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C-reactive protein and its associations with cardiometabolic risk factors and echocardiographic indicators of heart failure: results of "Know your heart" study in Arkhangelsk

Aim	To evaluate the relationship between high-sensitivity C-reactive protein (hsCRP) and echocardiographic (EchoCG) indicators of heart failure (HF) among adult population of the North region of Russia.
Material and methods	The Know Your Heart transversal study was performed in 2015–2017 on a random sample of adult population of Arkhangelsk aged 35–69 years (n=2381). The exclusion criterion for this study was a concentration of hsCRP >10 mg/l. The group of subclinical inflammation included 686 participants with hsCRP ≥2.0 mg/l; the comparison group consisted of 1158 participants with hsCRP <2.0 mg/l. Analysis included cardiometabolic risk factors, EchoCG indexes of left ventricular (LV) systolic and diastolic function and biomarkers (NT-proBNP, hsTroponin T, cystatin C). Linear and logistic regressions were used.
Results	The group with hsCRP ≥2.0 mg/l had higher rates of arterial hypertension, diabetes mellitus, HF, and myocardial infarction in history than the comparison group. The hsCRP level was independently associated with waist circumference (β=0.379, p <0.001), male gender (β= – 0.135, p<0.001), smoking (β=0.109, p<0.001), triglycerides (β=0.083, p<0.001), diastolic blood pressure (β=0.082, p<0.001), cystatin C (β=0.082, p<0.001), glycated hemoglobin (β=0.064, p=0.003), and low-density lipoproteins (LDL) (β=0.049, p=0.025). Independent predictors of subclinical inflammation included older age, smoking, abdominal obesity, elevated values of LDL (>3.0 mmol/l), triglycerides (>1.7 mmol/l), and cystatin C (>1.2 mg/l). hsCRP was independently negatively associated with LV ejection fraction, left atrial volume index, ratio of early to late LV diastolic filling velocity (p=0.003, p=0.002, p=0.005, respectively), which reflected the relationship of the increased content of hsCRP with impairment of LV systolic and diastolic function. A relationship between heart remodeling indexes and hsCRP concentration was shown.
Conclusion	In a sample of adult population from the North region of Russia, the hsCRP concentration was independently associated with cardiometabolic risk factors and structural and functional changes in the heart detected by EchoCG, which reflects a potential contribution of inflammation to heart remodeling and development of HF.

Keywords	C-reactive protein, risk factors, heart failure
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Introduction

The famous 19th-century German pathologist Rudolf Virchow was the first to recognize the role of inflammation in the pathogenesis of atherosclerosis. He wrote that atherosclerosis is an inflammation induced by cholesterol [1]. The idea of atherosclerosis being an inflammatory disease was further developed by prominent cardiologist, Professor Dr. Peter Libby, current president of the International Atherosclerosis Society [2]. In an interview, Dr. Libby mentioned the CANTOS study, in which the therapy aimed at a specific inflammatory cytokine effectively improved cardiovascular outcomes, which was of personal interest since it was he who hypothesized the role of interleukin-1

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(IL-1) in the pathogenesis of atherosclerosis in 1986 [2]. Improving cardiovascular risk assessment requires a personalized approach, which can be achieved by integrating the analysis of major cardiovascular risk factors and cardiovascular risk markers such as the levels of low-density lipoprotein (LDL-C) cholesterol and C-reactive protein (CRP) [3, 4].

Epidemiological evidence was obtained earlier of the correlation of basal IL-6 and high-sensitivity CRP (hs-CRP) in healthy people who subsequently developed diabetes. This evidence played an essential role in changing clinical practice [5, 6]. The clinical implication was the use of hs-CRP as an inflammatory biomarker to identify increased vascular risk in primary and secondary prevention of cardiovascular diseases [5, 6]. The hs-CRP levels >10 mg/L may represent a transient infection or other acute-phase response [6]. A lesser yet persistent increase in hs-CRP reflects the presence of a subclinical systemic inflammation that is associated with an increased risk of atherosclerosis [7], heart failure (HF), and worse prognosis in documented HF [8]. These findings are supported by the CANTOS trial, in which anti-inflammatory therapy with canakinumab 150 and 300 mg subcutaneously every 3 months reduces the rate of hospital admission for HF in patients with a history of myocardial infarction and ongoing subclinical inflammation (CRP≥2 mg/L) [9].

