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Role of inflammation, autotaxin and lipoprotein (a) in degenerative aortic valve stenosis in patients with coronary artery disease

Burdeynaya A. L., Afanasyeva O. I., Klesareva E. A., Tmoyan N. A., Razova O. A., Afanasyeva M. I., Ezhov M. V., Pokrovsky S. N.

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Aim. To study the relationship between the concentration of lipoprotein (a) (Lp (a)) and autotaxin (ATX) in patients with and without degenerative aortic valve stenosis (AoS) in the presence of coronary artery disease (CAD).

Material and methods. The study included 461 patients (mean age, 66±11 years, men, 323), 354 of whom had CAD with stenosis ⩾50% in at least one coronary artery according to angiography. Degenerative AoS was diagnosed with ultrasound. The control group consisted of 107 patients without CAD and degenerative AoS. Concentrations of Lp (a), ATX, lipids and blood cells were measured for all patients.

Results. CAD without degenerative AoS (group 1) was diagnosed in 307 patients, while 47 patients had CAD and degenerative AoS (group 2). Patients in both groups were older than patients in the control group (66±10, 74±8, and 61±13 years, respectively). The ATX level was lower in group 1 (median [25; 75%]: 495 [406; 583] ng/ml) than in the control group (545 [412; 654] ng/ml) or group 2 (545 [476; 605] ng/ml) ($p<0,05$ for all). Lp (a) was lower in the control group (14,5 [5,5; 36,0] mg/dl) than in group 1 (24,9 [9,7; 58,4] mg/dl) ($p<0,005$) and group 2 (23,8 [9,9; 75,7] mg/dL) ($p<0,05$). According to the logistic regression, an increased ATX level, regardless of age and other risk factors, was associated with degenerative AoS only in patients with CAD, while age and neutrophil to lymphocyte ratio were associated with the development of degenerative AoS both in patients with CAD and the general group.

Conclusion. An elevated Lp (a) level is associated with CAD regardless of the aortic valve involvement, while an increased concentration of ATX and neutrophil to lymphocyte ratio in patients with CAD were associated with degenerative AoS regardless of age and other risk factors.

Keywords: degenerative aortic valve stenosis, lipoprotein (a), autotaxin, neutrophil to lymphocyte ratio, coronary artery disease.

Relationships and Activities: none.

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Introduction

Degenerative aortic valve stenosis (AoS) is the most common valvular heart disease in Europe and North America, as well as in Russia. In developed countries, aortic stenosis is the second most common cardiovascular disease (CVD) after coronary artery disease (CAD) and systemic arterial hypertension with a revalence of 0,4% in the general population and 1,7% among people >65 years of age [1]. According to the Russian study, which included 3988 patients, the proportion of patients with AoS under the age of 60 was 0,5% and increased to 5,5% in people over 70 years old [2]. The initial period of the formation of degenerative AoS has similar mechanisms with atherosclerotic changes in both coronary and peripheral arteries [3]. The greatest role among atherogenic lipoproteins in the development of atherosclerosis is played by low density lipoproteins (LDL) and lipoprotein (a) (Lp (a)) [4]. Studies have shown that the accumulation of these atherogenic lipoproteins in the tissue of the aortic valve, as well as local inflammation, play a significant role in the pathogenesis of the formation of degenerative AoS [5]. According to a meta-analysis of a number of studies, statins have no effect on slowing the progression of aortic valve disease [6].

Autotaxin (ATX) — endonucleotide pyrophosphatase/phosphodiesterase 2 — a protein with phospholipase D activity and promoting the formation of lysophosphatidic acid, an active pro-inflammatory agent, is also associated with the development of aortic

stenosis. The performed immunohistochemical study demonstrated the joint localization of ATX, apoprotein (a) and oxidized phospholipids in the tissues of degeneratively altered aortic valves. In addition, ATX activity was found in the Lp (a) fractions isolated from the blood plasma of healthy donors [7].

The aim is to study the relationship between the concentration of Lp (a) and ATX in patients with and without degenerative AoS in the presence of CAD.

Material and methods

In a one-stage, open, single-center study on the basis of the Institute of clinical cardiology of A. L. Myasnikov Federal State Budgetary Institution "National Medical Cardiology Research Center" of the Ministry of Health of the Russian Federation, the patients who underwent inpatient treatment in the period from 2016 to 2018 (n=461) were included. The patients were divided into groups according to the presence of atherosclerotic lesions of the coronary arteries and degenerative AoS. Patients with chronic CAD who had stenosis >50% in at least one of the coronary arteries according to coronary angiography and without changes in the aortic valve according to echocardiography made up group 1 — only 307 (67%) patients. Group 2 consisted of patients with coronary artery disease with varying degrees of severity of degenerative AoS — 47 (10%) patients. The control group — 107 (23%) people, served as patients with unchanged coronary arteries and unaffected aortic valve, but with the possible presence of peripheral atherosclerosis, including with multifocal arterial lesions. The study did not include patients with congenital bicuspid aortic valve, history of rheumatic heart disease, infective aortic endocarditis, cancer accompanied by radiation and chemotherapy, and systemic connective tissue diseases. All patients were on standard drug therapy in accordance with Russian recommendations for their diseases.

The study was carried out in accordance with the principles of the Declaration of Helsinki; written informed consent was obtained from all patients prior to enrollment. The study was approved by the local Ethics Committee.

All patients underwent transthoracic two-dimensional echocardiography and doppler echocardiography to determine the state of the aortic valve. The diagnosis of degenerative AoS was established when the maximum blood flow velocity on the aortic valve >2,0 m/s and the average pressure gradient from the aortic valve >20 mm Hg according to the American guidelines for the management of patients with valvular heart disease.

A general clinical blood test was carried out, as well as determination of the concentration of total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL cholesterol) using kits (Biocon, Germany). The concentration of low density lipoprotein cholesterol (LDL cholesterol) was calculated using the Friedwald formula: LDL C=TC-HDL C-TG/2,2 (mmol/l), and the level of corrected LDL C (LDL corr) was also calculated, taking into account the cholesterol contained in Lp (a): LDL C corr=LDL C-0,3×Lp(a)/38,7 (mmol/l), where Lp(a) is the concentration of lipoprotein(a) in mg/dl [8]. The Lp (a) concentration was measured by enzyme-linked immunosorbent assay using monospecific polyclonal ram antibodies against human Lp (a), validated against commercial kits [9]. The level of ATX and C-reactive protein (CRP) in blood serum was determined using kits for enzyme-linked immunosorbent assay (Human ENPP-2/Autotaxin, "R&D", USA and "Vector-Best", Russia, respectively). The neutrophil-lymphocyte index (NLI) was calculated as the ratio of the absolute number of neutrophils to the absolute number of lymphocytes.

Statistical analysis was performed using the "MedCalc" package. Indicators with a normal distribution are presented as means with standard deviations, indicators with a distribution other than normal are presented as a median and values of the 25th and 75th percentiles. The Kolmogorov-Smirnov test was used to determine the normal distribution. To compare the frequency indicators between groups, Fisher's exact test and the χ^2 method were used. Differences were considered statistically significant at $p < 0,05$. Threshold values of various biochemical markers were calculated using the analysis of operating characteristics curves (ROC analysis). To assess the relationship of various factors with the presence of degenerative AoS, we used contingency table analysis and logistic regression methods.

Results

The characteristics of the examined groups are presented in Table 1. Patients from group 2 were older than patients from group 1 and the control group ($p<0,001$ when comparing each group with the control and among themselves). In the groups of patients with coronary artery disease, regardless of the presence of AoS, there was a predominance of the male sex in comparison with the control group. There was no difference between groups 1 and 2 in the presence of diabetes, arterial hypertension, hypercholesterolemia and myocardial infarction, but there were significant differences compared to the control group (Table 1). Most patients with CAD were on statin drug therapy.

The values of total cholesterol, LDL cholesterol and LDL cholesterol in the blood were comparable among patients with CAD, regardless of the presence of AoS, but were significantly lower than in the control group ($p<0,0001$) (Table 1), which is explained by the more frequent use of statins in patients of groups with CAD compared with the control group: 98% vs 80% ($p<0,05$).

Analysis of the concentration of Lp (a) showed that it is higher in patients with CAD (groups 1 and 2) compared with the control group. The concentration of ATX, on the contrary, was significantly lower in group 1 than in the control group or in group 2. At the same time, there was no significant difference between the 2 group, which included patients with AoS, and the control group (Figure 1).

It was noted that at an ATX level of <418,5 ng/ml, which corresponds to the 1st quartile, not a single patient was identified who had both CAD and degenerative AoS at the same time. A quarter of patients from this group had an ATX concentration >606 ng/ml, >70% of patients with an ATX concentration at the 1st quartile level belonged to the group with coronary

Table 1

Groups general characteristics

	Control group CAD- AoS- (n=107)	Group 1 CAD+ AoS- (n=307)	Group 2 CAD+ AoS+ (n=47)	p
Male, n (%)	51 (47%)	240 (78%)	32 (68%)	<0,05 for 1 and 2 vs control
Age, years	61±13	66±10	74±8	<0,001 for 1 и 2 vs control, 1 vs 2
Smoking, n (%)	15 (14%)	83 (27%)	11 (23%)	<0,05 for 1 vs control
Type 2 diabetes, n (%)	19 (18%)	90 (29%)	20 (42%)	<0,05 for 1 and 2 vs control
Arterial hypertension, n (%)	94 (87%)	288 (93%)	43 (91%)	
Hyperlipidemia, n (%)	88 (82%)	288 (93%)	45 (95%)	<0,05 for 1 and 2 vs control
Myocardial infarction, n (%)	2 (2%)	169 (55%)	24 (51%)	<0,001 for 1 и 2 vs control
Statins, n (%)	86 (80%)	302 (98%)	46 (98%)	<0,05 for 1 and 2 vs control
Total cholesterol, mmol/l	5,6±1,7	4,5±1,4	4,4±1,1	<0,001 for 1 и 2 vs control
LDL cholesterol, mmol/l	3,6±1,6	2,6±1,2	2,6±0,9	<0,001 for 1 и 2 vs control
LDL cholesterol corr, mmol/l	3,4±1,6	2,3±1,3	2,3±0,9	<0,001 for 1 и 2 vs control
Lp (a), mg/dl	14,5 [5,5;35,9]	24,9 [9,7;58,4]	23,8 [9,9;75,7]	<0,05 for 1 and 2 vs control
ATX, ng/ml	545 [412;654]	495 [406;583]	545 [477;605]	<0,05 for 2 vs 1 and control
CRP, mg/l	4,1 [3,4;6,1]	5,4 [4,4;6,3]	3,6 [2,7;5,9]	
ESR, mm/h	10 [5;19]	11 [5;21]	20 [10;47]	<0,05 for 2 vs 1 and control
NLI	1,5 [1,2;2,1]	1,7 [1,4;2,3]	2,0 [1,6;3,1]	<0,001 for 1 и 2 vs control, 1 vs 2

Note: ESR is the erythrocyte sedimentation rate. Data are presented as median [25%; 75% percentile] for indicators with a distribution other than normal, when comparing quantitative indicators, the Mann-Whitney U test was used, for indicators with a normal distribution — mean values ± standard deviation or absolute number of patients (%), when comparing quantitative indicators, Student's t-test was used.

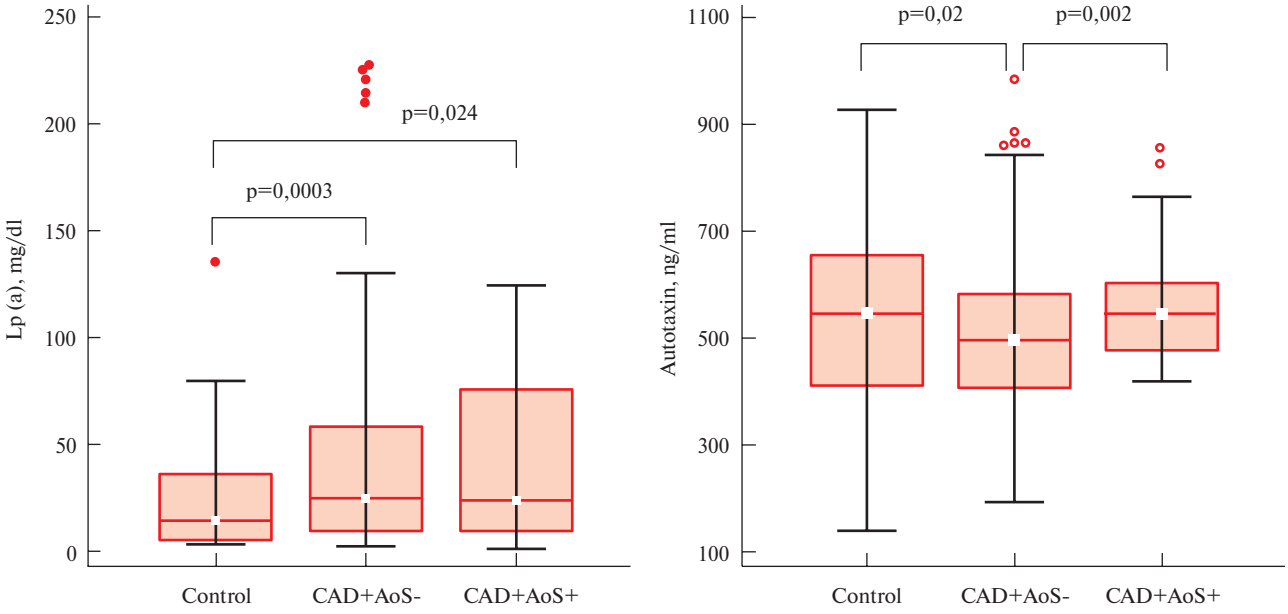

Figure 1 Levels of Lp (a) and ATX in the studied groups of patients.
Note: Data is presented as a Box-and-Whisker plot. Median [25%;75%] — Lp (a) in the group CAD+AoS- was 24,9 [9,7;58,4] mg/dL, in the group CAD+AoS+ — 23,8 [9,9;75,7] mg/dl, and in the control group 14,5 [5,5;35,9] mg/dl. Median [25%;75%] ATX in the group CAD+AoS- 495 [406;583] ng/ml, in the group CAD+AoS + this indicator was 545 [477;604] ng/ml, and in the control group 545 [412;654] ng/ml. AoC — aortic valve stenosis, CAD — coronary artery disease, Lp (a) — lipoprotein (a).

artery disease without AoS. A similar analysis of the distribution of patients relative to the upper and lower quartiles was performed for such indicators as Lp (a) and NLI (Figure 2). The ATX level corresponding to the upper quartile was most often found in patients with combined lesions of CAD and aortic valve, while an increased concentration of Lp (a) was associated with the presence of CAD regardless of the lesion of the aortic valve (Figure 2).

ROC analysis demonstrated a significant relationship between age (sensitivity 74,5%; specificity 65,5%, area under the curve 0,754), NLI (sensitivity

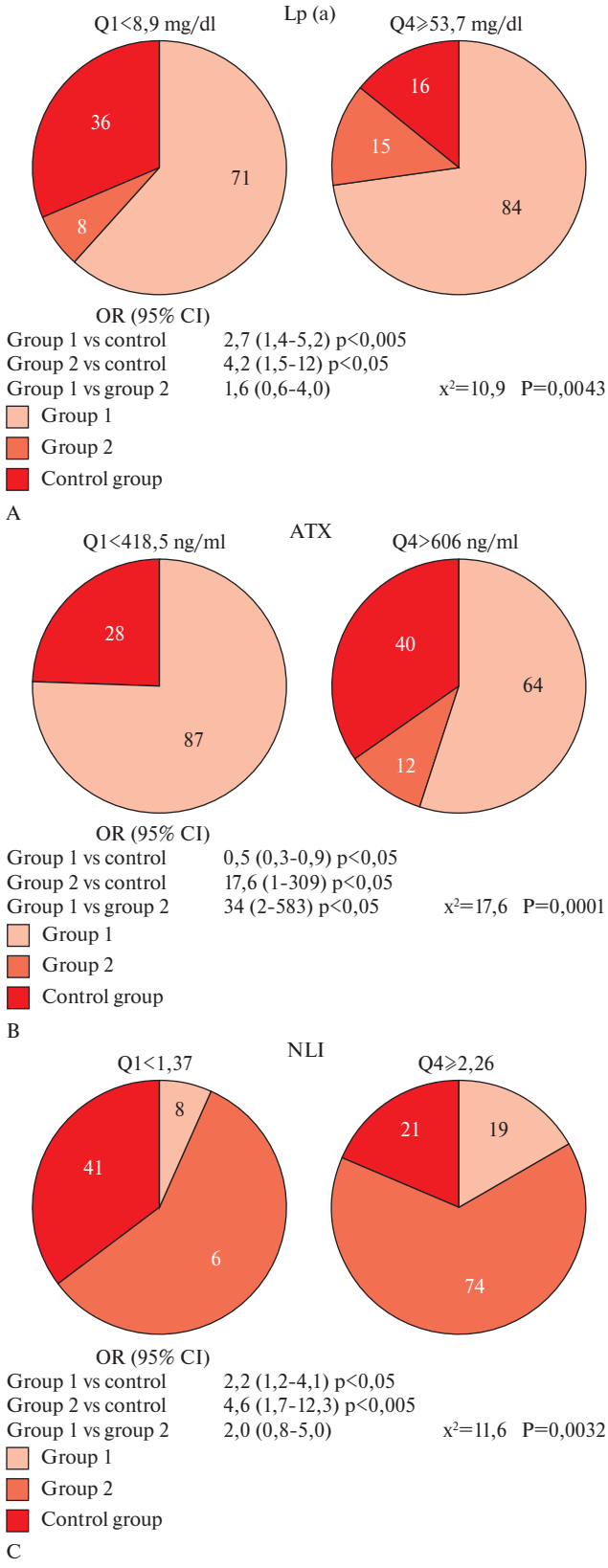

Figure 2 Frequency of CAD and degenerative AoS in patients with low and high levels of Lp (a) — *A*, ATX — *B* and NLI — *C*.

Note: the data are presented as the number of patients from different groups and OR of the presence of aortic stenosis in patients with the level of the studied parameters corresponding to the first (Q1) and fourth (Q4) quartiles of the distribution. ATX — autotaxin, Lp (a) — lipoprotein (a), NLI — neutrophil-lymphocyte index.

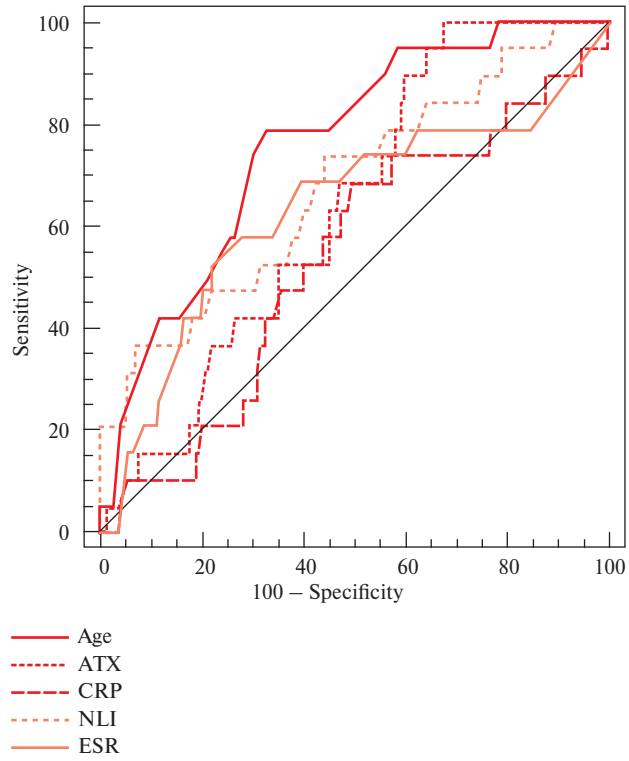

Figure 3 ROC analysis of the relationship between aortic valve lesions and the level of clinical indications and markers of inflammation.

Note: ATX — autotaxin, NLI — neutrophil-lymphocyte index, ESR — erythrocyte sedimentation rate, CRP — C-reactive protein.

36,2%; specificity 90,7%, area under the curve 0,642), ATX concentration (sensitivity 97,9%; specificity 33,82%, area under the curve 0,608) and erythrocyte sedimentation rate (sensitivity 57,9%; specificity 69,4%, area under the curve 0,654) and the presence of AoS in the examined patients (p<0,05 in all cases) (Figure 3).

According to logistic regression analysis, only age — odds ratio (OR)=1,11, 95% confidence interval (CI): 1,07-1,16 and NLI — OR=1,42, 95% CI: 1,16-1,75 (p <0,001 for both comparisons) were independently associated with degenerative AoS both in the general group of the examined patients and in the group of CAD patients. At the same time, in this model, it was not possible to demonstrate an independent relationship between the concentration of Lp (a) and ATX, on the one hand, and the presence of AoS, on the other. When analyzing only CAD patients, an increase in ATX concentration by one standard deviation (138 ng/ml) was associated with the presence of degenerative AoS in patients regardless of age and other risk factors (OR=1,6, 95% CI:1,09-2,2) (p<0,05).

Thus, the specific role of Lp (a) in the development of AoS in patients with already existing ischemic heart disease has not been identified; along with this, it was found that an increased concentration of ATX is associated with the development of AoS in patients with pre-existing ischemic heart disease.

