of cardiovascular events can decrease [9].

The data from the multicenter PARADIGM study also indicate an increase in the total calcium content in the structure of atherosclerotic plaques, as well as the absence of an effect on the degree of coronary artery stenosis. In particular, it was found that patients who were prescribed statin therapy (rosuvastatin and atorvastatin) showed a statistically significant slowdown in the progression of the total plaque volume (1.76 ± 2.40% versus 2.04 ± 2.37% per year) and no increase in the volume of the soft tissue component (0.49 ± 2.39% versus 1.06 ± 2.42% per year) was observed according to MSCT-CG data compared to individuals who did not receive these drugs [29; 30]. The NOTIFY-1 study ($n = 173$) found that patients who started statin prophylaxis earlier and were more adherent to treatment had significantly lower LDL-C levels compared with the standard treatment group (97.2 vs 115.3 mg/dL; $p = 0.005$, respectively) [31].

Thus, at this research stage, it is scientifically abd practically important to focus to focus on the use of CCI to assess its potential as a personal risk stratification tool and to determine its contribution to individual patient treatment decisions. However, the lack of randomized controlled trials on the cost-intensive use of coronary calcium remains a pressing issue, but the number of new studies in this area and their apparent usefulness mean that integration of coronary calcium into cardiovascular imaging and risk stratification is likely a matter of time rather than opportunity.

CONCLUSION

The presence of calcium in the coronary arteries in patients with non-obstructive coronary atherosclerosis is associated with a family history of premature coronary heart disease, disintegration of the autonomic regulation of cardiac function, expressed in the suppression of the activity of the parasympathetic division of the autonomic nervous system, and the absence of significant levels of humoral markers of sympathetic activity. Threshold values of LDL-C and copeptin have been determined, which in such patients can be used as markers of the presence or absence of coronary calcium. Independent predictors of the absence of coronary artery calcification (CCI = 0) in patients with non-obstructive coronary atherosclerosis are lipid spectrum parameters (total cholesterol, LDL-C, HDL-C) and copeptin levels, the presence of a family history of coronary heart disease, smoking, and HRV parameters associated with the regulation

of parasympathetic activity of the autonomic nervous system (SDANN, SDNNidx, rMSSD).

The limitations of this study included: 1) a small sample size of patients; 2) the absence of a control group of conditionally healthy individuals; 3) this study, did not evaluate the prognostic value of CCI.

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Grakova E.V. – collection and interpretation of clinical data, database compilation, statistical data processing, critical revision for important intellectual content, final approval of the manuscript for publication. Kopeva K.V. – interpretation of clinical data, performing daily ECG monitoring, drafting of the manuscript, final approval of the manuscript for publication. Maltseva A.N., Dasheeva A.S. – conducting scintigraphic studies, collection and interpretation of data, database compilation, final approval of the manuscript for publication. Zavadovsky K.V. – conducting scintigraphic studies, assessing blood flow parameters, drafting of the manuscript, final approval of the manuscript for publication. Gusakova A.M. – determination of serum biomarker levels, data collection and interpretation, database compilation, final approval of the manuscript for publication. Vorozhtsova I.N. – collection and interpretation of clinical data, critical revision for important intellectual content, final approval of the manuscript for publication. Antsiferova E.L., Shadrina Yu.L. – interpretation of clinical data, database filling, final approval of the manuscript for publication.

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Received 17.10.2024;
approved after peer review 04.11.2024;
accepted 14.01.2025