Currently, an active search is underway for new cardioprotective treatments in patients with a history of myocardial infarction to prevent left ventricular (LV) remodeling and HF [10, 11]. The Consortium for preclinicAl assESsment of cARdioprotective Therapies (CAESAR) has been established: a new paradigm for rigorous, accurate, and reproducible evaluation of putative infarct-sparing interventions in mice, rabbits, and pigs [12, 13]. The hs-CRP levels are also consistent with the severity and number of signs underlying metabolic syndrome (MS) and predict vascular risk in patients with significant insulin resistance. Ongoing inflammation-inhibition studies compare the diabetes incidence and the rate of vascular events partly for these reasons [14].

Evaluation of the correlations of elevated hs-CRP levels with other cardiometabolic risk factors, including high blood pressure (BP), elevated serum lipids, glycated hemoglobin (HbA_{1c}), and waist circumference (WC) in the general population may be useful to justify future developments in new areas of primary and secondary cardiovascular prevention. Namely, these include the effects on the inflammatory component of pathogenesis, since these combinations of cardiometabolic risk factors contribute to a varying degree to the activation of pathophysiological mechanisms-such as oxidative stress, endothelial dysfunction, apoptosis, cytokine and adipokine imbalances, inflammation-that cause microvascular dysfunction, fibrosis, myocardial remodeling and HF [15].

Objective

The study's objective was to assess the correlation between hs-CRP and cardiometabolic and echocardiographic signs of HF in the adult population of Northern Russia.

Material and Methods

The correlations between hs-CRP levels and HF markers were studied in the Learn Your Heart (LYH) study conducted in 2015–2017 using a random sample from the general population of four districts of Arkhangelsk from the ages of 35 to 69 years [16]. All subjects signed informed consent. The exclusion criterion was hs-CRP >10 mg/L.

Ethical Approval

The study was approved by the ethics committees of the Northern State Medical University, Arkhangelsk (Protocol No. 01/01–15 dated 27.01.2015), and the London School of Hygiene & Tropical Medicine (Protocol No. 8808 dated 24.02.2015).

Study Design and Subjects

The study design is cross-sectional. The LYH sample included 2,381 people, of whom 41.5% were male. The sampling method and characteristics of the sample have been described previously [16]. The hs-CRP levels were determined in 2,356 subjects of the LYH study. The mean value was 3.5 mg/L, the median was 1.6 mg/L, and 540 (22.9%) subjects had hs-CRP >3 mg/L. The final sample size was 1,844 when 156 (6.6%) patients with hs-CRP >10 mg/L and 356 (15.1%) patients with missing analysis data were excluded. Of the 1,844 subjects, 686 (37.2%) with hs-CRP≥2.0 mg/L were included in the subclinical inflammation group, and subjects with hs-CRP <2.0 mg/L (n = 1,158 [62.8%]) formed a reference group.

Anamnestic Data

Data on diabetes mellitus, hypertension, HF, history of myocardial infarction, and smoking status were collected through respondent interviews using a standardized questionnaire developed by Cook et al. [16].

Anthropometry and BP Measurements

Waist circumference was measured in centimeters using a measuring tape (Seca® 201; Seca Limited). Two

measurements were made, and their mean value was used. Abdominal obesity was defined as >102 cm for males and >88 cm for females (Adult Treatment Panel [ATP] III) [14]. Systolic and diastolic BP (SBP and DBP) was recorded in a standard way, in the brachial artery, using an OMRON 705 IT automatic blood pressure monitor (OMRON Healthcare) after seated rest for 5 minutes. Three measurements were taken with 2-minute intervals between measurements. The mean value of the second and third measurements was used.

Laboratory Findings

The sampling method has been described in [16]. The levels of serum hs-CRP and cystatin C, and whole blood HbA_{1C} (EDTA), were determined by the immunoturbidimetric assay (AU 680; Chemistry System Beckman Coulter). The levels of serum high-sensitivity cardiac troponin T (hs-cTnT) and N-terminal pro-brain natriuretic peptide (NT-proBNP) were determined by electrochemiluminescence immunoassay (ECLIA) (Cobas e411 Analyzer; Roche Diagnostics GmbH, Hitachi, Japan). The serum lipid levels (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides) were determined by the enzymatic colorimetric method (AU 680; Chemistry System Beckman Coulter).