Discussion

Lp (a) is a unique lipoprotein consisting of an LDL-like particle and apoprotein (a) [10]. This indicator was first described >50 years ago as a new genetic variant of LDL. Currently, an increased level of Lp (a) is recognized as an independent risk factor for the development of CAD [11]. In the last few years, Lp (a) has become interesting as a possible risk factor for the development of degenerative AoS [12]. In 2013, according to the results of genome-wide analysis, which included 38 thousand patients, within the framework of the international consortium CHARGE, a significant relationship was revealed between variation in the *LPA* gene and the development of degenerative AoS. The rs10455872 variant in this gene was associated with the development of aortic valve calcification regardless of gender and race [13]. Another large, prospective study EPIC (European Prospective Investigation into Cancer (EPIC) — Norfolk) showed that patients with the highest Lp (a) levels had an increased risk of developing AoS [14]. CCHS (Copenhagen City Heart Study) and CGPS (Copenhagen General Population Study), which included about 78 thousand patients, it was noted that the level of Lp (a) >90 mg/dL was associated with a 2,9-fold increase in the risk of developing AoS [15]. According to the obtained data, the level of Lp (a) was significantly higher in the groups of patients with CAD compared with the control group, regardless of the presence of AoS. Such results, apparently, confirm the leading role of the increased concentration of Lp (a) in early CAD development. Degenerative AoS, as a disease associated with older age, in patients with an elevated Lp (a) level may occur on the background of a previous CAD.

Along with Lp (a), the role of ATX in the development of degenerative AoS was also assessed. According to a "case-control" study by Nsaibia MJ, et al., which is included 300 patients with CAD, it was found that the level of ATX circulating in the blood is associated with the development of degenerative AoS in patients with CAD, and the combination of high ATX activity with a Lp (a) level >50 mg/dL 3,5 times increased the likelihood of developing degenerative AoS [16]. It is important to note that a distinctive feature of our protocol was the study of the control group, which included patients who did not have CAD or AoS. The results are comparable to those of Nsaibia MJ, et al. and are characterized by a significant difference in the level of ATX in patients with coronary artery disease with combined lesions of the aortic valve in comparison with patients with CAD without AoS. There were no significant differences in the average concentration of ATX between patients with AoS and patients in the control group. Thus, only with a combination of an increased level of Lp (a) and ATX, the latter becomes a factor contributing to the development of AoS. This conclusion is confirmed by the results of other studies, in which it was found that ATX is delivered to the tissue of the aortic valve as part of Lp (a). Bouchareb R, et al. demonstrated that ATX activity was increased 4,6 times in the Lp (a) fraction relative to that in the blood plasma of healthy donors. In addition, immunohistochemical analysis of the aortic valve tissue showed that ATX can be produced and secreted by the interstitial cells of the aortic valve, and its expression is associated with markers of inflammation [7].

The inflammatory response is widely discussed as an initiating factor in the development of degenerative AoS. To assess the contribution of inflammation, the authors analyzed NLI as a simple and accessible marker of the systemic inflammatory response. According to the results of several studies, this indicator was associated with the presence of coronary artery disease and AoS [17, 18].

According to our data, NLI is an indicator independent of other CVD risk factors, indicating the presence of AoS in patients with CAD. At the same time, an increased NLI is associated with the identification of both isolated CAD and CAD in combination with AoS compared with the control group, which confirms the role of active inflammation in the development of these CVDs.

According to Song J, et al., NLI and CRP may be new reliable predictors of the development of degenerative AoS; in addition, increased NLI is directly related to the severity of AoS in patients with both tricuspid aortic valve and bicuspid valve [18]. It should be noted that the authors did not find a difference in the CRP level either between the groups differing in the presence of AoS, or in comparison of each group with the control. An increase in CRP is observed in endogenous vascular inflammation accompanying the development of atherosclerosis, as well as in trauma and infection [19]. Since the control group consisted of inpatients with cardiovascular pathology, but without CAD and AoS, some patients had atherosclerotic lesions of peripheral arteries of varying severity. Previously, an association was found between elevated CRP levels and multifocal peripheral arterial disease in women [20], which explains the absence of differences between groups in this study.

Conclusion

The increased level of Lp (a), in contrast to the concentration of ATX, was not associated with the presence of degenerative AoS in patients with coronary artery disease with stenosing atherosclerosis of the coronary arteries. NLI, as a marker of systemic inflammation, demonstrated in this study an association independent of age and other risk factors with degenerative AoS in the presence of CAD.

Relationships and Activities: none.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Executive summary: heart disease and stroke statistics — 2013 update: a report from the American Heart Association. Circulation. 2013;127:143-52. doi:10.1161/CIR.0b013e31828124ad.
2. Khubulava GG, Gulyaev NI, Kravchuk VN, et al. Incidence of degenerative aortic stenosis in the patterns of valvular heart disease. Grudnaya i Serdechno-Sosudistaya Khirurgiya (Russian Journal of Thoracic and Cardiovascular Surgery). 2018;60(1):28-35. (In Russ.) doi:10.24022/0236-2791-2018-60-1-28-35.
3. Otto CM, Kuusisto J, Reichenbach DD, et al. Characterization of the early lesion of 'degenerative' valvular aortic stenosis: histologic and immunohistochemical studies. Circulation. 1994;90:844-53. doi:10.1161/01.cir.90.2.844.
4. Carità P, Coppola G, Novo G, et al. Aortic stenosis: insights on pathogenesis and clinical implications. J Geriatr Cardiol. 2016;13(6):489-98. doi:10.11909/j.issn.1671-5411.2016.06.001.
5. Capoulade R, Chan KL, Yeang C, et al. Oxidized Phospholipids, Lipoprotein(a), and Progression of Calcific Aortic Valve Stenosis. J Am Coll Cardiol. 2015;66(11):1236-46. doi:10.1016/j.jacc.2015.07.020.
6. Teo KK, Corsi DJ, Tam JW, et al. Lipid lowering on progression of mild to moderate aortic stenosis: meta-analysis of the randomized placebo-controlled clinical trials on 2344 patients. Can J Cardiol. 2011;27(6):800-8. doi:10.1016/j.cjca.2011.03.012.
7. Bouchareb R, Mahmut A, Nsaibia MJ, et al. Autotaxin derived from lipoprotein(a) and valve interstitial cells promotes inflammation and mineralization of the aortic valve. Circulation. 2015;132:67790. doi:10.1161/CIRCULATIONAHA.115.016757.
8. Dahlen GH. Incidence of Lp(a) lipoprotein among populations in "Lipoprotein(a)" ed. Scanu A. M. Academic Press. San Diego. 1990. C.151-75. ISBN-13: 978-0126209907. ISBN-10: 0126209901.
9. Afanasieva OI, Adamova IYu, Benevolenskaya GF, Pokrovsky SN. An immunoenzyme method for determining lipoprotein(a). Bull Exp Biol Med. 1995;120(10):398-401. (In Russ.) doi:10.1007/bf02444976.
10. Ellis KL, Boffa MB, Sahebkar A, et al. The renaissance of lipoprotein(a): brave new world for preventive cardiology? Prog Lipid Res. 2017;57-82. doi:10.1016/j.plipres.2017.09.001.
11. Malarstig A, Green FR, Lathrop M, et al. Genetic variants associated with Lp(a) lipoprotein level and coronary disease. N Engl J Med. 2009;361:2518-28. doi:10.1056/NEJMoa0902604.
12. Borrelli MJ, Youssef F, Boffa MB, Koschinsky ML. New Frontiers in Lp(a)-Targeted Therapies. Trends Pharmacol Sci. 2019;40(3):212-25. doi:10.1016/j.tips.2019.01.004.
13. Thanassoulis G, Campbell CY, Owens DS. Genetic associations with valvular calcification and aortic stenosis. N Engl J Med. 2013;368:503-12. doi:10.1056/NEJMoa1109034.
14. Arsenault BJ, Boekholdt SM, Dubé MP, et al. Lipoprotein(a) levels, genotype, and incident aortic valve stenosis: a prospective mendelian randomization study and replication in a case-control cohort. Circ Cardiovasc Genet. 2014;7:304-10. doi:10.1161/CIRCGENETICS.113.000400.
15. Kamstrup PR, Tybjærg-Hansen A, Nordestgaard BG. Elevated Lipoprotein(a) and Risk of Aortic Valve Stenosis in the General Population. J Am Coll Cardiol. 2014;63:470-7. doi:10.1016/j.jacc.2013.09.038.
16. Nsaibia MJ, Mahmut A, Boulanger MC. Autotaxin interacts with lipoprotein(a) and oxidized phospholipids in predicting the risk of calcific aortic valve stenosis in patients with coronary artery disease. J Intern Med. 2016;280:509-17. doi:10.1016/j.jacc.2019.01.070.
17. Tanındı A, Erkan AF, Alhan A, Töre HF. Arterial stiffness and central arterial wave reflection are associated with serum uric acid, total bilirubin, and neutrophil-to-lymphocyte ratio in patients with coronary artery disease. Anatol J Cardiol. 2015;15:396-403. doi:10.5152/akd.2014.5447.
18. Song J, Zheng Q, Ma X, et al. Predictive Roles of Neutrophil-to-Lymphocyte Ratio and C-Reactive Protein in Patients with Calcific Aortic Valve Disease. Int Heart J. 2019;60:345-51. doi:10.1536/ihj.18-196.
19. Sproston NR, Ashworth JJ. Role of C-Reactive Protein at Sites of Inflammation and Infection. Front Immunol. 2018;9:754. doi:10.3389/fimmu.2018.00754.
20. Afanasieva OI, Tmoyan NA, Klesareva EA, et al. The Relationship of the Concentration of Lipoprotein(a) and Markers of Inflammation With Multifocal Atherosclerosis in Women. Kardiologiia. 2019;59(10):39-48. (In Russ.) doi:10.18087/cardio.2019.10.n520.

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Relationship between depression and coronary artery disease in an open female and male population of a middle-urbanized city of Western Siberia

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Aim. To assess the associations between depression and coronary artery disease (CAD) in an open female and male population of a middle-urbanized city of Western Siberia.

Material and methods. Two cross-sectional epidemiological studies were carried out on an open population of a middle-urbanized Siberian city among men and women aged 25-64 years old. The prevalence of CAD was assessed based on standard epidemiological methods. To determine the severity of depression, the algorithms of the WHO program MONICA-Psychosocial were used. The severity of depression was assessed as low, moderate, and high. On the basis of the algorithm, the levels of depression were established: low and moderate levels — no sign, high level — presence of a sign.

Results. In an open population of 25-64 years old, a moderately urbanized Siberian city, the prevalence of CAD according to extended and lax epidemiological criteria prevailed in men, while strict epidemiological criteria did not reveal significant differences in the male and female subpopulations. In the female subpopulation, a tendency towards an increase in the prevalence of a high level of depression was revealed due to its predominance in young age groups.

It has been shown that the depression increases the probability of detecting CAD in accordance with the expanded epidemiological criteria in men and women by 21,07 and 16,04 times, respectively.

Conclusion. When using epidemiological criteria for CAD in the presence of depression, the probability of detecting CAD is higher, both in men and women. At the same time, the highest odds ratios are characteristic for a certain type of CAD, the least — CAD by probable signs.

Keywords: epidemiological study, coronary artery disease, depression, open population, sex differences.

Relationships and Activities: none.

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Introduction

Depressive disorders are one of the key psychosocial risk factors (PSF) for the development of cardiovascular diseases (CVD) [1, 2]. Depression has received the most attention from researchers over the past decades. Because of the overwhelming number of studies related to depression and CVD, recent US clinical guidelines include the screening and treatment of depression in patients with heart failure as the standard of care [3]. Depression is defined differently in CVD studies and can range from subclinical symptoms of depression to major depressive disorders [4, 5].

Associations of depression with CVD mortality were first identified in the middle of the last century, but only at the end of the 20th century, when studying mortality in populations with a high level of depression, data on a significant increase in cardiovascular and overall mortality were obtained, after which depression was recognized as an independent risk factor (RF) CVD. It has been shown that in patients with psychoemotional disorders, the pathophysiological mechanisms of the development of coronary artery disease (CAD) are manifested by the hyperproduction of coagulation factor IV and β-thromboglobulin, an increase in the levels of catecholamines in the blood and intracellular free calcium, which leads to an increased risk of CAD in due to increased thrombus formation [6]. In addition, psychological and social disorders in patients with CAD occur much more often than in the general population, causing complications of the disease, deteriorating health in general and reducing the quality of life [7, 8]. The results of a large clinical and epidemiological study to assess the prevalence of PSF in patients with CAD in the Russian Federation according

to KOMETA (Clinical-Epidemiological Program of Studying Psychosocial Risk Factors in Cardiological Practice in Patients with Arterial Hypertension and Ischemic Heart Disease) showed their relationship with traditional CVD RF [9].

In many studies, the prognosis of CAD development in connection with depressive manifestations has been studied, and it has been shown that, in the gender aspect, the prevalence of depression and other negative psychoemotional states in the general population in women in particular, significantly exceeds those in men [1, 10, 11]. With the most severe form of depression, a depressive episode, the highest risk of CVD complications is also noted [9]. In the Novosibirsk study, it was shown that death from cardiovascular causes in the group with depression was 2 times higher than in the general population [10]. As a result, the gender characteristics identified in relation to the CAD risks, depending on the high level of depression in Western Siberia at the level of a middle-urbanized city, are likely to be decisive for the possibilities of effectively changing the epidemiological situation of CVD in the region [12].

The aim of the study is to assess the associations between depression and coronary artery disease in an open population of a middle-urbanized city of Western Siberia in terms of gender.

Material and methods

On the open (unorganized) population of Tyumen, two cross-sectional epidemiological studies were carried out according to a single protocol among persons of both sexes — among men in 2010 and among women in 2016. Representative samples, stratified by sex and age, were formed in a computer version using the method of random numbers based on the list of names of the population of the Central Administrative District of the city. Initially, the information received was verified at the Tyumen Regional Address Bureau. The samples consisted of 1000 persons aged 25-64 (250 persons in each of the four decades of life). The criteria for enrollment in the population samples were males or females aged 25-64, registered and living in the Central Administrative District of Tyumen. The criteria for withdrawal from the population were refugees, students, soldiers and prisoners, which was established from the words of the subjects, the data were not included in the analytical array. Invitations were sent to those included in the population samples to participate in cardiological screening; in the absence of a response to the first invitation, up to three reminder letters were sent with an interval of 7-10 days, or attempts were made by telephone or personal contact with the study participants. The response to the study among men was 85,0%, among women — 70,3% (Table 1).

The study was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from all participants prior to enrollment.

As part of cardiac screening, resting electrocardiography was performed in the supine position in 12 leads. The prevalence of CAD was established according to the criteria adopted in epidemiological studies. Based on the results of electrocardiography processing using the Minnesota code and analysis of the World Health Organization (WHO) questionnaire for angina pectoris, an epidemiological diagnosis of CAD was established: 1) according to strict criteria - a "definite" form of CAD (DCAD); 2) according to non-strict criteria — "possible" form of CAD (PCAD). Strict and non-strict CAD criteria collectively defined CAD according to extended epidemiological criteria.

To determine the severity of depression, the algorithm of the WHO program MONICA-Psychosocial was used [13]. A depression scale form (Mopsy test) consisting of 15 statements was proposed. To answer each statement, 2 gradations are provided: "agree", "disagree". The severity of depression was assessed as low, moderate, high. On the basis of the algorithm, the levels of depression were established: low and moderate levels — the absence of a sign, a high level — the presence of a sign.

For the statistical processing of the study results, the program IBM STATISTICS 21.0 was used. To conduct a correct comparative analysis with data from other epidemiological studies, the indicators were standardized using the direct method of standardization. When processing the data obtained, the age structure of the urban population of the Russian Federation in the range of 25-64 years was used to standardize the indicators. Results for categorical variables are presented as fractions (in %). When assessing the statistical significance between the sample fractions of the population in the two groups, the Pearson's chi-squared test (χ^2) with Yates' correction for continuity was used. In the case of comparing three or more groups, the analysis of contingency tables was initially used, according to the criterion of "maximum

Table 1

The structure of subjects according to the data of cardiac screenings

Evaluation parameters	The number of subjects (male/female)	Age and sex groups, years (male/female)			
		25-34	35-44	45-54	55-64
Screening	850/703	177/122	228/207	231/159	214/215
CAD	130/75	4/3	19/16	36/22	71/74
DCAD	71/51	3/2	8/12	19/15	41/22
PCAD	59/24	1/1	11/4	17/7	30/12
High levels of depression	50/55	2/10	4/15	13/10	31/20

Note: PCAD — "possible" CAD, CAD — coronary artery disease, DCAD — "definite" CAD.

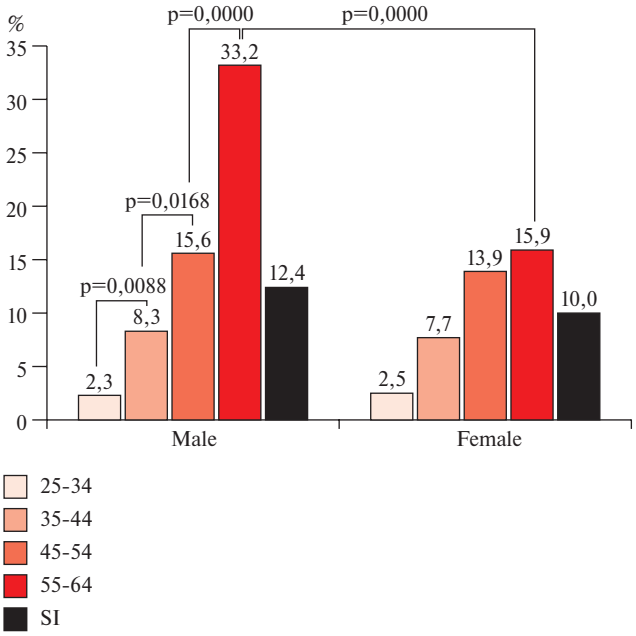

Figure 1 Prevalence of CAD according to extended epidemiological criteria in an open population of 25-64 years old, %.
Note: SI is an age-standardized indicator.

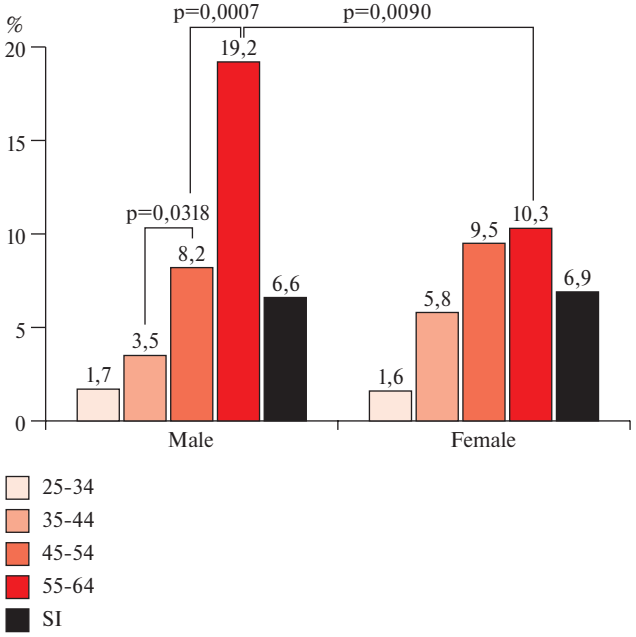

Figure 2 Prevalence of CAD according to strict epidemiological criteria in an open population of 25-64 years old, %.
Note: SI is an age-standardized indicator.

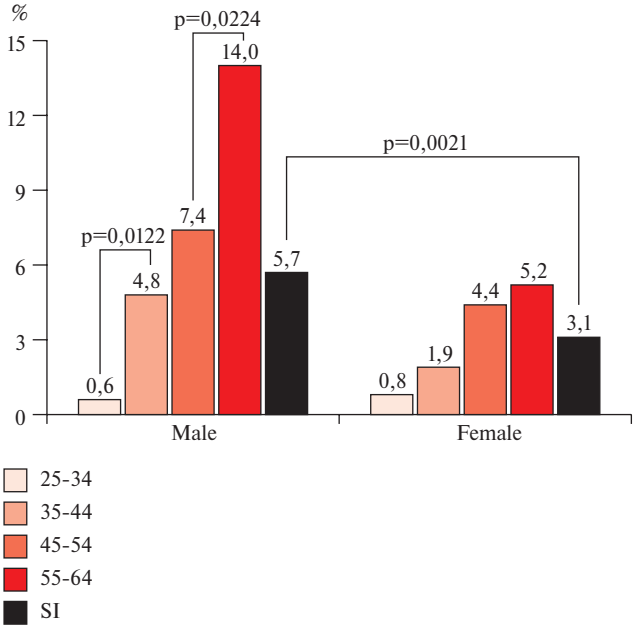

Figure 3 Prevalence of CAD according to non-strict epidemiological criteria in an open population of 25-64 years old, %.
Note: SI is an age-standardized indicator.

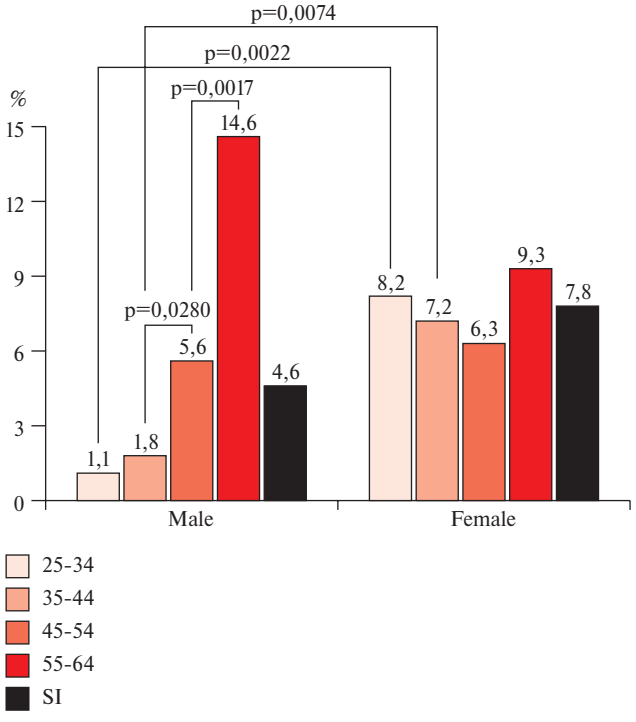

Figure 4 Prevalence of high levels of depression in men and women in an open population of 25-64 years old, %.
Note: SI is an age-standardized indicator.

likelihood chi-square", to establish statistically significant differences between the groups, followed by paired comparison of the groups. For the critical level of significance when testing statistical hypotheses, $p<0,05$ was taken based on the number of degrees of freedom. When paired comparisons in four or more independent groups, to exclude the problem of multiple comparisons, i.e., to eliminate the error of the first kind, the Bonferroni correction was applied. Associations of high levels of depression with the prevalence of CAD, its "definite" and "possible" forms (DCAD and PCAD), were determined by calculating odds ratios (OR) and their 95% confidence intervals (CI). In each case, the statistical significance of OR was assessed based on the values of 95% CI. If the CI included one, i.e., its upper limit was >1, and the lower one was <1,

Table 2

Indicators of the association of depression and different forms of CAD (epidemiological approach) in an open population of 25-64 years old

Presence/ absence of D	DCAD yes	DCAD no	OR	95% CI	PCAD yes	PCAD no	OR	95% CI	CAD according to extended criteria yes	CAD according to extended criteria no	OR	95% CI
Male												
D yes	32	18	39,84	19,61-80,90	3	47	1,06	0,31-3,65	35	15	21,07	10,76-41,26
D no	27	605			36	596			63	569		
Female												
D yes	19	49	26,53	10,63-66,26	6	50	5,88	2,05-16,86	25	43	16,04	8,04-32,00
D no	7	479			10	490			17	469		

Note: PCAD — "possible" CAD, D — depression, CI — confidence interval, CAD — coronary artery disease, DCAD — "definite" CAD, OR — odds ratio.

it was concluded that there was no statistical significance of the relationship between the factor and the outcome at a significance level of p>0,05.

Results

In an open urban population (on the model of Tyumen), the age-standardized CAD prevalence among men was 12,4%, among women it was significantly less — 10,0% (p=0,0074).

With increasing age, the prevalence of CAD according to extended epidemiological criteria increased significantly in the male subpopulation. In the age categories of the female subpopulation, the prevalence of CAD according to extended criteria was almost the same. Statistically significant differences in the prevalence of CAD in the gender aspect took place in the sixth decade of life — 33,2% in men and 15,9% in women (p=0,0000) (Figure 1). According to strict epidemiological criteria, the prevalence of CAD among men — age-standardized indicator (SI) =6,6%, and women — SI =6,9%, was practically the same (p=0,4233). The indicator significantly increased with age in men from the fourth to the fifth (p=0,0318) and from the fifth to the sixth decade of life (p=0,0007), remaining stable in women throughout the entire age range. Statistically significant differences in the prevalence of DCAD in the gender aspect were also established in the sixth decade of life — 19,2% in men and 10,3% in women (p=0,0090) (Figure 2). According to non-strict epidemiological criteria, the prevalence of PCAD in the male subpopulation increased significantly with age in the fourth (p=0,0122) and sixth decades of life (p=0,0224); in the female subpopulation, this tendency was not revealed. In the gender aspect according to PCAD SR, there were statistically significant differences with the priority for men compared with women — 5,7 and 3,1%, respectively (p=0,0021) (p=0,0021) (Figure 3).

The age-standardized indicator of high depression in the male subpopulation was 4,6%, in the female subpopulation — 7,8% (p=0,1294).

The high level of depression in men and women reached its absolute maximum in the 55-64 age group. In the age range, the high level of depression in men significantly increased from the fourth to the fifth — 1,8 vs 5,6% (p=0,0280) and from the fifth to the sixth decade of life — 5,6 vs 14,6% (p=0,0017), in women throughout the entire age period, the indicator remained practically the same. In the gender aspect, statistically significant differences in the prevalence of high levels of depression were noted at a young age with a priority for women — 25-34 years: 1,1% vs 8,2% (p=0,0022); 35-44 years: 1,8 vs 7,4% (p=0,0074) in men and women, respectively (Figure 4).

In an open urban population aged 25-64, associations between the prevalence of CAD and high levels of depression (OR) among men and women were determined. In both sexes, depression was significantly associated with the development of CAD. Thus, in the presence/absence of a high level of depression and the presence/absence of CAD according to extended criteria, OR =21,07 in the male subpopulation (95% CI: 10,76-41,26) and OR =16,04 in the female subpopulation (95% CI: 8,04-32,00) at a significance level of p<0,05. In the presence/absence of DACD and a high level of depression, OR =39,84 in the male subpopulation (95% CI: 19,61-80,90) and OR =26,53 in the female subpopulation (95% CI: 10,63-66,26).

Consequently, when using epidemiological criteria for defining CAD in the presence of depression, the chance of detecting CAD is higher in both men and women. At the same time, the highest OR indicators are characteristic for the registration of DCAD, the lowest — for PCAD (Table 2). The presence of depression increases the chance of defining CAD according to extended criteria by 21,07 and 16,04 times in men and women, respectively.

Discussion

In the scientific literature of the beginning of this century, it has been shown that in the pathogenetic chain of development of cardiovascular pathology,

depression is not so much a secondary psychoemotional reaction to CAD, but a proven independent RF of its development [1, 3, 6]. In addition, depression can be both a negative prognostic factor and provoke the development of CVD [4]. Previous works performed on the Tyumen population showed the importance of studying PSF and, in particular, negative psychoemotional states due to their high prevalence in the population, as well as their predictive value in relation to the development of CAD [11, 14].

The profile of psychoemotional RFs among women in the Tyumen population in the age aspect showed a significant prevalence of a high level of depression in not only middle-aged but also young age groups. This situation seems reasonable, since the prevalence of PSF in populations is interdependent and is determined by the combined interaction of factors of psycho-emotional stress and factors of chronic social stress, the prevalence of which, according to the results of previous studies, was very high in young women [15].

The results of global studies have demonstrated the effect of depression on severe complications of CAD, both directly under the influence of pathophysiological mechanisms, and indirectly, through the influence of behavioral RF of CVD. Depression can be aggravated by stressful events, while depression, as such, can provoke a reaction of the cardiovascular system to stress, eventually forming a vicious circle [4, 7]. At the same time, the possibility of changing the behavior and ways of the individual's response, including those that can reduce the risk of developing CAD, seems so far from a solution [8, 9]. The effectiveness of correcting and overcoming stress in society has not been studied enough, however, since PSF can be considered as internal resources subject to the person himself, the development of personal attitudes should become fundamental for a more positive attitude of the individual and an improvement in the quality of life [10].

In the presence/absence of CAD and a high level of depression in the Tyumen population aged 25-64, a high OR was revealed in men — 21,07, and the highest OR in the presence/absence of DCAD and a high level of depression in the male subpopulation was 39,84. The female subpopulation also showed a high OR in the presence/absence of CAD and DCAD and a high level of depression, although it is significantly lower than in men, despite the unfavorable situation regarding the prevalence of depression among Tyumen women. In accordance with the results obtained in this study, the scientific literature of the last decade has shown that despite the fact that depression is more common in female populations, men had a significantly higher relative risk of developing CVD at its high levels [2, 10]. In this respect, the results obtained on the Tyumen population are comparable with the data of global and domestic studies. At the same time, with regard to the OR obtained in the presence/absence of PCAD and a high level of depression, which is significantly higher and statistically significant in women compared to men, the situation can be justified by the greater emotional lability of women, and as a result, a higher risk of development "pre-illness" — "possible" forms of CAD.

Thus, in accordance with the European and world experience of carrying out preventive measures using a population strategy and a high-risk strategy, it is necessary to note the priority of the presented analysis of the results when constructing preventive programs using new social technologies of differentiated influence on high levels of PSF, taking into account gender characteristics [16].

Conclusion

In an open population of 25-64 years old, a moderately urbanized Siberian city, the prevalence of CAD according to extended and lax epidemiological criteria prevailed in men, while strict epidemiological criteria did not reveal significant differences in the male and female subpopulations.

In the female subpopulation, a tendency towards an increase in the prevalence of a high level of depression was revealed due to the prevalence of the indicator in the age categories of young age in the gender aspect.

It has been shown that the presence of depression increases the chance of detecting CAD according to extended epidemiological criteria in men and women by 21,07 and 16,04 times, respectively.

Relationships and Activities: none.

References

1. Oganov RG, Pogosova NV, Shalnova SA, et al. Depressive Disorders in General Medical Practice in KOMPAS Study: Outlook of a Cardiologist. Kardiologiia. 2005;8:38-44. (In Russ)
2. Dhar A, Barton D. Depression and the link with cardiovascular disease. Frontiers in Psychiatry. 2016;7:1-9. doi:10.3389/fpsyt.2016.00033.
3. Dunbar SB, Khavjou OA, Bakas T, et al. Projected costs of informal caregiving for cardiovascular disease: 2015 to 2035: a policy statement from the American Heart Association. Circulation. 2018;137(19):e558-77. doi:10.1161/cir.0000000000000570.
4. Vaccarino V, Badimon L, Bremner JD, et al. Depression and coronary heart disease: 2018 position paper of the ESC working group on coronary pathophysiology and microcirculation. Eur Heart J. 2020;41:1687-96. doi:10.1093/eurheartj/ehy913.
5. Tang B, Yuan S, Xiong Y, et al. Major depressive disorder and cardiometabolic diseases: a bidirectional Mendelian randomisation study. Diabetologia. 2020;63(7):1305-11. doi:10.1007/s00125-020-05131-6.
6. Wulsin LR, Singal BM. Do Depressive Symptoms Increase the Risk for the Onset of Coronary Disease? A Systematic Quantitative Review. Psychosomatic Med. 2003;65(2):201-10. doi:10.1097/01.psy.0000058371.50240.e3.
7. Pogosova NV, Oganov RG, Boytsov SA, et al. Psychosocial factors and life quality in coronary heart disease patients: results of the Russian part of international multicenter study EUROASPIRE IV. Cardiovascular Therapy and Prevention. 2017;16(5):20-6. (In Russ.) doi:10.15829/1728-8800-2017-5-20-26.
8. Nagibina YV, Kubareva MI, Knyazeva DS. Medical and social features of patients with coronary artery disease and depression. Cardiovascular Therapy and Prevention. 2019;18(6):142-51. (In Russ.) doi:10.15829/1728-8800-2019-1930.
9. Pogosova NV, Boytsov SA, Oganov RG, et al. Clinical-Epidemiological Program of Studying Psychosocial Risk Factors in Cardiological Practice in Patients With Arterial Hypertension and Ischemic Heart Disease: First Results of a Multicenter Study in Russia. Kardiologiia. 2018;58(9):47-58. (In Russ.) doi:10.18087/cardio.2018.9.10171.
10. Gafarov VV, Gromova EA, Gagulin IV, et al. Gender peculiarities of the risk of cardiovascular diseases in a population with symptoms of depression in Siberia (the WHO MONICA-psychosocial program). Terapevticheskii archiv. 2017;9(89):60-7. (In Russ.) doi:10.17116/terarkh201789960-67.
11. Akimova EV, Kayumova MM, Smaznova OV, et al. Psychosocial health component in Tyumen male population aged 25-64 years. The world of science, culture, education. 2012;32(1):257-60. (In Russ.)
12. Boytsov SA. Recent trends in and new data on the epidemiology and prevention of non-communicable diseases. Terapevticheskii archiv. 2016;1:4-10. (In Russ.) doi:10.17116/terarkh20168814-10.
13. Kuulasmaa K, Cepaitis Z, Joseph B, et al. for the WHO MONICA Project, total 245 coauthors. MONICA Monograph and Multimedia Sourcebook. Helsinki, 2003. 237 p. ISBN 92-4-156223-4.
14. Akimova EV, Smaznov VYu, Kayumova MM, et al. Selected parameters of chronic social stress in open population — association with the prevalence of ischemic heart disease. Cardiovascular Therapy and Prevention. 2014;13(6):28-31. (In Russ.) doi:10.15829/1728-8800-2014-6-28-31.
15. Akimov AM, Gakova EI, Akimova AA, et al. The associations between parameters of stress in the workplace and the nature of work in women of an open urban population. Siberian Medical Journal. 2016;4(31):76-9. (In Russ.) doi:10.29001/2073-8552-2016-31-4-76-79.
16. Maslennikova GYa, Oganov RG. Selection of optimal approaches to prevention of non-communicable diseases in in international partnership circumstances. Cardiovascular Therapy and Prevention. 2018;17(1):4-9. (In Russ.) doi:10.15829/1728-8800-2018-1-4-9.

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N-terminal propeptide of type III procollagen for predicting diastolic dysfunction in patients with myocardial infarction and preserved ejection fraction

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Aim. To study changes in the level of fibrotic scarring marker — the N-terminal propeptide type III procollagen (PIIINP) and structural and functional parameters with the assessment of diastolic function in patients a year after ST segment elevation myocardial infarction (STEMI) and preserved left ventricle (LV) contractility.

Material and methods. At first, the study included 120 (100%) STEMI patients. Next, patients with an LV ejection fraction (EF) ⩾50% were selected. The final analysis included 86 STEMI patients. Upon hospitalization, the patients underwent routine diagnostic tests, coronary angiography with stenting of culprit artery. Echocardiography and determination of venous blood PIIINP and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels was on the 1st (time point 1) and 12th day (time point 2) of disease and after a year (time point 3). To compare the obtained values of fibrotic scarring markers, a control group was formed, including 20 (100%) healthy volunteers, identical in age and sex with the studied sample.

Results. On the first day of MI, 25 (29,1%) patients with signs of diastolic dysfunction (DD) were identified among those with preserved LVEF. After 1 year, the number of such patients increased by 10% (n=9). Initially increased (relative to the control group) concentration of PIIINP on the first day (311,2 [220,1; 376,3] ng/ml) decreased by the 12th day (223,3 [195,3; 312,1] ng/ml) and returned to the initial values a year after the MI (312,6 [228,0; 383,8] ng/ml). The NT-proBNP concentration during the hospitalization period did not exceed the reference values and did not differ between 1 and 2 time points (p=0,127). One year later, the NT-proBNP concentration significantly exceeded the values of the previous determinations and amounted to 124,4 pg/ml (p=0,043). According to the ROC analysis, with a PIIINP ⩾387,8 ng/ml on the first day, the risk of DD increases (p=0,050, sensitivity, 84,62%, specificity, 55,56%) within a year after STEMI with preserved LVEF.

Conclusion. The threshold of PIIINP (⩾387,8 ng/ml) was established for the first day of MI, at which the risk of DD increases one year after the index event. An increase in NT-proBNP concentration one year after STEMI indicates the progression of heart failure.

Keywords: myocardial infarction, diastolic dysfunction, fibrotic scarring markers, heart failure.

Relationships and Activities: none.

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Introduction

Diastolic dysfunction (DD) of the left ventricle (LV) is currently the subject of scientific interest due to its high frequency among patients with cardiovascular diseases, including coronary artery disease (CAD), and an adverse effect on prognosis. The data on the formation of DD, its early diagnosis and the possibility of therapeutic effects are ambiguous [1]. It has been proven that DD can form independently from impaired contractile function. DD is directly related to impaired exercise tolerance and the patient's quality of life [2]. Systolic dysfunction is formed exclusively together with diastolic dysfunction, which excludes the possibility of an isolated variant [3]. As a rule, the long-term prognosis of patients with DD is disappointing due to a set of clinical factors and echocardiographic (EchoCG) indicators of LV myocardial function. There is an opinion that impaired diastolic function (DF) develops earlier than electrocardiographic signs of ischemia, impaired contractility. DF is one of the early indicators of myocardial ischemia in patients with angina pectoris [4], and fibrosis is one of the key mechanisms for the development and progression of LV myocardial dysfunction. Today, close attention of scientists is focused on the study of seromarkers of myocardial fibrosis and collagen precursors. There is particular scientific interest in markers characterizing the activity of the production and breakdown of collagen. Among others, collagen precursors of type I and type III are being actively studied [5]. The information available

for analysis on the existing connections of fibrotic seromarkers with structural and functional parameters of the heart on echocardiography, including after myocardial infarction (MI) with preserved LV ejection fraction (EF), are ambiguous, which determines the need for a more thorough study of this issue.

The aim is to study changes in the dynamics of biochemical fibrotic marker of the N-terminal propeptide type III procollagen (PIIINP) and structural and functional parameters with the assessment of diastolic function in patients a year after ST segment elevation myocardial infarction (STEMI) and preserved left ventricle (LV) contractility.

Material and methods

The study protocol was approved by the local ethics committee of the Research Institute for Complex Issues of Cardiovascular Diseases. The study included 120 STEMI patients. In 100% of cases, patients had indications for emergency hospitalization. The enrollment was carried out by the method of continuous sampling during 7 months of 2015.

Enrollment criteria:

1) diagnosis of STEMI, established according to the recommendations of the European Society of Cardiology (2015);

2) informed consent to participate in the study, signed by the patient;

3) patient >18 years old;

4) heart failure (HF) according to the Killip classification not >III.

Withdrawal criteria:

1) concomitant pathology, clinically significant at the time of enrollment (oncopathology, chronic diseases in the acute stage, mental illness);

2) acute coronary syndrome (as a complication of percutaneous coronary intervention or coronary artery bypass graft);

3) patients >80 years old;

4) the severity of HF according to the Killip classification — IV;

5) death of the patient on the first day of hospitalization.

The average age in the sample is 57,75 [52,4; 63,6] years. Women accounted for 24,3% (n=29); each of them was postmenopausal. The overwhelming part of the sample is represented by men, n=91 (75,8%). At the time of hospitalization, all the necessary examinations were carried out to verify myocardial infarction, including standard instrumental and laboratory ones. In addition, on admission, coronary angiography with stenting of culprit artery was performed in 100% of cases. EchoCG was performed on the 1st (time point 1), 12th day (time point 2) of disease and a year after myocardial infarction (time point 3) on the device "Aloka α-10 ProSound" in modes M- and B-, pulse-wave, continuous-wave doppler modes, in color flow mapping mode, in tissue doppler ultrasonography mode and color doppler M-mode (Color M-mode) using an ultrasonic matrix sensor 2-4 MHz. The study was performed in standard positions, with the patient on the left side (Clinical guidelines of RHFS-RSC-RSMSP (Russian Heart Failure Society — Russian Society of Cardiology — Russian Scientific Medical Society of Physicians), HF: chronic (CHF) and acute decompensated HF, diagnosis, prevention and treatment, 2018). To determine the LVEF, the Simpson method was chosen. In the studied sample, on the first day of MI, the mean values of LVEF in the range of 40-49% were determined in 3 (2,5%) patients, in 31 (26%) — LVEF <40%, LVEF ⩾50% was determined in 86 (71,6%) patients. To diagnose DD, the transmitral blood flow was assessed using the following indicators: peak E — the phase of rapid early ventricular filling (normal value of the indicator (N)=58-86 cm/s up to 50 years, 48-86 cm/s >50 years), peak A — the time of atrial contraction (N=30-50 cm/s up to 50 years, 45-73 cm/s >50 years), the ratio of the maximum velocities of the peaks E/A, the time of the flow of early diastolic filling (DT) using pulsed doppler echocardiography , E/Ea is the ratio of the maximum rate of rapid ventricular filling, isovolumic relaxation time of LV (IVRT) (N=70-90 ms). At each stage of the examination (time points 1, 2, and 3), the patients were determined the concentration of PIIINP, the N-terminal fragment of the brain natriuretic propeptide (NT-proBNP) in the venous blood serum, using the enzyme-linked immunosorbent assay with BCM Diagnostics kits (USA). To compare the obtained values of fibrotic markers, a control group was formed, including 20 (100%) healthy volunteers, identical in age (57,9 [52,5; 62,7] years) and gender (men — 15 (75%), women — 5 (25%)) with the studied sample. In the control group, the PIIINP concentration was 7,2 [6,8; 7,5] ng/ml, NT-proBNP ⩽70 pg/ml.

Table 1

Clinical and anamnestic data of STEMI patients included in the final analysis

Indicators	n	%
Female	23	26,7
Male	63	73,3
Smoking	61	71
Diabetes	17	19,8
Obesity (according to WHO classification BMI ⩾30 kg/m^2)	30	34,8
Hypertension	83	96,6
Hypercholesterolemia	28	32,4
Complicated family history of CAD	3	3,5
History of angina pectoris	27	31,5
History of CHF (according to anamnesis)	10	11,7
Postinfarction cardiosclerosis	7	8,3
Atrial fibrillation	6	6,9
Percutaneous coronary intervention (no earlier than one year prior to this study)	5	5,7
Chronic kidney disease	2	2,5
Peripheral artery disease	1	1,3

Note: WHO — World Health Organization, BMI — Body Mass Index.

During the period of hospitalization, patients received therapy in accordance with current national guidelines [6]. For further study, a sample was formed that included patients with LVEF ⩾50% (n=86). Table 1 shows the clinical and anamnestic characteristics of the studied sample. It can be seen that the majority of patients in the studied sample were characterized by the presence of risk factors for cardiovascular diseases; >70% were smokers. At least two thirds suffered from

Table 2

Changes in transmitral blood flow parameters over time during hospitalization and one year after STEMI

Indicators	Examination points			p
	Time point 1	Time point 2	Time point 3	
LVEF (%)	59 [54; 63]	62,0 [56,0; 65,0]*#	53 [47; 56]*	<0,001
E (cm/s)	57,0 [50,0; 70,0]	60,0 [49,0; 73,0]	60 [47; 69]	0,556
A (m/s)	70,0 [60,0; 79,0]	70,0 [58,0; 80,0]*	71 [59; 78]	0,011
E/A	0,80 [0,71; 1,22]	0,79 [0,68; 1,21]	0,77 [0,66; 1,13]	0,896
IVRT (m/s)	107,0 [104,0; 118,0]	106,0 [104,0; 118,0]	106,0 [103,0; 116,0]	0,157
DT (m/s)	196,0 [170,0; 224,0]	189,5 [170,0; 222,0]	210 [176,0; 228,0]	0,092
Em (cm/s)	7,0 [6,0; 8,0]	6,0 [5,0; 8,0]	6,0 [5,0; 8,0]	0,082
E/Em	8,8 [7,6; 11,4]	9,0 [7,5; 10,43]	8,9 [7,5; 10,50]	0,356

Note: * — p <0,05 versus point 1, # — p<0,05 versus point 3. E — phase of rapid early ventricular filling, A — atrial contraction time, E/A — ratio of maximum peak velocities, IVRT — time of isovolumic relaxation of the LV, DT — time of the flow of early diastolic filling, Em is the speed of movement of the lateral part of the fibrous annulus of the mitral valve, E/Em — ratio of the rate of transmitral flow in early diastole to the speed of movement of the lateral part of the annulus of the mitral valve.