Echocardiogram

Echocardiographic examinations were performed using a GE VividQ (GE Health Care) ultrasound device following the standard echocardiogram protocol of the LYH study [16]. LV systolic function was determined by the ejection fraction (EF), calculated using the Simpson method. The reduced EF was <40%. Left atrial volume index (LAVI), LV mass index (LVMI), and the ratio of peak velocities in early (E) and late (A) diastole (E/A) were used as echocardiographic parameters associated with HF. All structural echocardiographic parameters and the LV diastolic parameters were evaluated following the ESC/EAE (European Society of Cardiology/European Association of Echocardiography guidelines [17, 18].

Statistical Analysis

The categorical variables are presented as absolute values and percentages. Symmetrically distributed continuous variables are presented as the mean (M)±standard deviation (SD). The median (Me) and values corresponding to the first and third quartiles (Q1; Q3) are given for continuous variables with asymmetric distribution (hs-CRP, triglycerides, hs-cTnT, NT-proBNP). Asymmetrically distributed variables were included in the ln-transformed form in the subsequent analysis.

The group of LYH subjects with laboratory signs of subclinical inflammation (SI) (hs-CRP≥2.0 and <10.0 mg/L, further the SI+ group) and the group of LYH subjects without laboratory signs of subclinical inflammation (hs-CRP<2.0 mg/L; further the SI– group) were compared using Pearson's test ($\chi 2$) for the categorical variables and the independent-sample t-test for the continuous variables.

Multivariate step-by-step logistical regression was used to assess the correlations between subclinical inflammation and cardiometabolic risk indicators: LDL-C >3.0 mmol/L, WC >102 cm for male, >88 cm for female, HDL-C <1.0 mmol/L for male, <1.2 mmol/L for female, triglycerides >1.7 mmol/L, SBP≥140 mmHg, DBP≥90 mmHg, HbA_{1C}≥6.5%, cystatin C >1.2 mg/L. Analysis results are presented as odds ratio (OR).

Multivariate step-by-step linear regression was used to assess the correlation of hs-CRP and cardiometabolic risk and echocardiographic signs of HF: LVEF, LAVI, LVMI, E/A. Age, sex, smoking status, WC, HDL-C, LDL-C, triglycerides, SBP, DBP, cystatin C, hs-cTnT, HbA_{1C}, and history of myocardial infarction were introduced in all regression models to control the possible effects of the intervention. Multivariate linear regression was also used to evaluate the correlation of NT-proBNP and echocardiographic signs of HF. Analysis results are presented using the standardized β coefficient to compare the contributions of independent variables. Critical significance level was $p<0.05$. Statistical analysis was performed using Stata 12.1.

Results

Characteristics of the Compared Groups

Subjects of the SI+ group were 2.4 years older than those of the reference group. There were equally more female patients in both groups (Table 1). In the SI+ group, there were more smokers, patients with hypertension, diabetes mellitus, HF, and history of myocardial infarction than in the reference group. Lipid profile, WC, HbA_{1C}, cystatin C, hs-cTnT, and NT-proBNP differed significantly between the study groups. In the SI+ group, echocardiographic signs of cardiac remodeling were found: higher left heart structural parameters (LBMI and LAVI) and lower LV systolic and diastolic function indicators.

When interviewed for medical history, 193 subjects (10.2%) noted that they had HF. There were more such respondents in the SI+ group (13.5%) than in the SI– group (8.8%). NT-proBNP was also higher than in the SI– group (89.2 [45.1; 164.0] pg/mL versus 74.2 (41.1;

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Table 1. Characteristics of the subjects (n = 1844)

Parameter	SI+ group (n = 686)	SI- group (n = 1,158)	p[a]
Age, M±SD, years	54.8±9.5	52.4±9.7	<0.001
Sex, male, n (%)	280 (40.8)	449 (43.1)	0.339
Smoking, yes, n (%)	189 (27.6)	233 (20.1)	<0.001
Hypertension, n (%)	398 (58.0)	468 (40.6)	<0.001
History of myocardial infarction, n (%)	43 (6.3)	38 (3.3)	0.002
Diabetes mellitus, n (%)	63 (9.2)	73 (6.3)	0.022
Heart failure, n (%)	92 (13.5)	101 (8.8)	0.001
Waist circumference, M±SD, cm	96.4±12.9	87.1±12.2	<0.001
SBP, M±SD, mmHg	135.3±20.4	130.1±19.7	<0.001
DBP, M±SD, mmHg	85.3±11.4	82.3±11.6	<0.001
Total cholesterol, M±SD, mmol/L	5.5±1.1	5.4±1.1	0.003
HDL-C, M±SD, mmol/L	1.4±0.3	1.5±0.4	<0.001
LDL-C, M±SD, mmol/L	3.8±0.9	3.6±0.9	<0.001
Triglycerides, Me (Q1-Q3), mmol/Lb	1.5 (1.0; 2.0)	1.1 (0.8; 1.6)	<0.001
HbA_{1c}, M±SD, %	5.7±0.9	5.4±0.6	<0.001
Cystatin C, M±SD, mg/L	0.93±0.29	0.86±0.20	<0.001
Hs-troponin T, M±SD, ng/L[b]	6.4 (4.8; 8.8)	6.2 (4.5; 8.3)	0.020
NT-proBNP, Me (Q1; Q3), pg/mL[b]	89.2 (45.1; 164.0)	74.2 (41.1; 133.5)	<0.001
LVEF, M±SD, %	55.7±6.1	57.5±5.5	<0.001
LAVI, M±SD, mL/m²	12.3±4.5	11.9±4.1	0.095
LVMI, M±SD, g/m²	115.6±32.1	108.2±26.0	<0.001
E/A, M±SD	1.14±0.35	1.27±0.40	<0.001

[a], the p value for the quantitative variables was estimated using t-test for independent samples, Pearson's test (χ^2) was used for categorical variables. [b], the variable was included in the analysis in ln-transformed form for intergroup comparisons.

M, mean; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA_{1c}, glycated hemoglobin; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index; LVMI, left ventricular mass index; E/A, early/late diastole.

133.5) pg/mL, p<0.001]. Since this population sample included more conditionally healthy individuals with preserved LVEF (only 14 [0.7%] persons had LVEF <40%), there are grounds to believe that patients with HF and preserved EF predominated among those who had noted the presence of HF.

Correlations between hs-CRP and Cardiometabolic Risk Factors

Cardiometabolic factors independently associated with subclinical inflammation are older age, smoking, abdominal obesity, elevated LDL-C (>3.0 mmol/L), triglycerides (>1.7 mmol/L), and cystatin C (>1.2 mg/L) (Table 2).

The hs-CRP levels are correlated independently with WC, male sex, smoking, triglycerides, cystatin C, HbA_{1C}, and LDL-C (Table 3). The resulting regression model, which includes eight independent variables, explains the hs-CRP changes by 25%. WC, which is the main component of MS, makes the most significant contribution to hs-CRP change in this model.

It turned out that there was no independent correlation between age and hs-CRP in a multivariate model, unlike a small but significant age-related difference between the groups in this sample (Table 1) and the presence of a significant correlation between age and hs-CRP in a univariate regression model.

Correlations of hs-CRP and Echocardiographic Indicators of Heart Failure

Negative correlations were determined between hs-CRP and echocardiographic indicators of cardiac remodeling (LVEF, LAVI, E/A), reflecting the association of elevated levels of hs-CRP with the deterioration of LV systolic and diastolic functions (Table 4).