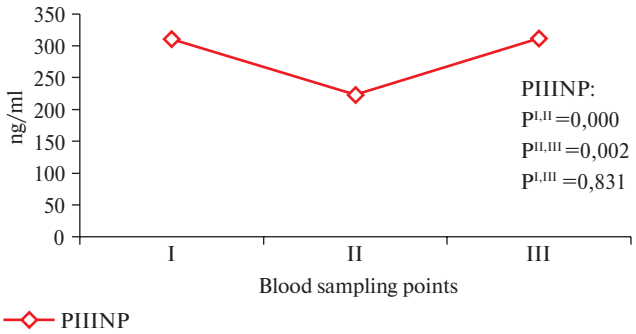

Figure 1 Dynamics of PIIINP concentration during 1 year after STEMI.

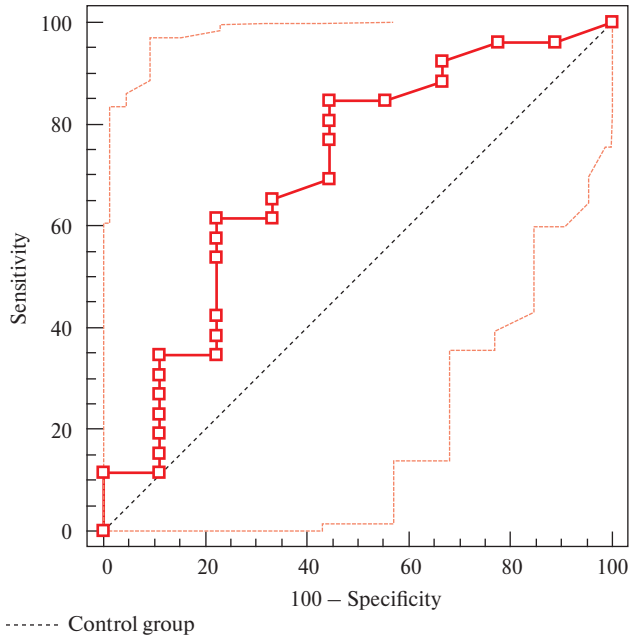

Figure 2 ROC curve for predicting DD during 1 year of follow-up after STEMI.

arterial hypertension for a long time. Hypercholesterolemia was quite often detected (32,5%). Disorders of carbohydrate metabolism accounted for 19,8%. At each stage of the study, the presence and severity of HF was assessed (acute — according to the Killip classification; I — n=76 (88,3%), II — n=8 (9,4%), III — n=2 (2,3%), IV — 0; chronic — according to the NYHA (New-York Heart Association) classification: signs of HF I and II functional classes (FC) were recorded in 84 cases (97,7%), III-IV FC — 2 (2,3%). At the annual stage, the presence of the following endpoints was assessed: death, decompensation of CHF, the presence of repeated hospitalizations for cardiovascular events during the follow-up period.

Statistica 7.0 software was used for statistical data processing. Comparison of two independent groups on a quantitative basis was carried out using the Mann-Whitney U-test. Dynamic changes in indicators in dependent groups were determined using the Wilcoxon test. The presence of a relationship between the variables was determined using the Spearman's rank correlation coefficient. Differences in the comparison groups were considered statistically significant at p<0,05.

Results

By the end of 1 year of follow-up, information on 86 patients was available to the analysis. 1 death was registered due to repeated MI. During the entire follow-up period, emergency hospitalizations for the progression of CAD and decompensation of CHF were noted in 5 (5,8%) cases, of which in 3 (3,5%) cases, there were repeated MI development. Angina pectoris of high FC (III-IV) was observed in 3 patients (3,5%). It should be noted that during the year of follow-up, some patients underwent planned revascularization: percutaneous coronary interventions with stenting were performed in 5 (5,8%) cases and in 1 case — coronary bypass graft.

During the year, patients received disaggregants — in 71%, β-blockers — in 80,3%, angiotensin-converting enzyme inhibitors — in 70,1%, calcium antagonists —

in 67%, nitrates — in 19%, anticoagulants — in 6,4%, statins — in 45% of cases.

Comparison of EF and indicators of transmitral blood flow was carried out between 1, 2 and 3 time points of examination (Table 2). The deterioration of LV systolic function became obvious in the form of a significant decrease in EF one year after the index event relative to the first day of the disease (p=0,018), 15 (17,6%) patients from the group with preserved EF moved to the group with a range of 40-49%. On the first day of MI, 29,1% (n=25) of patients with signs of DD were identified among those with preserved EF. A year later, there was an increase in the number of patients with signs of DD by 10% (n=9).

The concentration of PIIINP underwent changes during the follow-up period (Figure 1). Initially increased (relative to the values of the control group) concentration of this marker on the first day of the disease — 311,2 [220,1; 376,3] ng/ml, decreased by the 12th day of the disease — 223,3 [195,3; 312,1] ng/ml, and almost returned to the initial values at the annual stage of the examination — 312,6 [228,0; 383,8] ng/ml.

Fluctuations in the concentration of the studied indicator turned out to be significant and had highly significant differences both at the stationary stage and a year after the index event. The average value of the PIIINP concentration on the first day of the disease was significantly higher than that of the control group. Further changes in PIIINP concentration were still recorded in the range exceeding the control values.

A different dynamic was revealed when analyzing the concentration of NT-proBNP — a marker of CHF. During the hospitalization, the concentration of this marker did not exceed the reference values and was 98,5 on the first day [83,7; 103] and on the 12th day — 99,4 [87,2; 111,3] pg/ml, without significant differences between 1 and 2 detection points (p=0,127). A year later, the NT-proBNP concentration significantly exceeded the values of the previous determinations and amounted to 124,4 pg/ml (p=0,043).

In order to identify possible links between the echocardiography and the studied fibrotic markers, a correlation analysis was carried out, as a result of which the following statistically significant links were obtained: PIIINP on the first day/E 1 year, r=0,44, p=0,027, PIIINP on the first day/E/Em 1 year, r=0,45, p=0,024.

To determine the predictive value of PIIINP, determined on the first day of MI, in relation to DD one year after the development of the disease, an ROC analysis was performed. When constructing the ROC curve, the threshold level of the marker was selected step by step by the method of concentration selection when the total maximum sensitivity and specificity of the model was reached. As a result of the ROC-analysis, the concentration of PIIINP (on the first day of STEMI) was determined, associated with the risk of developing DD after a year (Figure 2).

Thus, at a PIIINP concentration of ⩾387,8 ng/ml on the first day, the risk of developing DD (p=0,050, sensitivity 84,62%, specificity 55,56%) increases within a year after STEMI with preserved LVEF.

Discussion

In the course of the study, it was possible to identify facts indicating the presence of a relationship between the fibrotic markers PIIINP and echocardiography indicators. This was confirmed by the correlations between the studied marker and the indicators of transmitral blood flow, characterizing the state of the DF of the LV myocardium. PIIINP is a protein formed during the synthesis of type III collagen [7]. According to some scientific sources, an increased concentration of this protein is considered as a predictor of deaths from diseases of the cardiovascular system or repeated hospitalizations due to worsening CHF [8]. Some studies have demonstrated the presence of correlations between the concentration of PIIINP in the blood and the volume fraction of type III collagen in the myocardium obtained during histological study [9].

In the modern scientific literature, there is no information on the presence of a relationship between the concentration of markers of myocardial fibrosis and the fact of the development of DD. According to the ROC analysis, at a PIIINP concentration of ⩾387,8 ng/ml on the first day of MI, the risk of developing DD in a year increase. Based on the data obtained, it can be assumed that an increase in PIIINP concentration is a marker of impaired myocardial relaxation due to a decrease in its elasticity. A similar pattern was obtained in the study [10].

Currently, one of the fundamental reasons for the development of DD is an increase in myocardial stiffness due to its fibrosis. The mechanism of transformation of asymptomatic DD into diastolic HF is still controversial. It is likely that the key link in this process is the imbalance of collagen in the myocardium [11]. It has been proven that the myocardium of a healthy person contains up to 2% of collagen by volume. Collagen type III, like type I, is the main representative of collagen in the myocardium. In addition, type I collagen has been shown to be responsible for stiffness and type III collagen for elasticity. Normally, the concentration of type III collagen prevails over the first type [11]. Collagens of both types are derived from procollagen precursors containing the C-terminal type I procollagen propeptide and PIIINP. The combination of these two types of collagens ensures the functional and structural integrity of cardiomyocytes and contributes to the maintenance of a certain direction of myofibrils in them [12]. Probably, the predominance of the synthesis of collagen types I and III over their breakdown leads to the accumulation of excess fibers, which is a trigger for the formation of myocardial fibrosis with subsequent disruption of DF [12].

The HF on the background of preserved LV systolic function is currently of increased interest among scientists due to its high frequency among patients after an acute coronary event and an unfavorable long-term prognosis. In this work, we managed to determine the value of the PIIINP concentration associated with the risk of developing LV DD and, as a consequence, the progression of CHF. However, it is worth mentioning that according to the results of the annual follow-up, a deviation from the standard treatment was revealed in the form of a low percentage of intake of almost all necessary classes of drugs, including angiotensin-converting enzyme inhibitors, which is due to the low adherence of patients to the prescribed drug treatment. This fact undoubtedly has a negative impact on the formation of LV DD.

For many years, the severity of heart failure has been strongly associated with impaired ventricular systole, the presence of which was judged by the value of LVEF. At the present stage, with the emergence of the myocardial theory of the pathogenesis of CHF, significant, and in most cases fundamental importance in the development and progression of HF, is given to the violation of DF, while emphasizing the great vulnerability of DF, the violation of which always precedes systolic, and in some cases, it can preserve the nature of isolated DF, as the basis of CHF. Determination of the serum NT-proBNP level is considered a standard procedure in the diagnosis of CHF. Previously, it was proved that BNP has a particular pathophysiological significance in the diagnosis of heart failure, in the stratification of the risk of cardiovascular diseases and in the assessment of the effectiveness of treatment of CHF [8]. The results of this study demonstrated a significant increase in the concentration of NT-proBNP in patients a year after the development of STEMI. This fact is a reflection of heart failure progression within a year after MI and, as the results show, including due to DD on the background of increased concentration of the fibrotic markers.

At the same time, the identification of CHF with preserved LVEF is especially important for patients without pronounced clinical manifestations of the disease. These signs include shortness of breath, weakness, tachycardia with preserved LVEF and in the absence of objective signs of HF, which can divert attention to other, non-cardiac causes of symptoms (respiratory pathology, detraining and/or overweight [13]. Despite the disturbing tendencies mentioned above, the question of optimal diagnosis remains open. This situation emphasizes the need for an integrated approach to the study of DF and encourages an active search for new biological markers of its impairment [14].

Conclusion

Within a year after the development of STEMI and preserved LVEF, there is a deterioration in LV systolic function and, in some cases, an aggravation of diastolic function. The threshold value of PIIINP (⩾387,8 ng/ml) was established, determined on the first day of the disease, at which the risk of developing DD increases one year after STEMI. An increase in NT-proBNP concentration one year after STEMI indicates the progression of heart failure.

Relationships and Activities: none.

References

1. Titova AL, Saiganov SA. Diastolic function of the left ventricle in patients with coronary heart disease who underwent coronary artery bypass surgery. Russian family doctor. 2014;18(3):10-7. (In Russ.)
2. Bartosh FL, Bartosh LF, Adonina TS. Features of diastolic function of the left ventricular myocardium in patients with hypertension with atrial fibrillation. Arterial hypertension. 2012;18(2):142-7. (In Russ.) doi:10.18705/1607-419X-2012-18-2-142-147.
3. Shilov SN, Teplyakov AT, Yakovleva IL, et al. Clinical and pathogenetic relationship of chronic heart failure, type 2 diabetes mellitus and osteoporosis. Complex problems of cardiovascular diseases. 2018;7(1):6-13. (In Russ.) doi:10.17802/2306-1278-2018-7-1-6-1.
4. Weber K, Sun Y, Campbell S. Structural remodeling of the heart by fibrous tissue: Role of circulating hormones and locally produced peptides. Eur Heart J. 1995;16 Suppl N:12-8. doi:10.1093/eurheartj/16.suppl_n.12.
5. Karetnikova VN, Kashtalap VV, Kosareva SN, Barbarash OL. Myocardial fibrosis: current aspects of the problem. Therapeutic Archive. 2017;89(1):88-93. (In Russ.) doi:10.17116/terarkh201789188-93.
6. Mareev VYu, Ageev FT, Arutyunov GP, et al. National recommendations of the OSSN, RKO and RNMOT for the diagnosis and treatment of CHF (fourth revision). J Heart Fail. 2013;14(7)(81):379-472. (In Russ.)
7. Drapkina OM, Zyatenkova EV. Markers of fibrosis in patients with metabolic syndrome. Russian Medical J. 2016;26:1727-31. (In Russ.)
8. Belenkov YuN, Oganov RG. Cardiology: national leadership. M.: GEOTAR-Media, 2012. p. 535. (In Russ.) ISBN: 978-5-9704-2733-0.
9. Matyal R, Skubas NJ, Shernan SK, Mahmood F. Perioperative assessment of diastolic dysfunction. Anesth Analg. 2011;113(3):449-72. doi:10.1213/ANE.0b013e31822649ac.
10. Drapkina OM, Gegenava BB. Type III procollagen N-terminal propeptide as a possible serum marker of myocardial fibrosis in patients with type 2 diabetes. Cardiovascular Therapy and Prevention. 2018;17(3):17-21. (In Russ.) doi:10.15829/1728-8800-2018-3-17-21.
11. Drapkina OM, Zyatenkova EV. Assessment of the level of N-terminal collagen type III propeptide in patients with chronic heart failure and metabolic syndrome. Cardiovascular Therapy and Prevention. 2015;14(6):42-7. (In Russ.) doi:10.15829/1728-8800-2015-6-42-47.
12. Putyatin AN, Kim LB. Extracellular matrix of the heart and postinfarction reparative fibrosis (part 1). Vestnik SAFU. Series: Biomedical Sciences. 2016;4:54-66. (In Russ.) doi:10.17238/issn2308-3174.2016.4.54.
13. Kovar F, Knazeje M, Mokan M. Risk Stratification and Invasive Strategy in NSTE-ACS [Electronic Resource]. URL: http://cdn.intechopen.com/pdfs/19478/InTech-Risk_stratification_and_invasive_strategy_in_nste_acs.pdf (date access: 25.09.2013).
14. Mrikaev DV. Diastolic dysfunction of the left ventricle in patients with heart failure. Creative cardiology. 2017;11(2):145-58. (In Russ.) doi:10.24022/1997-3187-2017-11-2-145-158.

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Prognostic significance of atherosclerosis of one or two vascular systems in patients with high and very high cardiovascular risk

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Aim. To study the prognostic significance of atherosclerosis of one and several vascular systems in patients with high and very high cardiovascular risk (CVR).

Material and methods. The study included 171 patients with high (26,9%) and very high (73,1%) CVR. All patients underwent duplex ultrasound of the carotid and lower limb arteries. The composite endpoint (CE) was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization.

Results. The follow-up period lasted 31,1 (17,8; 47,9) months. CE events occurred in 29 (16,9%) patients: cardiovascular death — 3 (1,75%) patients; nonfatal myocardial infarction — 7 (4,09%) patients; nonfatal stroke — 6 (3,51%) patients; coronary revascularization — 13 (7,60%) patients. Cumulative survival of patients with high and very high CVR with atherosclerotic plaques in the same vascular system did not significantly differ from that in patients with intact peripheral arteries (p=0,977). The event-free survival of patients with combined lesions of the carotid and lower limb arteries was significantly lower in comparison with patients with one vascular system involvement (p=0,011). The combined lesion of the carotid and lower limb arteries was associated with an increase in the relative risk (RR) of adverse cardiovascular events (RR, 3,15 (95% CI, 1,02-9,74; p=0,046), adjusted for sex, age, and peripheral arterial disease symptoms.

Conclusion. In patients with high and very high CVR, atherosclerotic lesion of two vascular systems of peripheral arteries is associated with an increase in the RR of adverse cardiovascular events, adjusted for sex, age, and peripheral arterial disease symptoms. The presence of atherosclerotic plaques in one vascular bed was not associated with an increase in the risk of CE events.

Keywords: atherosclerosis, multifocal atherosclerosis, diabetes, adverse cardiovascular events.

Relationships and Activities: none.

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Introduction

Precise stratification of cardiovascular risk (CVR) is one of the most important and difficult problems of modern cardiology. The urgency of this problem remains both within primary and secondary prevention of cardiovascular diseases (CVD) [1, 2]. The need to improve the algorithms for classifying the risk of cardiovascular accidents in high and very high-risk patients, among other things, is associated with the introduction of new expensive drugs into clinical practice, the use of which across national health systems is most effective in terms of cost-benefit analysis in patients with the highest risk of adverse cardiovascular events [3, 4]. This contributed to the appearance of the extreme CVR category in clinical guidelines and the search for phenotypes associated with it [5]. For example, it was found that among patients without diagnosed CVD, but with severe calcification of the coronary arteries (Agatston index ⩾1000), the risk of cardiovascular events was higher than that for patients with established CVD [6]. The use of various non-invasive methods of cardiovascular imaging, serum and molecular genetic markers is a leading approach in the modernization of CVR classification systems.

Multifocal atherosclerosis (MFA), defined as a symptomatic or clinically significant lesion of two or more vascular territories, has been considered in the last few years as a separate prognostically unfavorable phenotype of atherosclerosis [7, 8]. At the same time, even asymptomatic atherosclerotic lesions of several vascular territories are associated with an increase in the relative risk (RR) of adverse cardiovascular events and overall mortality [9]. The need for systematic screening to detect MFA in high and very high-risk patients is

currently being debated [10]. However, current clinical guidelines do not support this strategy due to the limited available data demonstrating the effectiveness of this approach in terms of clinical benefits and costs [11]. The study of the prognostic significance of various variants of peripheral arterial lesions in patients with different CVR status is a prerequisite for introducing routine screening into clinical practice to detect MFA.

The aim is to study the prognostic significance of atherosclerotic lesions of one and several vascular territories in patients with high and very high CVR.

Material and methods

The study included men and women aged 35-70 years of high and very high CVR, directed by the attending physician for duplex ultrasound scanning (DUS) of the carotid arteries and/or lower limb arteries in order to clarify CVR. The assessment of CVR was carried out in accordance with the recommendations of the European Society of Cardiology for the correction of dyslipidemia 2019 [12]. The study protocol was approved by the Ethics Committee (meeting protocol No. 1 dated January 14, 2017). All patients signed informed consent to participate in the study. The withdrawal criteria for the study were the following clinical conditions: acute period of cerebral and coronary circulation disorders; severe impairment of liver and kidney function (decreased glomerular filtration rate (GFR) <30 ml/min/1,73 m^2); malignant neoplasms; mental illness; alcohol and substance abuse.

All patients underwent blood sampling in the morning on an empty stomach. The following parameters were determined: total cholesterol (C), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glycated hemoglobin, highly sensitive C-reactive protein (hsCRP), creatinine (with subsequent calculation of GFR according to the formula CKD- EPI).

All patients underwent DUS of the carotid arteries and lower limb arteries. The study was carried out in B-mode, color mapping mode, pulsed and power doppler ultrasonography. The following vessels were examined from both sides in longitudinal and cross sections along the entire length: common carotid arteries (CA) with bifurcation of common CA, internal CA, external CA, common femoral arteries, superficial femoral arteries, popliteal arteries, tibioperoneal trunk, anterior tibial arteries, posterior tibial arteries.

Atheroma was considered a focal thickening of the intima-media complex (IMC) >1,5 mm or 0,5 mm more than the surrounding IMC thickness, or 50% more than the IMC thickness of the adjacent parts of the vessel [13]. The percentage of stenosis was measured planimetrically in B-mode over the diameter in the cross-section of the vessel. The percentage of stenosis was determined according to the ECST method (The European Carotid Surgery Trial). When atheromas were detected, stenosing the vascular lumen, the maximum stenosis in a particular patient was determined. The study was carried out with a linear transducer with a frequency of 10 MHz on a digital ultrasonic multifunctional diagnostic scanner of an expert class "Samsung Medison EKO7" (Republic of Korea).

The composite endpoint (CE) was cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and coronary revascularization.

Statistical analysis of the obtained data was carried out on a personal computer using Micrososft Excel software and the package for statistical data analysis IBM SPSS Statistics, version 18. Qualitative variables were described by absolute and relative frequencies (percentages). Quantitative variables were described by the median (Me) indicating the interquartile range (Q_1-Q_3) in the case of a discrepancy between the distribution of the value to the normal, mean (M) and standard deviation (SD) — in the case of a normal distribution of the indicator. Survival analysis in groups was performed using the Kaplan-Meier method; the log-rank test was used to compare the two curves. Observations in which the studied outcome occurred were designated as completed. Observations were considered censored if they did not have an outcome at the end of the study. Cox regression stepwise analysis was used to identify risk factors for survival. The time before the outcome was considered a dependent (predicted) feature, and the factors under study were considered independent. The critical level of significance for all statistical data analysis procedures used was taken equal to $p<0,05$.