Correlations of Cardiac Remodeling Indicators and NT-proBNP

Table 2. Correlations between subclinical inflammation (hs-CRP≥2 mg/L and <10 mg/L) and cardiometabolic risk (n=1844)

Parameter	OR[a]	95% CI	AOR[b]	95% CI
Age, years				
• 35–49	1.00	–	–	–
• 50–59	1.48	1.17–1.87	1.19	0.93–1.53
• 60–69	1.73	1.37–2.18	1.32	1,03–1.70
Sex, male	0.91	0.75–1.10	–	–
Smoking	1.51	1.21–1.88	1.94	1.52–2.47
Abdominal obesity[c]	3.66	2.97–4.52	3.40	2.73–4.22
HDL-C, <normal[d]	2.06	1.57–2.70	-	-
LDL-C, >3.0 mmol/L	1.49	1.19–1.88	1.30	1.01–1.66
Triglycerides, >1.7 mmol/L	2.19	1.77–2.72	1.46	1.16–1.84
SAD≥140 mmHg	1.57	1.28–1.93	-	-
DBP≥90 mmHg	1.53	1.24–1.89	-	-
Cystatin C >1.2 mg/L	3.42	1.94–6.01	2.13	1.18–3.85
HbA_{1c}≥6.5%[e]	2.24	1.43–3.51	-	-

[a], univariate logistical regression analysis; [b], multivariate logistic regression, reverse step-by-step approach;
[c], waist circumference >102 cm for males, >88 cm for females (ATP III);
[d], HDL-C <1.0 mmol/L for males, <1,2 mmol/L for females;
[e], American Diabetes correlation, 2019.

hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; CI, confidence interval; AOR, adjusted odds ratio; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1c}, glycated hemoglobin; ATP III, Adult Treatment Panel III.

Table 3. Correlations between hs-CRP and cardiometabolic risk factors (n=1844)

Parameter	Univariate analysis[b]		Multivariate analysis[c]	
	Standard coefficient β	p	Standard coefficient β	p
Age	0.172	<0.001	-	-
Sex, male	0.031	0.190	-0.135	<0.001
Smoking, yes	0.093	<0.001	0.109	<0.001
WC	0.444	<0.001	0.379	<0.001
HDL-C	-0.022	<0.001	-	-
LDL-C	0.015	<0.001	0.049	0.025
Triglycerides[a]	0.293	<0.001	0.083	<0.001
SBP	0.213	<0.001	-	-
DBP	0.215	<0.001	0.082	<0.001
Cystatin C	0.204	<0.001	0.082	<0.001
HbA_{1C}	0.192	<0.001	0.064	0.003

[a], the variable was included in the analysis in ln-transformed form;
[b], a simple linear regression model for each variable;
[c], multiple linear regression, reverse step-by-step approach;
only independent β regression coefficients are included in the table.

hs-CRP, high-sensitivity C-reactive protein;
WC, waist circumference; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol;
SBP, systolic blood pressure; DBP, diastolic blood pressure;
HbA_{1C}, glycated hemoglobin.

Positive correlations between the echocardiographic indicators (LVMI and LAVI) that characterize structural changes of the heart when differing from the reference values, and NT-proBNP, the main biomarker of HF (Table 5). A positive association of NT-proBNP with age and female sex were confirmed. No reliable correlation of LVEF with NT-proBNP was obtained, which can be explained by a higher number of conditionally healthy persons with preserved LVEF in this population sample (99.3%).

Discussion

In 1997, the prospective Physicians' Health Study, which described the elevated levels of hs-CRP in healthy individuals many years before the first vascular event, answered the question of whether elevated CRP is a result or a cause of ischemia [6, 19]. This study also showed that subclinical systemic inflammation, which was identified by measuring the hs-CRP levels, was stable for a long time and that anti-inflammatory acetylsalicylic acid significantly modified the effects of hs-CRP on the vascular risk [19]. Possibilities of primary cardiovascular prevention with anti-inflammatory agents determine the relevance of epidemiological studies aimed at establishing the rate of elevated hs-CRP in the population.

Our random sample of the adult population of Arkhangelsk included 2,356 male and female patients from the ages of 35–69 with the median hs-CRP level of 1.6 mg/L: 23% had hs-CRP >3 mg/L, and only 6.6% had hs-CRP >10 mg/L. The median level of hs-CRP in the US population is about 2 mg/L, and approximately 25% of the total population have hs-CRP >3 mg/L [6], which is comparable to our data obtained for the first time in the population of Northern Russia.

Table 4. Correlations between echocardiographic signs of heart failure and cardiometabolic risk factors (n=1844)

Parameter	Dependent variables [a]							
	LVEF		LAVI		LVMI		E/A	
	β	p	β	p	β	p	β	p
hs-CRP[b]	-0.075	0.003	-0.075	0.002	-	-	-0.058	0.005
Age	-	-	0.156	<0.001	0.137	<0.001	-0.453	<0.001
Sex, male	-	-	-	-	0.150	<0.001	-0.045	0.023
Smoking, yes	-	-	-	-	0.055	0.009		
WC	-0.110	<0.001	0.122	<0.001	0.195	<0.001	-0.123	<0.001
HDL-C	0.068	0.006	-	-	-	-	-	-
LDL-C	-	-	-0.060	0.008	-0.043	0.037	-	-
Triglycerides[b]	-	-	-	-	-	-	-0.069	0.001
SBP	0.104	0.010	0.190	<0.001	0.127	<0.001	0.091	0.009
DBP	-0.197	<0.001	-0.162	<0.001	-	-	-0.288	<0.001
HbA_{1c}	-	-	-	-	-	-	-	-
Cystatin C	-	-	-	-	-	-	-	-
hs-troponin-T[b]	-0.087	<0.001	0.090	<0.001	0.141	<0.001	-	-
History of myocardial infarction	0.089	<0.001	-0.107	<0.001	-0.109	<0.001	-	-

[a], multivariate linear regressions and reverse step-by-step approach were used. All 14 independent variables were included in each regression model. Only significant independent β regression coefficients are provided in the table;
[b], the variable was included in the analysis in ln-transformed form.
hs-CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction; LAVI, left atrial volume index;
LVMI, left ventricular mass index; E/A, early/late diastole; WC, waist circumference; HDL-C, high-density lipoprotein cholesterol;
LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA_{1C}, glycated hemoglobin.

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Table 5. Correlations between NT-proBNP[b] levels and echocardiographic measurements (n=1,884)

Parameter	β[a]	p
Age	0.418	<0.001
Sex, female	0.263	<0.001
Smoking, yes	0.067	0.001
LVMI	0.175	<0.001
LAVI	0.136	<0.001
LVEF	-0.030	0.140
E/A	0.169	<0.001

[a], multiple linear regression was used;
[b], the variable was included in the analysis in ln-transformed form.

LVMI, left ventricular mass index; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; E/A, early/late diastole.

The CRP level measured by highly sensitive immunological assays (hs-CRP) <1 mg/L (low), 1–3 mg/L (middle), and >3 mg/L (high) correlate linearly with the increased risk of cardiovascular complications among other traditional risk factors [6]. In this study, the percentage of people with diabetes mellitus and a history of myocardial infarction was significantly higher in the main group (hs-CRP≥2.0 and <10.0 mg/L), which is consistent with the available evidence that CRP is closely correlated to both diseases regardless of classic risk factors [5, 20–23]. Analysis of the WOSCOPS findings showed that CRP increases informative prediction value for both outcomes (coronary artery disease and new cases of diabetes mellitus) as well as MS and other risk factors [14].

The multivariate regression analysis identified a range of factors independently associated with subclinical inflammation in the residents of Arkhangelsk: elderly age, smoking, abdominal obesity, elevated levels of LDL-C, triglycerides, and cystatin C. The findings of this study showed that WC makes the most significant contribution to hs-CRP changes. The combination of MS and elevated CRP is known to significantly increase the risk of coronary artery disease and diabetes mellitus [14]. Analysis of the correlation of hs-CRP with other known cardiovascular risk factors has revealed its positive correlation with LDL-C. Libby et al. [24] demonstrate the involvement of inflammation in the pathogenesis of atherothrombosis and the role of interaction between adhesion molecules, cytokines, circulating mononuclear cells, modified LDL-C, and vascular endothelium in maintaining the risk of MI and stroke, which is consistent with our findings.

We also demonstrated the correlation between cystatin C and hs-CRP. According to the literature, high levels of cystatin C were found as well as high levels of CRP [25]. Inflammation combined with atherogenic changes may be associated with cystatin C and cardiovascular risk [25]. According to the literature, the levels of plasma cystatin C depends on age [26, 27], body mass index [26, 28], sex [26, 27], smoking [28], and high levels of CRP [26, 27].