Results

202 patients were examined according to a single protocol. 31 patients were excluded from the study due to loss to follow-up. The study included 171 patients with high and very high CVR (response rate was 84,6%). A very high risk was found in 125 (73,1%) patients: 123 (71,9%) participants had established atherosclerotic CVD at the time of enrollment in the study, 2 (1,17%) — CVR on the SCORE scale (Systematic Coronary Risk Evaluation) was ⩾10%. High CVR was registered in 46 (26,9%) patients: 12 (7,02%) patients had a significantly increased level of one of the risk factors, 17 (9,94%) patients showed a decrease in GFR <60 ml/min/1,73 m^2, in 4 (2,34%) — type 2 diabetes (D) without damage to target organs and CVR factors, in 13 (7,60%) — CVR on the SCORE scale was 5-9%. The clinical characteristics of the patients are presented in Table 1.

Table 2 shows the results of DUS of the carotid arteries and the lower limb arteries.

Thus, >66% of patients had concomitant atherosclerotic lesions of the CA and lower limb arteries. Atheromas in one of the studied vascular territories were detected in 24,5% of patients. In 8,77% of patients, atheroma was not found in the carotid arteries and lower limb arteries.

In comparison with patients with lesions of one vascular territory, patients with atheroma in two vascular territories were statistically significantly more likely to suffer from type 2 diabetes (43,6 vs 17,1%, $p<0,0001$), stable coronary artery disease (41,4 vs 80,0%, $p=0,001$), and also significantly more often received disaggregant (78,3 vs 53,5%, $p=0,019$) and beta-blockers (61,7 vs 41,4%, $p=0,020$) therapy. It should also be noted that only 64,9% of patients at the time of enrollment in the study received statin therapy. At the same time, the proportion of patients who achieved the corresponding target levels of LDL cholesterol among patients with

Table 1

Clinical characteristics of patients included in the study

Indicator	Patients (n=171)
Age, years, Me (Q_1-Q_3)	61,0 (55,0-66,0)
Male/female, n (%)	92 (53,8)/79 (46,2)
Body mass index, kg/m^2, Me (Q_1-Q_3)	28,7 (25,0-31,9)
Obesity, n (%)	68 (39,7)
Abdominal obesity, n (%)	115 (67,2)
Smoking, n (%)	49 (28,6)
Coronary artery disease, n (%)	118 (69,0)
Postinfarction cardiosclerosis, n (%)	53 (31,0)
Myocardial revascularization, n (%)	44 (25,7)
History of stroke, n (%)	10 (5,84)
Intermittent claudication, n (%)	37 (21,6)
Type 2 diabetes, n (%)	69 (40,3)
Arterial hypertension, n (%)	149 (87,1)
Chronic heart failure, n (%)	99 (57,9)
Disaggregants, n (%)	119 (69,6)
Beta-blockers, n (%)	96 (56,1)
Inhibitors of the RAAS, n (%)	121 (70,7)
Diuretics, n (%)	27 (15,8)
Statins, n (%)	111 (64,9)
Oral hypoglycemic drugs, n (%)	48 (28,0)
Insulin therapy, n (%)	26 (15,2)
Total cholesterol, mmol/l, Me (Q_1-Q_3)	4,96 (3,90-6,17)
LDL cholesterol, mmol / l, Me (Q_1-Q_3)	2,93 (1,95-3,97)
HDL cholesterol, mmol / l, Me (Q_1-Q_3)	1,22 (1,00-1,52)
Triglycerides, mmol/l, Me (Q_1-Q_3)	1,54 (1,12-2,05)
HsCRP, mg / L, Me (Q_1-Q_3)	2,16 (1,04-4,41)
Glycated hemoglobin, %, Me (Q_1-Q_3)	5,50 (4,90-6,50)
GFR, ml/min / 1,73 m^2, Me (Q_1-Q_3)	60,0 (52,0-71,0)

Note: RAAS — renin-angiotensin-aldosterone system, HsCRP — highly sensitive C-reactive protein, Q_1-Q_3 — interquartile range.

Table 2

Results of CA and lower limb arteries DUS

Indicators	Patients (n=171)
Atheroma in CA, n (%)	142 (83,0)
MaxSt CA,%, Me (Q_1-Q_3)	35,0 (25,0-45,0)
CA stenosis ⩾50%, n (%)	36 (21,0)
Atheroma in the lower limb arteries, n (%)	129 (75,4)
Lower limb artery stenosis ⩾50%, n (%)	55 (32,2)
Intact CA and lower limb arteries, n (%)	15 (8,77)
Atheroma in vascular territory, n (%)	42 (24,5)
Atheroma in two vascular territories, n (%)	114 (66,6)

Note: MaxSt — maximum stenosis, Q_1-Q_3 — interquartile range.

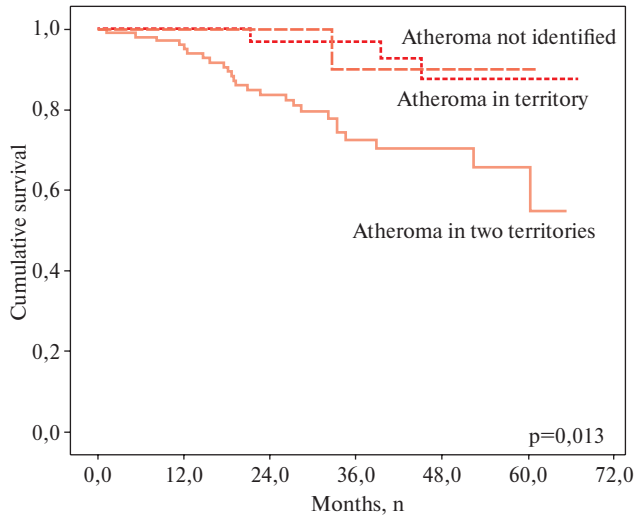

Figure 1 Results of the analysis of Kaplan-Meier curves in relation to the development of adverse cardiovascular events depending on the number of affected vascular territories.

lesions of one or more vascular regions were comparable (16,5 vs 18,3%; p=0,468).

The duration of the follow-up period was 31,1 (17,8; 47,9) months. CE events occurred in 29 (16,9%) patients: cardiovascular death was registered in 3 (1,75%) patients; nonfatal myocardial infarction — in 7 (4,09%) patients; nonfatal stroke — in 6 (3,51%) patients; coronary revascularization — in 13 (7,60%) patients. An analysis was carried out aimed at assessing the prognostic significance of various variants of peripheral arterial lesions in relation to the development of events that make up the CE. Kaplan-Meier curves showing patient survival depending on the number of affected vascular territories are shown in Figure 1.

Cumulative survival of high and very high-risk patients with atheroma in vascular territory did not statistically significantly differ from that in patients with intact peripheral arteries (p=0,977). In contrast, the event-free survival of patients with combined lesions of the carotid arteries and lower limb arteries was statistically significantly lower compared to patients with a single vascular lesion (p=0,011). According to Cox regression analysis, adjusted for sex and age, the presence of atheroma in vascular territory was not associated with an increase in the RR of the occurrence of events included in the CE (RR 0,32; 95% confidence interval (CI): 0,095-1,077; p=0,066). The combined lesion of the carotid and lower limb arteries was associated with a 3,23-fold increase in the RR for adverse cardiovascular events (95% CI: 1,06-9,87; p=0,040) adjusted for gender and age. Moreover, the statistical significance of this type of vascular lesion as a predictor of cardiovascular events persisted regardless of the presence of symptoms of peripheral arterial disease (after adjusting for a history of stroke or intermittent claudication) — RR 3,15 (95% CI: 1,02-9,74; p=0,046). However, when factors such as gender, age, smoking, obesity, diabetes, coronary artery disease, LDL cholesterol and GFR levels were added to the model, the effect of concomitant peripheral arterial disease at

the CE became statistically insignificant (RR 2,13; 95% CI: 0, 64-7,11; p=0,217).

Discussion

Discussion It is now generally accepted that patients with high and very high CVR represent an extremely heterogeneous group, significantly differing in the residual risk of cardiovascular events during therapy [14]. This requires a search for new markers and phenotypes, the use of which in clinical practice will improve the risk stratification in this category of patients [15].

The main results of the study are: 1) in patients with high and very high CVR, atherosclerosis of one basin of the peripheral arteries was not associated with an increase in the RR of adverse cardiovascular events in comparison with patients with intact peripheral arteries; 2) the presence of atheroma in two vascular territories was associated with an increase in the RR of cardiovascular events by 3.15 times, adjusted for gender, age, and the presence of symptoms of peripheral arterial lesions.

Previously, it was found that the prevalence or burden of systemic atherosclerosis is one of the main determinants of the long-term prognosis of patients [16]. Thus, it has been demonstrated that the presence of symptomatic peripheral arterial lesions is associated with an increased risk of adverse cardiovascular events in patients with myocardial infarction [17]. A study by Miao B, et al, including 1302856 patients with established atherosclerotic CVD or >3 risk factors, found a statistically significant increase in the RR of major cardiovascular events as the number of vascular lesions increased [18]. Thus, both symptomatic and asymptomatic lesions of several vascular pools are a predictor of an adverse prognosis, including in patients with high and very high CVR.

In low/moderate-risk patients, imaging of the atheroma in vascular territory in accordance with current clinical guidelines is sufficient to reclassify a patient to the high CVR group and, in most cases, initiate pharmacological correction of risk factors [5]. In our opinion, in patients with high and very high CVR, the most justified is the so-called multifocal ultrasound approach [19, 20]. In this category of patients, atheroma imaging in vascular territory (with stenosis <50%) as part of a standard ultrasound protocol does not provide additional prognostic information. Identification of MFAs and/or assessment of indicators of the burden (load) of atherosclerosis of a particular vascular territory are some of the least costly methods that make it possible to personalize the assessment of CVR [21]. In this case, the absence of symptoms of atherosclerotic lesions of the carotid arteries or lower limb arteries should not be a contraindication to screening ultrasound examination, because the very fact of the presence of atheroma has predictive value. The relatively low incidence of severe asymptomatic atherosclerotic lesions of these vascular territories, requiring prophylactic revascularization, should not be considered as a factor limiting the feasibility and effectiveness of diagnostic intervention [22].

Diabetes and smoking are classic risk factors for diseases associated with atherosclerosis, including MFA [20]. The presence of diabetes is associated with a statistically significant increase in the RR of the presence of MFA and the development of adverse cardiovascular events [23, 24]. The synergistic effects of diabetes and MFA on the development of cardiovascular catastrophes may explain the lack of statistical significance of the effect of MFA on the risk of CE when type 2 diabetes is added to the predictive model in this study. A number of authors consider the combination of diabetes and atherosclerotic lesions of several vascular territories as an independent malignant cardiovascular phenotype [25].

Conclusion

In patients with high and very high CVR, atherosclerotic lesion of the two vascular pools of the peripheral arteries was associated with an increase in the RR of adverse cardiovascular events, adjusted for gender, age, and the presence of symptoms of peripheral arterial disease. The presence of atheroma in vascular territory was not associated with an increase in the risk of events constituting CE.

Relationships and Activities: none.

References

1. Lazzeroni D, Coruzzi P. Risk stratification in secondary cardiovascular prevention. Minerva Cardioangiol. 2018;66(4):471-6. doi:10.23736/S0026-4725.18.04648-0.
2. Boitsov SA, Pogosova NV, Bubnova MG, et al. Cardiovascular prevention 2017. National guidelines. Russ J Cardiol. 2018;23(6):7-122. (In Russ.) doi:10.15829/1560-4071-2018-6-7-122.
3. Annemans L, Packard CJ, Briggs A, Ray KK. 'Highest risk-highest benefit' strategy: a pragmatic, cost-effective approach to targeting use of PCSK9 inhibitor therapies. Eur Heart J. 2018;39(27):2546-50. doi:10.1093/eurheartj/ehx710.
4. Kontsevaya AV, Mukaneeva DK, Myrzamatova AO, et al. Economic damage of risk factors associated with morbidity and mortality from major chronic non-communicable diseases in Russia in 2016. Cardiovascular Therapy and Prevention. 2020;19(1):48-55. (In Russ.) doi:10.15829/1728-8800-2020-1-2396.
5. Kukharchuk VV, Ezhov MV, Sergienko IV, et al. Diagnostics and correction of lipid metabolism disorders in order to prevent and treat atherosclerosis. Russian recommendations. VII revision. Atherosclerosis and dyslipidemia. 2020;1(38):7-40. (In Russ.) doi:10.34687/2219-8202.JAD.2020.01.0002.
6. Blankstein R, Chandrashekhar Y. Extensive Coronary Artery Calcifications: No Longer Primary Prevention! JACC Cardiovasc Imaging. 2020;13:183-5. doi:10.1016/j.jcmg.2019.12.007.
7. Bonaca MP. Polyvascular disease and risk: When two is not better than one. Vasc Med. 2018;23(6):531-3. doi:10.1177/1358863X18796936.
8. Gutierrez JA, Mulder H, Jones WS, et al. Polyvascular Disease and Risk of Major Adverse Cardiovascular Events in Peripheral Artery Disease: A Secondary Analysis of the EUCLID Trial. JAMA Netw Open. 2018;1(7):e185239. doi:10.1001/jamanetworkopen.2018.5239.
9. Zhang Q, Wang A, Zhang S, et al. Asymptomatic polyvascular disease and the risks of cardiovascular events and all-cause death. Atherosclerosis. 2017;262:1-7. doi:10.1016/j.atherosclerosis.2017.04.015.
10. Barbarash OL, Kashtalap VV. A patient with coronary artery disease and multifocal atherosclerosis. how to optimize the prognosis? Medical advice. 2018;(16):32-8. (In Russ.) doi:10.21518/2079-701X-2018-16-32-38.
11. Aboyans V, Ricco JB, Bartelink MEL, et al. 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS): Document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries Endorsed by: the European Stroke Organization (ESO)The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) and of the European Society for Vascular Surgery (ESVS). Eur Heart J. 2018;39(9):763-816. doi:10.1093/eurheartj/ehx095.
12. Mach F, Baigent C, Catapano AL, et al.; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020;41(1):111-88. doi:10.1093/eurheartj/ehz455.
13. Sprynger M, Rigo F, Moonen M, et al.; EACVI Scientific Documents Committee. Focus on echovascular imaging assessment of arterial disease: complement to the ESC guidelines (PARTIM 1) in collaboration with the Working Group on Aorta and Peripheral Vascular Diseases. Eur Heart J Cardiovasc Imaging. 2018;19(11):1195-221. doi:10.1093/ehjci/jey103.
14. Rossello X, Bueno H, Pocock SJ, et al. Predictors of allcause mortality and ischemic events within and beyond 1 year after an acute coronary syndrome: results from the EPICOR registry. Clin Cardiol. 2019;42:111-9. doi:10.1002/clc.23116.
15. Rossello X, Dorresteijn JA, Janssen A, et al. Risk prediction tools in cardiovascular disease prevention: A report from the ESC Prevention of CVD Programme led by the European Association of Preventive Cardiology (EAPC) in collaboration with the Acute Cardiovascular Care Association (ACCA) and the Association of Cardiovascular Nursing and Allied Professions (ACNAP). Eur J Prev Cardiol. 2019;26(14):1534-44. doi:10.1177/2047487319846715.
16. Calais F, Eriksson Östman M, Hedberg P, et al. Incremental prognostic value of coronary and systemic atherosclerosis after myocardial infarction. Int J Cardiol. 2018;261:6-11. doi:10.1016/j.ijcard.2018.02.035.
17. Eriksson Östman M, Calais F, Rosenblad A, et al. Prognostic impact of subclinical or manifest extracoronary artery diseases after acute myocardial infarction. Atherosclerosis. 2017;263:53-9. doi:10.1016/j.atherosclerosis.2017.05.027.
18. Miao B, Hernandez AV, Alberts MJ, et al. Incidence and Predictors of Major Adverse Cardiovascular Events in Patients With Established Atherosclerotic Disease or Multiple Risk Factors. J Am Heart Assoc. 2020;9(2):e014402. doi:10.1161/JAHA.119.014402.
19. Ershova AI, Boytsov SA, Drapkina OM, Balakhonova TV. Ultrasound markers of premanifest atherosclerosis of carotid and femoral arteries in assessment of cardiovascular risk. Russ J Cardiol. 2018;23(8):92-8. (In Russ.) doi:10.15829/1560-4071-2018-8-92-98.
20. Ershova AI, Balakhonova TV, Ivanova AA, et al. The problem of cardiovascular risk stratification depending on the severity of carotid and femoral artery atherosclerosis. Cardiovascular Therapy and Prevention. 2020;19(2):75-81. (In Russ.) doi:10.15829/1728-8800-2020-2441.
21. Genkel VV, Kuznetsova AS, Sumerkina VS, et al. The prognostic value of various carotid ultrasound parameters in patients at high and very high cardiovascular risk. Int J Cardiol. 2019;292:225-9. doi:10.1016/j.ijcard.2019.06.038.
22. Ihle-Hansen H, Vigen T, Ihle-Hansen H, et al. Prevalence of Carotid Plaque in a 63- to 65-Year-Old Norwegian Cohort From the General Population: The ACE (Akershus Cardiac Examination) 1950 Study. J Am Heart Assoc. 2018;7(10):e008562. doi:10.1161/JAHA.118.008562.
23. Genkel VV, Salashenko AO, Shamaeva TN, et al. Atherosclerosis of peripheral arteries in patients with coronary artery disease and type 2 diabetes mellitus. Therapeutic archive. 2019;91(10):54-62. (In Russ.) doi:10.26442/00403660.2019.10.000106.
24. Zhao Y, Evans MA, Allison MA, et al. Multisite atherosclerosis in subjects with metabolic syndrome and diabetes and relation to cardiovascular events: The Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2019;282:202-9. doi:10.1016/j.atherosclerosis.2018.12.005.
25. Verma S, Mazer CD, Bhatt DL. The perils of polyvascular disease in type 2 diabetes. Lancet Diabetes Endocrinol. 2018;6(12):914-6. doi:10.1016/S2213-8587(18)30311-5.

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Comparative analysis of tobacco smoking intensity among young and middle-aged women of one administrative district of Tyumen in 1996-2016

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Aim. To study the changes of tobacco smoking intensity among young and middle-aged women of one administrative district of Tyumen in 1996-2016.

Material and methods. Cross-sectional epidemiological studies were conducted on representative samples of women aged 25-64 years in 1996 and 2016. The category of smokers was ranked by age group and depending on the number of cigarettes smoked per day. The analysis included women of two categories — young age (25-44 years old) and middle age (45-64 years old). Women were considered high-intensity smokers if they smoked >10 cigarettes per day. According to this parameter, all smokers were divided into those with low and high smoking intensity.

Results. According to the results, a negative 20-year dynamics was revealed — an increase in the tobacco smoking intensity in the population due to the category of young women. In young women over a 20-year period with a stable prevalence of tobacco smoking, a redistribution from low to high intensity of tobacco smoking was established — the prevalence of high-intensity smokers over low-intensity ones in 2016 with inverse proportions at the first screening. In middle-aged women, over a 20-year period, with a tendency towards an increase in tobacco smoking prevalence from the first to the second screening, the prevalence of low-intensity smokers over high-intensity smokers remains.

Conclusion. Within the large-scale federal programs, it is necessary to direct efforts to reduce the intensity of tobacco smoking among women in middle-urbanized Siberian cities, focusing mainly on the category of young age.

Keywords: tobacco smoking intensity, comparative analysis, women, young age, middle age.

Relationships and Activities: none.

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Introduction

Tobacco smoking is one of the most important modifiable risk factors (RF) for the development of cardiovascular diseases (CVD). According to a systematic review, tobacco smoking among people with CVD is associated with a reduced risk of overall death [1]. In the Russian population, according to G. Ya. Maslennikova and R. G. Oganov, the loss of life expectancy at working age among women caused by tobacco smoking amounted to 5,6 years in total, and due to premature death from CVD — 9 years [2].

An increase in the prevalence of tobacco smoking among women was noted in the second half of the 20th century in most countries of Western Europe. Tobacco smoking among women then spread widely to Latin America, Japan, South and Central Europe [3]. The creation and promotion of women's tobacco brands began in the United States even earlier, in the mid-1920s, when advertising formed an association of the image of a smoking woman with the world of glamor and a symbol of women's freedom [4]. In the Russian Federation (RF), tobacco smoking among women has historically been significantly less prevalent than in most European countries; however, over the 20-year period of monitoring the Russian population among women, there has been a steady increase in smoking prevalence on the background of an increase in its intensity [5]. In addition, according to the data obtained on the Russian sample, at the end of the last century women who lived in cities smoked more often, while in the current century the frequency of this RF no longer depends on the urbanization of the population [5, 6].

The experience of many countries has shown that in order to reduce the frequency of smoking and achieve effective results in the prevention of noncommunicable diseases in specific conditions, it is necessary not only to state policy aimed at reducing the prevalence and intensity of tobacco smoking, but also to take into account the results of scientific research on the real situation of tobacco smoking in each region [7, 8]. At the same time, there is insufficient scientific data on the dynamics of tobacco smoking intensity in Russia, especially among women, although such studies can demonstrate the real response of the population to

Table 1

The structure of the examined Tyumen population of women at screenings in 1996 and 2016 by age and prevalence of tobacco smoking

Age groups (years)	I screening, number of subjects	I screening, number of smokers		II screening, number of subjects	II screening, number of smokers		p-differences between smokers at I and II screenings
		abs.	%		abs.	%	
25-44	400	136	34,0*	329	120	36,5*	p=0,4862
45-64	413	50	12,1	374	87	23,3	p=0,0000
25-64	813	186	22,9	703	207	29,4	p=0,0036
SI	813	186	23,1	703	207	31,2	p=0,0036

Note: an asterisk (*) denotes statistically significant differences between the indicator in the groups of 25-34 and 45-54 years old (I screening — p=0,0000; II screening — p=0,0001).

measures taken by the state to combat this RF of CVD and other non-communicable diseases [5, 9].

The aim is to determine the dynamics of the tobacco smoking intensity among young and middle-aged women in one of the administrative districts of Tyumen in 1996-2016.

Material and methods

On an open (unorganized) population of women in the Central Administrative District (CAD) of Tyumen, two cross-sectional studies were conducted according to a single protocol — a baseline study (1996) and repeated cardiac screening (2016). Representative samples, stratified by sex and age, were formed in a computer version using the method of random numbers based on the names of the electoral lists of the population of the district. Initially, the information received was verified at the Tyumen Regional Address Bureau. The samples consisted of 1 thousand persons aged 25-64, 250 persons in each age decade of life. The criteria for enrollment in the population sample were females aged 25-64 years registered and living in the Central Administrative District of Tyumen. The criteria for withdrawal from the population were refugees, students, soldiers and prisoners, which was established from the words of the subject; these data were not included in the analytical array. Each resident included in the population sample was invited to take part in a cardiac screening. Involvement of the population to participate in the screening in the absence of a response to the first invitation was carried out by sending three reminder letters with an interval of 7-10 days or by an attempt to telephone or personal contact with potential participants.

The response on screening in 1996 was 81,3%, on screening in 2016 — 70,3%.

The prevalence of tobacco smoking was determined on cardiac screenings using a questionnaire tested within Cooperative Study on Multifactorial Prevention of Coronary Artery Disease. The questionnaire was developed at the Research Institute of Preventive Cardiology of the USSR Academy of Medical Sciences (currently, the Federal State Budgetary Institution "National Medical Research Center of Preventive Medicine" of the Ministry of Health of the Russian Federation) on the basis of adapted international methods. According to the questionnaire, the subjects who smoked at least one cigarette/day were considered to be regular smokers. In addition, individuals who smoked irregularly, never smoked and quit smoking were identified [10]. To determine the intensity of smoking, the first two positions (regular and irregular smokers) were considered together as "smokers" (Table 1). Further, the category of smokers was ranked according to age groups and depending on the number of cigarettes smoked/day. Women were considered to be heavy smokers if they smoked >10 cigarettes/day, according to this parameter, the category "smokers" was divided into smokers with low and high smoking intensity [5]. In accordance with the age classification adopted by the World Health Organization in 2015, two age groups were included in the analysis for this study — young age (25-44 years) and middle age (45-64 years) [11].

The research was carried out in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the local Ethics Committee. Written informed consent was obtained from all participants prior to enrollment.

For the statistical processing of the study results, the program IBM STATISTICS 21.0 was used. Using the data of the census of the population of the Russian Federation with the age structure of the Russian urban population, the results of the study were standardized by age. Results for categorical variables are presented as fractions (in %). When assessing the statistical significance between the sample fractions of the population in the two groups, the Pearson's chi-squared test (χ^2) with Yates' correction for continuity and Fisher's exact test were used. In the case of comparing three or more groups, the analysis of contingency tables was initially used, according to the criterion of "maximum likelihood chi-square" (ML Chi-square), to establish statistically significant differences between the groups, followed by paired comparison of the groups. For the critical level of significance when testing statistical hypotheses, $p<0,05$ was taken based on the number of degrees of freedom. When paired comparisons in four or more independent groups, to exclude the problem of multiple comparisons, i.e., to eliminate the error of the first kind, the Bonferroni correction was applied. The essence of the Bonferroni correction was to recalculate the significance level p for multiple paired comparisons using the formula p_0/n, where p_0 is the initially specified level of statistical significance (0,05), n is the number of paired comparisons.

Results

In accordance with the data in Table 1, the age-standardized indicator (SI) of the prevalence of tobacco smoking among women in the Central Administrative District of Tyumen was 23,1% and 31,2%, respectively,

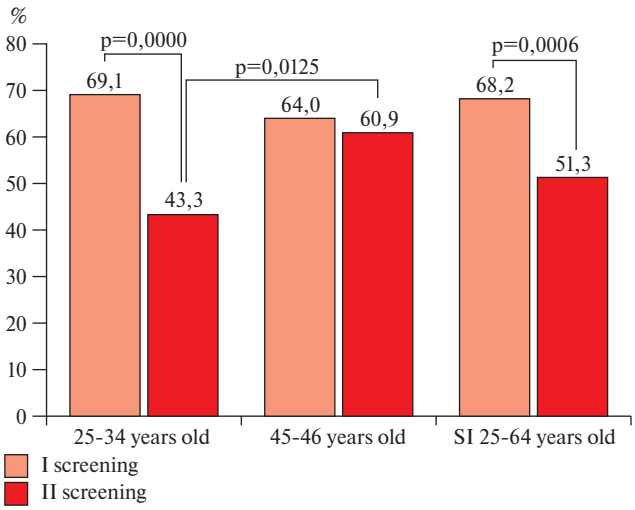

Figure 1 Dynamics of low intensity of tobacco smoking among women of the Tyumen population for the period 1996-2016, %.

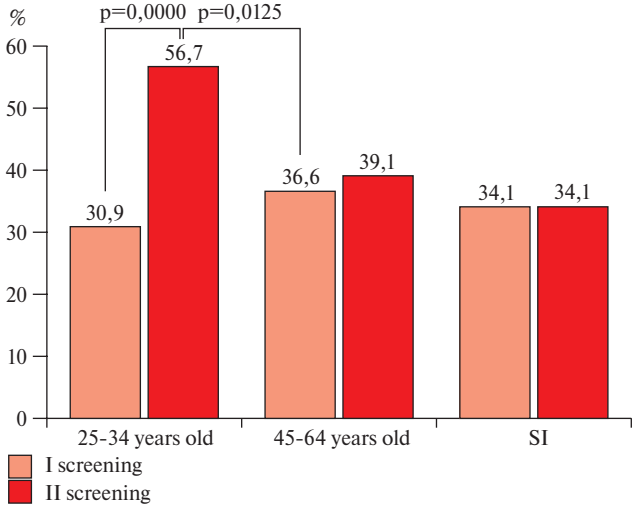

Figure 2 Dynamics of high intensity of tobacco smoking among women of the Tyumen population for the period 1996-2016, %.

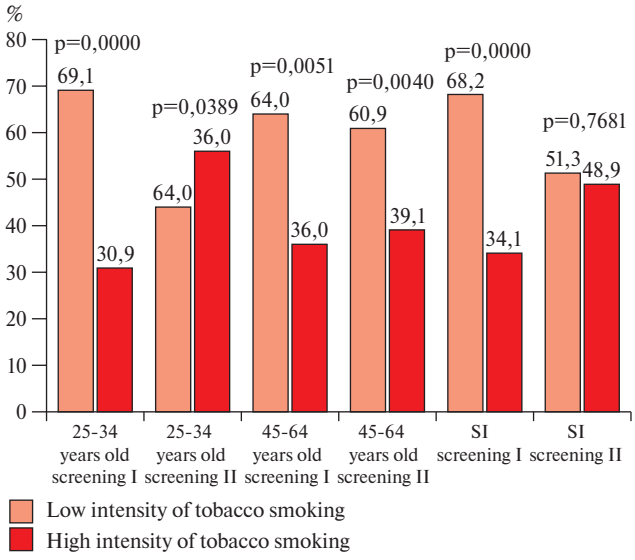

Figure 3 Dynamics of the intensity of tobacco smoking among women of the Tyumen population according to the data of the 1st and 2nd screenings, %.

according to the data of the first and second cardiac screening, the upward trend in the indicator at the second screening was statistically significant (p=0,0036). At the same time, a statistically significant increase in the prevalence of tobacco smoking over 20 years took place only among middle-aged women — 12,1 vs 23,3% (p=0,0000), among young women the prevalence of tobacco smoking remained almost stable — 34,0 vs 36,5% (p=0,4862) (Table 1).

Statistically significant differences in the prevalence of tobacco smoking between the categories of young and middle age were established according to the results of both the first — 34,0 vs 12,1% (p=0,0000), and the second cardiac screening — 36,5 vs 23,3% (p=0,0001), with higher indicators among young women (Table 1).

The SI of low intensity of tobacco smoking among women in the Central Administrative District of Tyumen showed a statistically significant tendency to decrease, and amounted to 68,2 and 51,3% according to the data of the first and second cardiac screening, respectively (p=0,0006). The twenty-year dynamics of a decrease in the low intensity of tobacco smoking in the Tyumen population was determined by the negative dynamics of a decrease in SI at a young age — 69,1 vs 43,3% (p=0,0000), while among middle-aged women the indicator remained almost stable — 64,0 vs 60,9% (p=0,7206) (Figure 1).

According to the results of the first screening, there were no significant differences between the categories of young and middle age in terms of low intensity of tobacco smoking — 69,1% vs 64,0% (p=0,5080). At the same time, according to the results of the second cardiac screening between these age categories, a statistically significant upward tendency of the indicator was determined — 43,3 vs 60,9% (p=0,0125) (Figure 1).

The SI of high intensity of tobacco smoking among women in the Central Administrative District of Tyumen was 34,1 and 49,8% according to the data of the first and second cardiac screening, respectively, a statistically significant increase in the indicator to the second screening was revealed (p=0,0006). Twenty-year dynamics towards the growth of high intensity of tobacco smoking in the Tyumen population was determined by a negative statistically significant tendency towards an increase in the indicator at a young age — from 30,9 to 56,7% (p=0,0000), while among middle-aged women the indicator remained practically stable — 36,0 vs 39,1% (p=0,7206) (Figure 2).

Statistically significant differences in the detection of high-intensity tobacco smoking in women of different age categories were established according to the results of the second cardiac screening with the highest indicators among young women — 56,7 vs 39,1% (p=0,0125). At the first screening, the indicator practically did not differ between age categories — 30,9 vs 36,0% (p=0,5080) (Figure 2).

An analysis of the study results of two independent samples showed that from the end of the last century to the 20s of this one, the priorities in relation to the intensity of tobacco smoking among women have changed significantly (Figure 3). So, according to the results of the first screening for the parameter of low intensity of tobacco smoking, residents of Tyumen demonstrated a statistically significant prevalence over the parameter of high intensity of both SI — 68,2 vs 34,1% (p=0,0000), and the corresponding indicators in the groups of young — 69,1 vs 30,9% (p=0,0000) and middle ages — 64,0 vs 36,0% (p=0,0051). By the second screening, SI in terms of the distribution of low and high intensity of tobacco smoking in Tyumen women became almost the same — 51,3 vs 49,8% (p=0,7681). In middle age, the tendency for the prevalence of low intensity of tobacco smoking over high one, inherent in the distribution of indicators at the first screening, remained — 60,9 vs 39,1% (p=0,0040). At the same time, in the group of 25-44 years old at the second screening, a statistically significant increase in high intensity of smoking over low intensity was revealed — 43,3 vs 56,7% (p=0,0389); in other words, among young women, the tendencies in the intensity of tobacco smoking were reversed.

Thus, over 20 years, the situation among women who smoke in the Tyumen population has changed dramatically. According to a study of two independent samples, with a general tendency towards an increase in the prevalence of tobacco smoking over a 20-year period, there was a change in priorities from low to high intensity of tobacco smoking, mainly at the expense of young women (Figure 3).

Discussion

In the mid-90s, sufficient attention was not paid to the problem of tobacco smoking, but today the situation has changed for the better. Among Russian women, the prevalence and intensity of smoking was traditionally low compared to European women [2], however, despite the measures taken by the government of the Russian Federation to limit tobacco smoking [8], an increase in the intensity of tobacco smoking among women was revealed in the Tyumen population over a 20-year observation period [12]. Measures such as pictorial warnings on tobacco products, banning smoking in public places, increasing the cost of tobacco products do not have a significant effect; moreover, in the Tyumen population, there was an increase in the prevalence of tobacco smoking among middle-aged women and, which is especially alarming, an increase in the intensity of tobacco smoking among young women.

According to the data of the global GATS (Global Adult Tobacco Survey), the prevalence of smoking among women from 2009 to 2016 decreased by 8%, at the same time, according to the data of Balanova YuA et al. [5], there is an increase in the prevalence and intensity of female smoking during the same observation period in the Russian Federation. An increase in the prevalence and intensity of tobacco smoking among women is noted in China, Indonesia, Bangladesh, as well as in Southern Europe [3, 13].

According to the 1996 baseline study, the prevalence and intensity of smoking among Tyumen women turned out to be quite high in comparison with the all-Russian data, but comparable with the data of the Siberian region, in particular, with the results of the Novosibirsk screening in 1995 [14, 15]. Analysis of the results on the Russian sample showed a significant increase in the prevalence and intensity of tobacco smoking from 1993 to 2013 [5]. Similar data were obtained from the monitoring of the Novosibirsk population carried out within the MONICA project (Monitoring trends and determinants in Cardiovascular disease), where in the age group 25-44 years from 1995 to 2014 there was a consistent increase in the prevalence and intensity of tobacco smoking in women [16].

The present results on the increase in the intensity of smoking among women seem to be justified, since the study was carried out on two independent samples during the period of the global socio-economic reforms in the Russian Federation [6]. The reforms carried out could not but have a significant impact on the change of priorities, mainly at a young age, including the Western way of life, where female tobacco smoking by the beginning of this century was much higher than in Russia [3, 11, 17]. Large-scale preventive programs in economically developed countries have significantly reduced these indicators, while in the Russian Federation, and in particular, at the level of the Siberian region, the preventive measures taken at the federal level were clearly insufficient.

The results obtained are comparable with the official data on the prevalence and dynamics of tobacco smoking in the Tyumen region, where, in accordance with the general tendencies in the Russian Federation, the situation among women turned out to be much worse than among men. Thus, since the beginning of the anti-tobacco campaign, the number of smokers in Tyumen has decreased by 10%, however, such positive changes were not observed among women, moreover, there is an increase in tobacco smoking among young women. With regard to the intensity of tobacco smoking, sociological studies in Tyumen have been carried out since 2014 without ranking by sex and age, however, in general, for the adult population during this period, there is a decrease in its intensity [18]. Consequently, the data of official statistics do not allow us to judge the vector of movement of the epidemiological situation in relation to the intensity of tobacco smoking among women in Tyumen for the period under study, while the results of the presented study, conducted on two independent samples, can serve as a scientific basis

for effective planning of a program for the primary prevention of CVD in the region.

Thus, within the framework of significant large-scale events at the federal level, it is necessary to direct efforts to reduce the intensity of tobacco smoking among women in medium-urbanized Siberian cities, paying special attention to the category of young age.

Conclusion

According to the results of a study of two independent samples of the Central Administrative District of Tyumen, a negative 20-year dynamics of growth in the intensity of tobacco smoking in the population was revealed due to the category of young women. In young women of the Tyumen population over a 20-year period, with a stable prevalence of tobacco smoking, a redistribution of priorities from low to high intensity of tobacco smoking was established — the prevalence of high-intensity smokers over low-intensity smokers at the second screening, while the situation was reversed at the first screening. In middle-aged women of the Tyumen population over a 20-year period, with a tendency to an increase in the prevalence of tobacco smoking at the first and second screenings, the prevalence of smokers with low intensity over smokers with high intensity remains.

Relationships and Activities: none.

References

1. Critchley JA, Capewell S. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease. JAMA. 2003;290:89-97. doi:10.1001/jama.290.1.86.
2. Maslennikova GYa, Oganov RG. Medical and socioeconomic damage caused by smoking in the Russian Federation: diseases of circulatory system. Preventive medicine. 2011;3:19-27. (In Russ.)
3. Ng M, Freeman MK, Fleming TD. Smoking Prevalence and Cigarette Consumption in 187 Countries, 1980-2012. JAMA. 2014;311(2):183-92. doi:10.1001/jama.2013.284692.
4. Ezzati M, Riboli E. Behavioral and dietary risk factors for noncommunicable diseases. New Engl J Med. 2013; 365(10):954-62. doi:10.1056/NEJMra1203528.
5. Balanova YuA, Shal'nova SA, Deev AD, et al. Smoking prevalence in Russia. What has changed over 20 years? Preventive medicine. 2015;6:47-52. (In Russ.) doi:10.17116/profmed201518647-52.
6. Shalnova SA, Maksimov SA, Balanova YuA, et al. Adherence to a healthy lifestyle of the Russian population depending on the socio-demographics. Cardiovascular Therapy and Prevention. 2020;19(2):2452. (In Russ.) doi:10.15829/1728-8800- 2020-2452.
7. Giovino G, Mirza S, Samet J, et al. For The GATS Collaborative Group Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys. Lancet. 2012;380(9842):668-79. doi:10.1016/S0140-6736(12)61085-X.
8. Gambaryan MG, Boytsov SA. Progress of monitoring the execution of Federal Law No. 15-FZ "On the protection of citizens' health from exposure to second-hand tobacco smoke and consequences of tobacco consumption" in the subjects of the Russian Federation. Preventive medicine. 2015;5:15-28. (In Russ.) doi:10.17116/profmed201518515-28.
9. Maslennikova GYa, Oganov RG. Selection of optimal approaches to prevention of non-communicable diseases in international partnership circumstances. Cardiovascular Therapy and Prevention. 2018;17(1):4-9. (In Russ.) doi:10.15829/1728-8800-2018-1-4-9.
10. Chazova LV, Baubinene AV, Glazunov IS. Cooperative research on multifactorial prevention of coronary artery disease and its development into an integral program. Therapeutic archive. 1985;11:44-7. (In Russ.)
11. Naja S, El Din Makhlouf MM, Chebab MAH. An ageing world of the 21st century: a literature review. Int J Community Med Public Health. 2017;4(12):4363-9. doi:10.18203/2394-6040.ijcmph20175306.
12. Gakova EI, Akimov MYu, Kayumova MM, Kuznetsov VA. Gender specifics of the attitudes toward tobacco smoking in various educational levels and family status among economically active men and women in Tyumen city. Cardiovascular Therapy and Prevention. 2017;16(5):57-62. (In Russ.) doi:10.15829/1728-8800-2017-5.
13. Carreira H, Pereira M, Azevedo A, Lunet N. Trends in the prevalence of smoking in Portugal: a systematic review. BMC Public Health. 2012;12:958.
14. Akimov AM. Attitudes to smoking in open population depending on education and character of labor. The Siberian Medical Journal. 2014;29(3):122-5. (In Russ.)
15. Gafarov VV, Pak VA, Gagulin IV, Gafarova AV. Epidemiology and prevention of chronic noncommunicable diseases during 20 years and during the period of social-economic crisis in Russia. Novosibirsk: SB RAMS, 2000. 284 p. (In Russ.) ISBN: 5-93239-018-2.
16. Denisova D, Malyutina S, Kozik V. Age gradient of smoking prevalence in Russia. European J Public Health. 2015;25(suppl 3):241. doi:10.1093/eurpub/ckv173.074.
17. Akimov AM, Gakova EI, Kayumova MM, et al. Stress in the family of young people in the gender aspect. Vrach. 2019;30(12):60-2. (In Russ.) doi:10.29296/25877305-2019-12-16.
18. Zakharchenko NM, Kamynina OYu. Methodical recommendations "School for smoking cessation". Tyumen, 2017. 59 p. (In Russ.)

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Positive effects of renal denervation on markers of cardiovascular inflammation and left ventricular mass. 24-months follow-up

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Aim. To study the long-term effect of renal denervation (RDN) on left ventricular mass (LVM) and inflammatory markers in resistant hypertensive patients.

Material and methods. Forty-one patients with resistant hypertension and 24-h blood pressure (BP) 158,7±15,8/87,3±14,6 mmHg, aged 56,6±10,2 years, were enrolled in the study and undergone RDN. Mean 24-h BP, left ventricular mass (transthoracic echocardiography), high sensitivity C-reactive protein (hsCRP), interleukin-1β (IL-1β), IL-6, IL-10) and tumor necrosis factor alpha (TNF-α) were assessed at baseline and 2 years after the RDN.

Results. A baseline prevalence of left ventricular hypertrophy (LVH) was 90,2%. Two years after RDN LVM and interventricular septum (IVS) decreased significantly ($p<0.05$ for both). Decrease in myocardial mass (ΔLVM >0 g) was documented in 24 patients. The regression of LVM was accompanied by a significant decrease in levels of inflammatory markers — hsCRP by 38,3% (p=0,031), TNF-α by 60,7% (p=0,009), IL-1β — by 71,1% (p=0,001), and IL-10 by 58,2% (p=0,001). In patients in the absence of LVM regression only TNF-α decreased significantly (-68,8%, p=0,001). There was no correlation between changes of LVM and the inflammatory markers at 24 months after RDN.

Conclusion. The RDN in RH patients may have long-term cardioprotective effect in terms of significant regress of LVH, which may be partly attributed to the regress in systemic or myocardial inflammation.

Keywords: resistant hypertension, cardioprotective efficacy, left ventricular hypertrophy, renal denervation, inflammation.

Relationships and Activities: none.

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Introduction

Despite the progress in the development of antihypertensive pharmacotherapy a prevalence of uncontrolled arterial hypertension (AH) is still very high. Major classes of antihypertensive drugs can reduce blood pressure (BP), on average, by -9.1/-5.5 mm Hg when administered as monotherapy and around -30/-15 mm Hg when 3 drugs are used in combination [1]. It is obviously not enough for effective treatment of severe AH with BP higher than 180 mm Hg. Therefore, a significant proportion of treated hypertensives remain uncontrolled or treatment-resistant. The risk of stroke and myocardial infarction in patients with resistant hypertension (RH) is twice as high as in those with controlled hypertension.