In addition to identifying the correlations between hs-CRP and cardiometabolic risk factors, we attempted to establish the associations between these factors and echocardiographic indicators, which allowed collecting new data. For example, the most significant predictors of echocardiographic changes in regression models were hs-cTnT, WC, and BP, and to a lesser extent, lipid and hs-CRP levels to a lesser extent. Analysis showed that hs-CRP was negatively associated with LVEF and diastolic function (E/A). Moreover, structural and functional changes in the heart were shown to be associated with NT-proBNP levels. Hemodynamic stress/myocardial tension (pressure/stretching of the cardiac cavities and vessels) is known to be the main stimulus for releasing natriuretic peptides.

In a meta-analysis of individual patient data, which included findings of 10 studies and 9,289 patients with chronic HF, hs-cTnT was added to the prediction model along with the established risk markers (sex, age, ischemic etiology, LVEF, glomerular filtration rate, and NT-proBNP) and significantly improved risk prediction for all-cause and cardiovascular mortality and cardiovascular hospitalizations. Each biomarker can be associated with one or more links of the HF pathogenesis. The multimarker strategy based on a new platform, which includes the measurement of 48 to 96 different biomarkers, allows identifying the mechanisms involved in the pathogenesis in various patients with HF [29]. For example, an analysis of a panel of 48 different biomarkers in patients with acute HF with and without concomitant diabetes mellitus found a potent cluster of biomarkers in patients with diabetes mellitus associated with inflammation and fibrosis, such as IL-6, periostin, and CRP, which is likely to show a specific activation of these pathways, but not in patients without diabetes [30]. Studies comparing new biomarkers with traditional risk factors and clinical state are still relevant [31]. In our study, components of MS (WC reflecting central obesity, BP, HDL-C, triglycerides) are associated with both hs-CRP and echocardiographic indicators that characterize myocardial dysfunction and the risk of HF. In 2015, Perrone-Filardi et al. presented a review of the modern literature on the role of MS in the pathogenesis of HF [15] that reflects various influence mechanisms of all components of this syndrome, which contribute to cardiac remodeling and the development of HF. A positive correlation of NT-proBNP and the

echocardiographic indicators reflecting structural changes in the heart (LVMI and LAVI) was shown.

The present study is limited by the cross-sectional design, which does not allow clearly assessing the causality, and the inability to evaluate the correlations of other biomarkers and immune cells with the rates of myocardial remodeling. In our previous small study, patients with HF and preserved EF and HF with moderately reduced EF of ischemic genesis had significant correlations between echocardiographic indicators and levels of NT-proBNP, transforming growth factor beta (TGF-β), and matrix metalloproteinase 12 (MMP-12), which reflect various pathophysiological mechanisms of myocardial remodeling. LVEF and LV end-systolic dimension and systolic function were associated with myocardial stretch biomarker NT-proBNP. LBMI was associated with MMP-12, and LV end-diastolic dimension was associated with TGF-β. The soluble inductor of Fas-mediated apoptosis (sFasL) and TGF-β were found to be correlated, as were the soluble receptor of apoptosis (sFas) and MMP-12 [32]. MMPs are known to be involved in tissue remodeling, angiogenesis, cell proliferation and differentiation, and apoptosis. They contribute to the cleavage of membrane receptors, the release of apoptosis ligands, such as FasL, and activation and deactivation of chemokines and cytokines [33].

In this context, the study of the immune component of HF pathogenesis appears to be promising. In 2019, Andreadou et al. discussed the role of immune cells as cardioprotection targets and new therapeutic approaches to the prevention of HF [10].

The results of our study prove the clinical significance of isolating a phenogroup of patients with central obesity and subclinical inflammation (hs-CRP≥2 mg/L and <10 mg/L) and their monitoring of the biomarkers (hs-CRP, cystatin C, NT-proBNP, hs-cTnT) as well as echocardiographic indicators of diastolic function and LV hypertrophy, which will potentially improve the detection of early stages of HF with preserved EF.

Conclusion

In the population sample of the adult population of Northern Russia, independent correlations of hs-CRP with cardiometabolic risk factors (MS components, LDL-C, and cystatin C) and with echocardiographic structural and functional indicators (LVEF, LAVI, LVMI, E/A) were identified, which reflects the potential involvement of inflammation in myocardial remodeling and the development of HF.

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