According to meta-analysis of cross-sectional and longitudinal studies including 3325 patients, left ventricular hypertrophy (LVH) is diagnosed in 55-75% of patients with RH [2]. A negative effect of LVH on clinical course and the outcomes of myocardial infarction has been shown in a large observational study [3]. Also, LVH negatively affected the infarct size in experimental research [4]. The LVH is independent predictor of systolic dysfunction [5], sudden cardiac death and cardiovascular death. Reduction of LVH or left atrium size due to antihypertensive

Table 1

Baseline patients' characteristics

	Mean±SD or (%)
Number of patients	41
Age, years	56,6±10,2
Gender, males	14 (34,1%)
Duration of the disease, years	15,7±7,8
Diabetes	21 (51,2%)
CAD	21 (51,2%)
24 h SBP, mmHg	158,7±15,8
24 h DBP, mmHg	87,3±14,6
LVM, g	262,1±72,3
Serum creatinine, μmol/l	81,6±19,2
eGFR, ml/min/m^2	77,7±17,3
BP lowering drugs:	4,3±0,9
– Beta-blockers	33 (80,5%)
– ACE-inhibitor	22 (53,7%)
– Calcium channel blockers	32 (78,0%)
– Diuretic	41 (100%)
– Antagonist of aldosterone	15 (36,6%)
– Angiotensin receptor blockers	15 (36,6%)
– Alpha-adrenoblockers	1 (2,4%)
– Centrally acting	9 (21,9%)

Note: CAD — coronary artery disease, ACE-inhibitor — angiotensin converting enzyme inhibitor.

Table 2

Structure of antihypertensive therapy at baseline and 24 months after RDN

Parameters	Baseline (% of patients)	24 months (% of patients), p
Beta-blockers	80,5	82,9, p=0,78
Diuretic	100	100
ACE-inhibitor	53,7	60,9, p=0,50
Calcium channel blockers	78,0	87,8, p=0,24
Angiotensin receptor blockers	36,6	36,6
Alpha-adrenoblockers	2,4	0, p=0,31
Centrally acting	21,9	24,3, p=0,79
Antagonist of aldosterone	36,6	41,5, p=0,65

Note: ACE-inhibitor — angiotensin converting enzyme inhibitor.

Table 3

Levels of inflammatory markers before and 24 months after RDN in patients without regress of LVM

	Baseline, M (SD)	24 m, M (SD)	p
IL-1β, pg/ml	3,4 (3,1)	0,9 (0,3)	0,10
IL-6, pg/ml	3,7 (3,2)	3,3 (2,4)	0,65
IL-10, pg/ml	5,9 (4,4)	2,9 (1,5)	0,26
hsCRP, mg/l	3,8 (3,4)	3,5 (3,2)	0,53
TNF-α, pg/ml	5,4 (3,6)	1,9 (1,0)	0,001

Table 4

Levels of inflammatory markers before and 24 months after RDN in patients with regress of LVM

	Baseline, M (SD)	24 m, M (SD)	p
IL-1β, pg/ml	3,0 (2,7)	0,7 (0,3)	0,001
IL-6, pg/ml	3,7 (2,5)	4,3 (3,5)	0,84
IL-10, pg/ml	6,0 (3,3)	2,5 (0,5)	0,001
hsCRP, mg/l	4,8 (3,2)	2,9 (2,4)	0,03
TNF-α, pg/ml	4,4 (3,6)	1,6 (0,6)	0,009

pharmacotherapy can have a positive effect on a risk of major cardiovascular events [6].

A role of inflammation in the development of AH and hypertensive organ damage has been widely discussed in recent decades. A variety of pro-inflammatory and inflammatory markers have been studied for their relationship with the progression of the disease, especially, high sensitivity C-reactive protein (hsCRP), interleukins and tumor necrosis factors.

One of the most promising therapeutic developments potentially capable to solve the problem of RH is catheter based renal denervation (RDN). Treatment of RH with RDN demonstrates regress of LVH, but with low predictability, and even in the absence of BP response. Also, long-term effects of RDN on LVH are not well studied.

Aim of the study is to determine the long-term effect of RDN on left ventricular mass (LVM) and inflammatory markers in patients with resistant hypertension.

Material and methods

We performed a retrospective analysis of the data from the single center study of RDN in RH patients conducted in the Cardiology Research Institute of Tomsk National Medical Research Center.

Study inclusion criteria were: hypertensive patients of both genders, 18-80 years old, office BP >160/90 mmHg (systolic/diastolic, respectively) despite treatment with maximum tolerated doses of 3 antihypertensive drugs in, one of which was a diuretic. All patients provided written informed consent before inclusion in the study. The patients were excluded if they had secondary hypertension, 24-h mean systolic blood pressure (SBP) <135 mm Hg, glomerular filtration rate (by MDRD formula) (eGFR) <30 mL/min/m^2, pregnancy, extended disease of the renal arteries, severe comorbidity significantly increasing risk of the intervention. The patients meeting eligibility criteria underwent RDN procedure and were followed up for a period up to 3 years. Patients were instructed to maintain concomitant drug therapy as stable as possible during the follow-up.

There were 6-, 12-, 24- and 36-months follow-up examination to assess the effectiveness and safety of renal denervation. The results of the annual observation were presented earlier. This study presents research data from 41 RH patients completed 2 year follow up. Baseline characteristics of the patients and structure of antihypertensive pharmacotherapy are summarized in the table 1. There were no deviation from the schedule of taking the drugs. Control was carried out by interviewing patients.

The following parameters were analyzed at baseline and 24 months after treatment:

1. 24-h mean SBP and DBP obtained from ambulatory BP monitoring. Only data with more than 80% of successful measurements were accepted for the analysis.

2. The thickness of interventricular septum (IVS) and posterior wall of left ventricle, LVM and indexed LVM assessed by transthoracic echocardiography. LVH was diagnosed if indexed LVM was more than 95 g/m^2 and 115 g/m^2 for women and men respectively.

3. hsCRP, interleukin-1β (IL-1β), IL-6, IL-10 and tumor necrosis factor alpha (TNF-α) measured in a blood serum by enzyme-linked immunosorbent assay (ELISA) in the absence of acute inflammation or exacerbation of chronic pathology.

4. Serum creatinine, eGFR (MDRD).

Statistical analysis: Measurement data that followed a normal distribution were expressed as mean±SD. Between-group differences in continuous (interval) variables were assessed using T-test, Chi-square test was used to asses differences in categorical variables. Continuous relationships between interval variables were evaluated using Pearson correlation coefficients, t statistic was used to assess a significance of the relationships. A p-value <0.05 was considered as significant.

Results

Two years after RDN the 24-hour BP was significantly decreased compared to baseline (-13.1/-7.4 mm Hg SBP/DBP respectively, p<0.001 for both). The analysis of patient-reported data on the antihypertensive drug use has shown no significant changes in concomitant drug therapy throughout the follow-up (4.14±0.89 vs 4.37±0.93, p<0.16) (table 2).

The baseline prevalence of LVH in the study sample was 90.2%. Two years after RDN LVM was decreased significantly from 269.9±71.7 to 254.6±58.1 g, p=0,048 mainly due to decrease in IVS from 14.0±1.5 to 13.5±1.5 g, p=0,015 whereas PW thickness did not change (12.9±1.7 g at baseline and 12.8±1.7 g, p=0,56).

Decrease in myocardial mass (ΔLVM >0 g) was documented in 24 patients. The regression of LVM was accompanied by significant decrease of inflammatory markers: the hsCRP by 38.3% (p=0.031), TNF-α by 60.7% (p=0.009), IL-1β — by 71.1% (p=0.001), IL-10 by 58.2% (p=0.001) except IL-6 that did not change (table 3).

In contrast, there was no significant changes inflammatory markers level in the absence of LVM regress (ΔLVM <0 g, n=17). Only TNF-α decreased significantly (-68.8%, p=0.001) (table 4). In a both cases (with and without regress of LVH) BP decreased significantly at two years after RDN 24-h (-8.5/-5.8 and -17.3/-8.5 mm Hg respectively (p<0.01 for both).

There was no correlation between changes of LVM and inflammatory markers at 24 months after RDN. There were no serious adverse events associated with the RDN.

Discussion

RDN as a method of endovascular treatment of RH demonstrates cardioprotective effects but the magnitude of the effects is highly variable. Previous studies of cardioprotective efficacy of RDN were conducted in small patient groups and had a short duration, mainly, up to one year. The regression of LVM and atrial size after RDN was confirmed in metanalysis of 12 studies with twelve months follow up including 382 patients in total [7]. There was no relationship between cardiac changes and BP reduction after RDN in these studies. Regress of LVM and reduction of the volume of subendocardial damage assessed by contrast enhanced MRI were demonstrated in 35 RH patients over 1 year follow-up after RDN in our center [8]. Currently there are only a few publications on the long-term cardioprotective efficacy of RDN. The study in 18 patients with RH has shown a definite 24-month cardioprotective effect of RDN: regression of LVH was detected in 70.6% cases, the prevalence of concentric remodeling dropped by 47.1%. Cardiac changes were not related to the BP lowering after RDN [9].

The relationship between inflammation and hypertension has been shown in a number of studies [10]. Levels of IL-1β, IL-6, TNF-α in hypertensive patients are significantly higher compared to normotensives [11]. In particular, it has been shown that hsCRP known as a marker of vascular inflammation and remodeling is also involved in the development of LVH [12], has strong association with hypertension [13] and predicts cardiovascular complications in hypertensive patients.

The experimental studies demonstrated that mechanisms of the LVH regression after RDN are not limited to the decrease in sympathetic activity and blood pressure. The levels of expression of myocardial TNF, IL-6, TLR-4 may also be relevant in this regard. An experimental study of RDN performed in spontaneously hypertensive rats has shown that compared to the control Wistar Kyoto spontaneously hypertensive rats had markedly higher blood pressure, LVMI and protein expression of TLR4, NF-ϰB, TNF-α and IL-6 in the myocardium, which were significantly reduced after RDN in contrast with sham-operated animals [14].

In 2015 a group of German authors published a study that documented a significant decrease in IL-6 and CRP whereas an increase in matrix metalloproteinases (MMP-2, MMP-9) at 6 months after RDN [15].

The main finding of our study is that the IVS thickness and LVM assessed by echocardiography decreased significantly at 24 months after RDN. Thus, the RDN in RH patients may have long-term cardioprotective effect, which at least in part may be attributed to the regress in systemic or myocardial inflammatory activity. In spite of the research limitations (small sample, absence of control group) the results obtained are scientific interest and demand continuing the research.

Relationships and Activities: none.

References

1. Bramlage P, Hasford J. Blood pressure reduction, persistence and costs in the evaluation of antihypertensive drug treatment — a review. Cardiovasc Diabetol. 2009;27:8-18. doi:10.1186/1475-2840-8-18.
2. Cuspidi C, Vaccarella A, Negri F, et al. Resistant hypertension and left ventricular hypertrophy: an overview. J Am Soc Hypertens. 2010;4(6):319-4. doi:10.1016/j.jash.2010.10.003.
3. Kannel WB, Sorlie P, Castelli WP, et al. Blood pressure and survival after myocardial infarction: the Framingam study. Am J Cardiol. 1980;45(2):326-30. doi:10.1016/0002-9149(80)90654-2.
4. Koyanagi S, Eastham CL, Harrison DG, et al. Increased size of myocardial infarction in dogs with chronic hypertension and left ventricular hypertrophy. Circulation Research. 1982;50(1):55-62. doi:10.1161/01.res.50.1.55.
5. Drazner MH, Rame JE, Marino EK, et al. Increased left ventricular mass is a risk factor for the development of a depressed left ventricular ejection fraction within five years: the Cardiovascular Health Study. J Am Coll Cardiol. 2004;43(12):2207-15. doi:10.1016/j.jacc.2003.11.064.
6. Gerdts E, Wachtell K, Omvik P, et al. Left atrial size and risk of major cardiovascular events during antihypertensive treatment Losartan intervention for endpoint reduction in hypertension trial. Hypertension. 2007;49(2):311-6. doi:10.1161/01.hyp.0000254322.96189.85.
7. Lu D, Wang K, Liu Q, et al. Reductions of left ventricular mass and atrial size following renal denervation: a meta-analysis. Clin Res Cardiol. 2016;105(8):648-56. doi:10.1007/s00392-016-0964-2.
8. Sitkova ES, Mordovin VF, Ripp TM, et al. Positive effects of renal denervation on left ventricular hypertrophy and subendocardial damage. "Arterial'naya Gipertenziya" ("Arterial Hypertension"). 2019;25(1):46-59. (In Russ.) doi:10.18705/1607-419X-2019-25-1-46-59.
9. Tsioufis C, Papademetriou V, Dimitriadis, et al. Long-term effects of multielectrode renal denervation on cardiac adaptations in resistant hypertensive patients with left ventricular hypertrophy. J Hum Hypertens. 2016;30(11):714-9. doi:10.1038/jhh.2015.127.
10. Dinh QN, Drummond GR, Sobey CG, et al. Roles of inflammation, oxidative stress and vascular dysfunction in hypertension. Biomed Res Int. 2014;2014:406960. doi:10.1155/2014/406960.
11. Bautista LE, Vera LM, Arenas IA, et al. Independent association between inflammatory markers (C-reactive protein, interleukin-6, and TNF-alpha) and essential hypertension. J Human Hypertens. 2005;19(2):149-54. doi:10.1038/sj.jhh.1001785.
12. Mehta SK, Rame JE, Khera A, et al. Left Ventricular Hypertrophy, Subclinical Atherosclerosis, and Inflammation. Hypertens 2007;49(6):1385-91. doi:10.1161/hypertensionaha.107.087890.
13. Blake GJ, Rifai N, Buring JE, et al. Blood pressure, C-reactive protein, and risk of future cardiovascular events. Circulation. 2003;108(24):2993-9. doi:10.1161/01.cir.0000104566.10178.af.
14. Jiang W, Tan L, Guo Y, et al. Effect of renal denervation procedure on left ventricular hypertrophy of hypertensive rats and its mechanisms. Acta Cir Bras. 2012;27(11):815-20. doi:10.1590/S0102-86502012001100012.
15. Dörr O, Liebetrau C, Möllmann H, et al. Beneficial effects of renal sympathetic denervation on cardiovascular inflammation and remodeling in essential hypertension. Clin Res Cardiol. 2015;104(2):175-84. doi:10.1007/s00392-014-0773-4.

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Nuclear imaging of chemotherapy-induced cardiotoxicity

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The high efficiency of modern chemotherapy has made it possible to achieve great success in the treatment of cancer. Cardiovascular adverse effects are a major disadvantage of anticancer therapy, often requiring low and less effective doses or even drug withdrawal. Nuclear imaging techniques are the most sensitive in early detection of left ventricular damage and dysfunction during chemotherapy. This review presents modern data on the potential of nuclear imaging of cardiotoxicity.

Keywords: cardiotoxicity, cardio-oncology, anthracyclines, heart failure, nuclear imaging.

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Over the past several decades, early diagnosis and the development of new anticancer drugs have significantly improved the prognosis of cancer patients. Unfortunately, many of these drugs have a number of cardiac side effects, in particular related to the so-called cardiotoxicity. Its early detection and treatment are one of the tasks of modern cardio-oncology, and the solution of this task not only reduces the incidence of cardiovascular complications, but also provides better treatment for the underlying disease [1]. The most common cardiotoxic effects are caused by drugs such as anthracyclines, cyclophosphamide, monoclonal antibodies, and tyrosine kinase inhibitors. Unfortunately, the available knowledge about the pathophysiology of cardiotoxicity is not exhaustive, resulting in detecting it in most cases already at the stage of manifestation of cardiovascular disease. Irreversible cardiotoxic effects are caused by the production of free radicals in cells, impaired adrenergic functions and, ultimately, the death of cardiomyocytes due to calcium overload. Among the cardiovascular complications of chemotherapy are not only the development of left ventricular (LV) systolic dysfunction and heart failure (HF), but also myocarditis, arrhythmias, thrombosis, coronary, pericardial and valvular pathology [2]. However, it is the decrease in LV contractility that is the most frequently observed manifestation of cardiotoxicity, and it is associated with increased mortality during and after chemotherapy [3]. Chemotherapy-induced cardiotoxicity is defined as a decrease in LV ejection fraction (EF) due to hypokinesia (diffuse or more pronounced in the interventricular septum), with the appearance of congestive HF symptoms. A decrease in LVEF by at least 5%, or to a value <55% with the appearance of congestive HF signs and symptoms, or by at least 10% or to a value <50% without HF symptoms is considered significant from baseline values [4]. A decrease in EF by more than 10% or to a value of <50% is a clinical reason for discontinuation of the prescribed anticancer drug [5].

Thus, it is the assessment of LVEF in dynamics that is most important for identifying criteria for cardiotoxicity. In this case, the most accurate assessment of changes in LVEF plays a special role, that imposes significant requirements on the quality of images and intra-/inter-operator reproducibility [6]. It should be emphasized that with different research methods, the norm is a different value of LVEF [7-9]. Echocardiography (EchoCG) and magnetic resonance imaging (MRI) are the most commonly used imaging methods for non-invasive assessment of LV contractility. Two-dimensional echocardiography is the most accessible method, but its accuracy is low due to geometric assumptions, and the variability in measuring LVEF is about 10%, therefore, the possibility to reliably record a decrease in EF in dynamics by 5-10% by this method is considered doubtful [6]. Three-dimensional echocardiography is a more accurate method for measuring LV volume and function [10]. Nevertheless, echocardiography can be performed with sufficient accuracy only in 60% of patients with limited acoustic window, in particular, after mastectomy [11]. A more accurate method for assessing the functional parameters of the heart is MRI due to the low variability of LVEF measurement (from 2,4% to 7,3%), the absence of deficiencies in echocardiography and the possibility

of structural assessment of the myocardium, including edema and fibrosis [12]. Currently, the assessment of LVEF in dynamics using MRI is most often used as a verification method in assessing the effectiveness of cardioprotective drugs [13, 14]. The disadvantages of MRI are the duration of the study (10-20 min), the limitations in patients with claustrophobia and the presence of implanted devices, as well as the high cost, especially given the need for several repeated studies.

Radionuclide diagnostic (RND) methods such as: scintigraphy, single-photon emission computed tomography (SPECT), and positron emission tomography (PET) also play an important role in the assessment and follow-up of cancer patients who have been prescribed potentially cardiotoxic chemotherapy. The main advantage of RND methods, which plays a special role in these cases, is the proven high reproducibility and operator independence due to fully automatic data collection [7, 15]. Moreover, in addition to the possibility of an accurate assessment of EF and a sensitive assessment of its dynamics, RND has a number of other indicators for non-invasive assessment of earlier biological processes preceding anatomical and even more functional damage to the myocardium [16].

Radionuclide (tomo)ventriculography. Planar ECG-synchronized ventriculography (MUGA) with labeled erythrocytes has been a proven method for over 40 years [17]. In this study, a series of summation images of the cardiac cavities is recorded at several (usually 16) stages of the cardiac cycle. This allows with high accuracy and reproducibility to assess the volume of the cavity and LVEF, including in cancer patients [18]. In a study involving patients with non-Hodgkin's lymphoma and doxorubicin therapy at a high cumulative dose, the method sensitivity was 90% and the specificity was 72% in predicting the development of chronic HF [19]. These data were supplemented with a study that showed that there can be significant discrepancies between clinical symptoms of HF and decrease in LVEF. Thus, in 66% of patients with a clinical picture of doxorubicin-induced HF, there was no significant decrease in LVEF according to planar MUGA [20]. It is obvious that patients with chronic HF and intact LVEF constitute a separate category that requires a deeper study of the myocardium than an assessment of only its contractile ability [21, 22].

The tomographic variant of radionuclide ventriculography — radionuclide tomoventriculography (RTVG) — allowed raising the sensitivity of assessing myocardial contractility disorders to a new level. It became possible to more accurately assess disorders of global and local contractility, systolic and diastolic function of both the LV and the right ventricle, which, according to some studies, made it possible to more accurately monitor and personalize therapy in patients with HF [20]. There is evidence that the EF values slightly underestimated in RTVG compared to radionuclide ventriculography (both equilibrium and first-pass) and EchoCG, however, in general, these methods have good cross-correlation [23]. At the same time, the maximum accuracy of calculating LVEF based on RTVG data depends on a number of factors, including on the number of images within the R-R interval (preferably 16) and the quality of the study protocol. New life for ventriculographic techniques can be given by the introduction of new models of single-photon tomographs based on cadmium-zinc-telluride (CZT) detectors [24].

Scintigraphy with ^{111}In-antimyosin. Antimyosin is a specific marker of myocardial cell damage and necrosis. It binds to intracellular myosin in violation of the integrity of the sarcolemma, causing irreversible damage to cells. The accumulation of ^{111}In-labeled antimyosin has been studied in myocardial infarction, myocarditis, heart transplant rejection, and anthracycline cardiotoxicity [25]. Scintigraphy and SPET with this radiopharmaceutical (RP) may play a role in the subclinical assessment of LV dysfunction [26]. In particular, after a cycle of courses of anthracycline chemotherapy in patients with breast cancer without cardiovascular risk factors or previous chemotherapy or radiotherapy of the mediastinum, the accumulation of labeled antimiosin was indicated, and the level of accumulation of this RP correlated with a subsequent decrease in LVEF. In patients with increased accumulation of this RP in the myocardium (heart/mediastinal accumulation ratio $\geqslant$1,9) with a cumulative dose of doxorubicin of 240-300 mg/m^2 a more pronounced decrease in LVEF (>10%) was developed with a subsequent cumulative dose of 420-600 mg/m^2 [25]. In addition, in patients with a persistent decrease in EF, the accumulation of ^{111}In-antimyosin was more pronounced compared with those in whom the decrease in EF was reversible — 1,83±0,37 vs 1,52±0,21 ($p<0,01$) [27]. Thus, scintigraphy with ^{111}In-antimyosin turned out to be useful as a marker of an increased risk of developing HF in patients who are on therapy with high doses of anthracyclines, including for identifying patients with a higher probability of developing irreversible LV dysfunction, which will require discontinuation of this drug.

Scintigraphy with ^{123}I-meta-iodine-benzylguanidine (MIBG). MIBG is a structural analogue of norepinephrine, but it does not undergo metabolism, accumulating in presynaptic adrenergic terminals and thus allowing them to be visualized. Chemotherapy activates the body's compensatory response in the form of an increase in the activity of the adrenergic and renin-angiotensin systems to preserve the blood supply to organs, namely, an increase in the release of norepinephrine is noted, which leads to the depletion of its deposits and a decrease in the activity of its carrier hNET1 [28]. This leads to a decrease in the capture of MIBG and an acceleration of its removal. A number

of studies have shown that a decrease in the relative accumulation of MIBG in the myocardium (H/M <1,9) is more often observed in patients taking a higher dose of doxorubicin, and is a predictor of a decrease in LVEF in the future [25].

Scintigraphy with ^{111}In-trastuzumab. Anthracyclines therapy in cancer patients can increase the expression of human epidermal growth factor receptor 2 (HER2) by cardiomyocytes. In patients previously treated with anthracyclines, trastuzumab, a drug with a direct effect on HER2, can cause cardiotoxic effects by inhibiting not only HER2 tumor cells, but also cardiomyocytes, which activates apoptotic mechanisms and enhances anthracycline-induced oxidative stress. Thus, scintigraphy with ^{111}In-labeled trastuzumab (^{111}In-Tz) can be used to assess the level of HER2 expression by cardiomyocytes, and, therefore, the risk of LV dysfunction in patients receiving this drug [29]. In a study by Behr, et al. ^{111}In-Tz scintigraphy was performed in 20 patients with metastatic HER2/neu-positive breast cancer who were previously treated with anthracyclines and are scheduled for trastuzumab therapy. The accumulation of ^{111}In-Tz in the myocardium was noted in 7 patients, of whom 6 subsequently developed II-IV HF of functional class according to NYHA (New-York Heart Association), while none of the 13 patients without the accumulation of this RP had adverse cardiovascular events [30]. However, in a subsequent study [31], these results could not be repeated; in general, the rationale for using this RP in terms of predicting the development of trastuzumab-induced cardiotoxicity requires further substantiation.

Scintigraphy with ^{99m}Tc-annexin V. Apoptosis of cardiomyocytes plays a decisive role in the development of cardiomyopathies, and is observed in many ischemic, inflammatory and reactive conditions, including anthracycline-induced cardiomyopathy and myocarditis [32]. In cells that have triggered the apoptosis mechanism, proteases and sphingomyelinases are activated at an early stage, followed by exposure of phosphatidylserine molecules on the outer membrane of the cell. Annexin-V has a high affinity for phosphatidylserine and, thus, allows visualization of apoptotic processes in cells [33]. Studies of scintigraphy with labeled annexin V were carried out in animals; there was an increased accumulation of this RP in the myocardium in acute and chronic doxorubicin-induced cardiomyopathy with signs of apoptosis. At the same time, signs of oxidative stress were confirmed by histological analysis [34]. The clinical use of this RP requires further research.

Scintigraphy with^{123}I-fatty acid. Chemotherapy with drugs of the taxane class (docetaxel, paclitaxel) is used in the treatment of breast, lung and ovarian cancer. The use of these drugs is associated with the risk of ischemic and arrhythmic side effects with a certain probability of developing HF. In particular, taxanes have a damaging effect on the transport systems in cardiomyocytes, which leads to impaired storage of free fatty acids in the cytosolic lipid pool and a decrease in the level of mitochondrial absorption of free fatty acids for beta-oxidation. Scintigraphy with 123-iodine-labeled phenyl-methyl-pentadecanoic acid (^{123}I-BMIPP) is used to assess violations of the biochemical processes of oxidation of free fatty acids [35]. A number of studies have shown a decrease in the accumulation of ^{123}I-BMIPP in the myocardium during chemotherapy, including both doxorubicin and taxanes. At the same time, a decrease in the accumulation of this RP in the myocardium depends on the cumulative dose of doxorubicin and is associated with a more pronounced decrease in LVEF in the future [35].

PET with ^{18}F-fluorodeoxyglucose (^{18}F-FDG). The use of PET in cardio-oncology looks promising, since the most common RP for PET, ^{18}F-FDG, has long won a solid position both for assessing the prevalence of a tumor process and response to therapy, and for assessing myocardial metabolism, which is an important step in assessing its viability. In addition, PET with ^{18}F-FDG is used to detect inflammation (for example, in myocarditis) [36], to monitor the therapeutic response in primary heart lymphoma, and to assess metastatic lesions of the pericardium [37]. However, chemotherapy does not cause significant disturbances in glucose metabolism in cardiomyocytes according to PET with ^{18}F-FDG; its level may even increase on the background of a decrease in fatty acid intake. This is probably due to the partial transition of myocardial metabolism towards aerobic glycolysis under conditions of the occurrence of hypoxic processes in the myocardium on the background of chemotherapy [38, 39]. PET with neurotropic RP (^{11}C-hydroxyephedrine) reveals a decrease in β-adrenergic receptor density in patients with HF and decreased LVEF, but these processes are not specific for chemotherapy-induced cardiotoxicity [40].

Scintigraphy and SPET with ^{99m}Tc-MIBI and ^{99m}Tc-tetrofosmin. Myocardial perfusion scintigraphy is the most demanded study in nuclear cardiology, it also has certain prospects for imaging signs of cardiotoxicity. The performance of this study with ECG-synchronization (S-SPET) is currently an integral part of the protocol of perfusion scintigraphy at rest and after exercise testing to assess transient myocardial ischemia in patients with suspected or established coronary artery disease. Initial acquisition of end-diastolic and end-systolic LV volumes in automatic mode, improvement of the quality of detecting systems and image processing programs led to the fact that the accuracy and reproducibility of perfusion S-SPET in assessing LVEF is not inferior to tomoventriculography [41]. Like RTVG, perfusion S-SPET in the modern version provides the speed and time parameters of the expulsion of blood from the LV into systole and its filling in diastole.

The most important advantage of ECG-synchronized studies with ^{99m}Tc-MIBI or tetrofosmin is the simultaneous comparison of LV myocardial contractility with its cellular perfusion [42]. The mechanism for assessing myocardial perfusion using these RP is based on the fact that they are both lipophilic cations that penetrate into the cardiomyocyte by passive diffusion (along an electrochemical gradient) in proportion to myocardial blood flow. The further fate of these two RPs inside the cell differs. While tetrofosmin predominantly accumulates in the cytosol, ^{99m}Tc-MIBI is more sensitive to differences in the potential of the outer membrane of the cardiomyocyte and the mitochondrial membrane, which has the greatest negative charge. As a result, ~90% of intracellular ^{99m}Tc-MIBI accumulates in intact mitochondria, thus reflecting the preservation of the cell's energy chains [43]. Toxic effects of anthracyclines, including associated with oxidative stress, cause direct damage to mitochondria and, as a consequence, a decrease in the uptake of ^{99m}Tc-MIBI by them [44]. This is manifested by the appearance of diffuse changes in the accumulation of RP in the myocardium, which can be reliably visualized at the current level of image quality. According to our own preliminary data, such initial changes in perfusion can occur during several courses of chemotherapy and be reversible; however, when they worsen, they are already visually interpreted as signs of diffuse fibrosis and become partially irreversible. At the same time, the severity of such diffuse perfusion disorders can be expressed in quantitative units, which, upon reaching a certain threshold, become an unfavorable prognostic sign in terms of the absence of an increase in EF after withdrawal or replacement of the polychemotherapy regimen [45].

A new direction in the assessment of cardiotoxicity using SPET with ^{99m}Tc-MIBI may be the assessment of the rate of its removal from the myocardium. This approach is borrowed from the biphasic radionuclide mammography method, which is widely used in the diagnosis and assessment of the response to breast cancer therapy. The principle of this method is that ^{99m}Tc-MIBI also accumulates in the mitochondria of some tumor cells, in particular, malignant tumors of the breast and lungs. In this case, the accumulation of ^{99m}Tc-MIBI in cancer cells depends not only on the activity of cell proliferation, but also on the presence of mechanisms for removing this RP from the cell. In particular, the presence of P-glycoprotein on the tumor cell membrane increases its protection, mediating the rapid elimination of foreign substances, including molecules of anticancer drugs. Thus, the acceleration of the removal of ^{99m}Tc-MIBI from the tumor focus, according to biphasic mammoscintigraphy, is an important sign of its drug resistance [46]. As applied to myocardial scintigraphy, this means that the accelerated removal of ^{99m}Tc-MIBI from cardiomyocytes is an earlier marker of mitochondrial damage, even at the stage of disrupting of energy chains work and reducing the potential of its matrix, i.e., before irreversible changes occur, which are already manifested by a decrease in the level of accumulation of RP [42, 47, 48].

In general, cardiotoxicity is one of the main and clinically and prognostically significant side effects of anticancer therapy. A decrease in LVEF is the most validated criterion for assessing the presence of myocardial damage during or after chemotherapy. However, a decrease in myocardial function occurs only when there is significant damage to it, and compensatory mechanisms are exhausted [49]. In this case, the time for taking cardioprotective measures is lost, since myocardial damage becomes irreversible and leads to the development of chronic HF [50]. Thus, in cardio-oncology there is a need for new non-invasive methods — inexpensive, more sensitive in terms of recognizing signs of cardiotoxicity at the subclinical stage, and providing prognostic information to reduce mortality in cancer patients. There are interesting prospects for early detection of myocardial damage by nuclear imaging using new molecular indicators that can help identify patients at high risk of developing LV dysfunction who are undergoing chemotherapy. Further experimental and clinical studies are required to implement these techniques and RP.

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References

1. Pudil R. The Future Role of Cardio-oncologists. Card Fail Rev. 2017;3(2):140-2. doi:10.15420/cfr.2017:16:1.
2. Albini A, Pennesi G, Donatelli F, et al. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Natl Cancer Inst. 2010;102(1):14-25. doi:10.1093/jnci/djp440.
3. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. BMC Cancer. 2010;10:337. doi:10.1186/1471-2407-10-337.
4. Mitani I. Doxorubicin cardiotoxicity: Prevention of congestive heart failure with serial cardiac function monitoring with equilibrium radionuclide angiocardiography in the current era. J Nucl Cardiol. 2003;10(2):132-9. doi:10.1067/mnc.2003.7.
5. Eschenhagen T, Force T, Ewer MS, et al. Cardiovascular side effects of cancer therapies: a position statement from the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2011;13(1):1-10. doi:10.1093/eurjhf/hfq213.
6. Thavendiranathan P, Grant AD, Negishi T, et al. Reproducibility of echocardiographic techniques for sequential assessment of left ventricular ejection fraction and volumes: application to patients undergoing cancer chemotherapy. J Am Coll Cardiol. 2013;61(1):77-84. doi:10.1016/j.jacc.2012.09.035.
7. Zamorano JL, Lancellotti P, Rodriguez Munoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(36):2768-801. doi:10.1093/eurheartj/ehw211.
8. Sanft T, Denlinger CS, Armenian S, et al. NCCN Guidelines Insights: Survivorship, Version 2.2019. J Natl Compr Canc Netw. 2019;17(7):784-94. doi:10.6004/jnccn.2019.0034.
9. Chung R, Ghosh AK, Banerjee A. Cardiotoxicity: precision medicine with imprecise definitions. Open Heart. 2018;5(2):e000774. doi:10.1136/openhrt-2018-000774.
10. Dorosz JL, Lezotte DC, Weitzenkamp DA, et al. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. J Am Coll Cardiol. 2012;59(20):1799-808. doi:10.1016/j.jacc.2012.01.037.
11. Santoro C, Arpino G, Esposito R, et al. 2D and 3D strain for detection of subclinical anthracycline cardiotoxicity in breast cancer patients: a balance with feasibility. Eur Heart J Cardiovasc Imaging. 2017;18(8):930-6. doi:10.1093/ehjci/jex033.
12. Grothues F, Smith GC, Moon JC, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002;90(1):29-34. doi:10.1016/s0002-9149(02)02381-0.
13. Gulati G, Heck SL, Rosjo H, et al. Neurohormonal Blockade and Circulating Cardiovascular Biomarkers During Anthracycline Therapy in Breast Cancer Patients: Results From the PRADA (Prevention of Cardiac Dysfunction During Adjuvant Breast Cancer Therapy) Study. J Am Heart Assoc. 2017;6(11):e006513. doi:10.1161/JAHA.117.006513.
14. Pituskin E, Mackey JR, Koshman S, et al. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): A Randomized Trial for the Prevention of Trastuzumab-Associated Cardiotoxicity. J Clin Oncol. 2017;35(8):870-7. doi:10.1200/JCO.2016.68.7830.
15. Curigliano G, Lenihan D, Fradley M, et al. Management of cardiac disease in cancer patients throughout oncological treatment: ESMO consensus recommendations. Ann Oncol. 2020;31(2):171-90. doi:10.1016/j.annonc.2019.10.023.
16. D'Amore C, Gargiulo P, Paolillo S, et al. Nuclear imaging in detection and monitoring of cardiotoxicity. World J Radiol. 2014;6(7):486-92. doi:10.4329/wjr.v6.i7.486.
17. Walker J, Bhullar N, Fallah-Rad N, et al. Role of Three-Dimensional Echocardiography in Breast Cancer: Comparison With Two-Dimensional Echocardiography, Multiple-Gated Acquisition Scans, and Cardiac Magnetic Resonance Imaging. J Clin Oncol. 2010;28(21):3429-36. doi:10.1200/jco.2009.26.7294.
18. van Royen N, Jaffe CC, Krumholz HM, et al. Comparison and reproducibility of visual echocardiographic and quantitative radionuclide left ventricular ejection fractions. Am J Cardiol. 1996;77(10):843-50. doi:10.1016/s0002-9149(97)89179-5.
19. Nousiainen T, Jantunen E, Vanninen E, et al. Early decline in left ventricular ejection fraction predicts doxorubicin cardiotoxicity in lymphoma patients. Br J Cancer. 2002;86(11):1697-700. doi:10.1038/sj.bjc.6600346.
20. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin. Cancer. 2003;97(11):2869-79. doi:10.1002/cncr.11407.
21. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200. doi:10.1093/eurheartj/ehw128.
22. Farrell MB, Galt JR, Georgoulias P, et al. SNMMI Procedure Standards/EANM Guideline for Gated Equilibrium Radionuclide Angiocardiography. J Nucl Med Technol. 2020;48:126-35. doi:10.2967/jnmt.120.246405.
23. Hacker M, Hoyer X, Kupzyk S, et al. Clinical validation of the gated blood pool SPECT QBS® processing software in congestive heart failure patients: correlation with MUGA, first-pass RNV and 2D-echocardiography. Int J Cardiovasc Imaging. 2005;22(3-4):407-16. doi:10.1007/s10554-005-9031-1.
24. Agostini D, Marie PY, Ben-Haim S, et al. Performance of cardiac cadmium-zinc-telluride gamma camera imaging in coronary artery disease: a review from the cardiovascular committee of the European Association of Nuclear Medicine (EANM). Eur J Nucl Med Mol Imaging. 2016;43(13):2423-32. doi:10.1007/s00259-016-3467-5.
25. Carrio I, Estorch M, Berna L, et al. Early assessment of doxorubicin cardiotoxicity with 111In-antimyosin and 123I-MIBG studies. J Nucl Cardiol. 1995;2(2):S25. doi:10.1016/s1071-3581(05)80188-6.
26. Estorch M, Carrió I, Martínez-Duncker D, et al. Myocyte cell damage after administration of doxorubicin or mitoxantrone in breast cancer patients assessed by indium 111 antimyosin monoclonal antibody studies. Journal of Clinical Oncology. 1993;11(7):1264-8. doi:10.1200/jco.1993.11.7.1264.
27. Valdés Olmos RA, ten Bokkel Huinink WW, ten Hoeve RFA, et al. Usefulness of indium-111 antimyosin scintigraphy in confirming myocardial injury in patients with anthracycline-associated left ventricular dysfunction. Ann Oncol. 1994;5(7):617-22. doi:10.1093/oxfordjournals.annonc.a058933.
28. Triposkiadis F, Karayannis G, Giamouzis G, et al. The Sympathetic Nervous System in Heart Failure. J Am Coll Cardiol. 2009;54(19):1747-62. doi:10.1016/j.jacc.2009.05.015.

29. de Korte MA, de Vries EGE, Lub-de Hooge MN, et al. 111Indium-trastuzumab visualises myocardial human epidermal growth factor receptor 2 expression shortly after anthracycline treatment but not during heart failure: A clue to uncover the mechanisms of trastuzumab-related cardiotoxicity. Eur J Cancer. 2007;43(14):2046-51. doi:10.1016/j.ejca.2007.06.024.
30. Rudlowski C, Werner R, Becker A. Trastuzumab and Breast Cancer. N Engl J Med. 2001;345(13):995-8. doi:10.1056/nejm200109273451312.
31. Perik PJ, Lub-De Hooge MN, Gietema JA, et al. Indium-111–Labeled Trastuzumab Scintigraphy in Patients With Human Epidermal Growth Factor Receptor 2 — Positive Metastatic Breast Cancer. J Clin Oncol. 2006;24(15):2276-82. doi:10.1200/jco.2005.03.8448.
32. Peker C, Sarda-Mantel L, Loiseau P, et al. Imaging apoptosis with (99m)Tc-annexin-V in experimental subacute myocarditis. J Nucl Med. 2004;45(6):1081-6.
33. Bennink RJ, van den Hoff MJ, van Hemert FJ, et al. Annexin V imaging of acute doxorubicin cardiotoxicity (apoptosis) in rats. J Nucl Med. 2004;45(5):842-8.
34. Panjrath GS, Patel V, Valdiviezo CI, et al. Potentiation of Doxorubicin Cardiotoxicity by Iron Loading in a Rodent Model. J Am Coll Cardiol. 2007;49(25):2457-64. doi:10.1016/j.jacc.2007.02.060.
35. Saito K, Takeda K, Imanaka-Yoshida K, et al. Assessment of fatty acid metabolism in taxan-induced myocardial damage with iodine-123 BMIPP SPECT: Comparative study with myocardial perfusion, left ventricular function, and histopathological findings. Ann Nucl Med. 2003;17(6):481-8. doi:10.1007/bf03006439.
36. Nensa F, Kloth J, Tezgah E, et al. Feasibility of FDG-PET in myocarditis: Comparison to CMR using integrated PET/MRI. J Nucl Cardiol. 2018;25(3):785-94. doi:10.1007/s12350-016-0616-y.
37. Lee JC, Platts DG, Huang Y-TT, et al. Positron emission tomography combined with computed tomography as an integral component in evaluation of primary cardiac lymphoma. Clin Cardiol. 2010;33(6):E106-8. doi:10.1002/clc.20725.
38. Borde C, Kand P, Basu S. Enhanced myocardial fluorodeoxyglucose uptake following Adriamycin-based therapy: Evidence of early chemotherapeutic cardiotoxicity? World J Radiol. 2012;4(5):220-3. doi:10.4329/wjr.v4.i5.220.
39. Bauckneht M, Ferrarazzo G, Fiz F, et al. Doxorubicin Effect on Myocardial Metabolism as a Prerequisite for Subsequent Development of Cardiac Toxicity: A Translational (18)F-FDG PET/CT Observation. J Nucl Med. 2017;58(10):1638-45. doi:10.2967/jnumed.117.191122.
40. Vesalainen RK, Pietila M, Tahvanainen KU, et al. Cardiac positron emission tomography imaging with [11C]hydroxyephedrine, a specific tracer for sympathetic nerve endings, and its functional correlates in congestive heart failure. Am J Cardiol. 1999;84(5):568-74. doi: 10.1016/s0002-9149(99)00379-3.
41. Abidov A, Germano G, Hachamovitch R, et al. Gated SPECT in assessment of regional and global left ventricular function: an update. J Nucl Cardiol. 2013;20(6):1118-43; quiz 1144-6. doi:10.1007/s12350-013-9792-1.
42. Safee ZM, Baark F, Waters ECT, et al. Detection of anthracycline-induced cardiotoxicity using perfusion-corrected (99m)Tc sestamibi SPECT. Sci Rep. 2019;9(1):216. doi:10.1038/s41598-018-36721-5.
43. Piwnica-Worms D, Kronauge JF, Chiu ML. Enhancement by tetraphenylborate of technetium-99m-MIBI uptake kinetics and accumulation in cultured chick myocardial cells. J Nucl Med. 1991;32(10):1992-9.
44. Chaiswing L, Cole MP, St Clair DK, et al. Oxidative damage precedes nitrative damage in adriamycin-induced cardiac mitochondrial injury. Toxicol Pathol. 2004;32(5):536-47. doi:10.1080/01926230490502601.
45. Prus Y, Sergienko I, Ansheles A, et al. Effect Of Chemotherapy On Myocardial Perfusion And Function. Atherosclerosis. 2019;287:e253. doi:10.1016/j.atherosclerosis.2019.06.779.
46. Mohan HK, Miles KA. Cost-effectiveness of 99mTc-sestamibi in predicting response to chemotherapy in patients with lung cancer: systematic review and meta-analysis. J Nucl Med. 2009;50(3):376-81. doi:10.2967/jnumed.108.055988.
47. Carboni GP. A novel clinical indicator using cardiac technetium-99m sestamibi kinetics for evaluating cardiotoxicity in cancer patients treated with multiagent chemotherapy. Am J Cardiovasc Dis. 2012;2(4):293-300.
48. Matsuo S, Nakajima K, Kinuya S. Evaluation of Cardiac Mitochondrial Function by a Nuclear Imaging Technique using Technetium-99m-MIBI Uptake Kinetics. Asia Ocean J Nucl Med Biol. 2013;1(1):39-43. doi:10.7508/aojnmb.2013.01.008.
49. Popat S, Smith IE. Therapy Insight: anthracyclines and trastuzumab–the optimal management of cardiotoxic side effects. Nat Clin Prac Oncol. 2008;5(6):324-35. doi:10.1038/ncponc1090.
50. McGowan JV, Chung R, Maulik A, et al. Anthracycline Chemotherapy and Cardiotoxicity. Cardiovasc Drugs Ther. 2017;31(1):63-75. doi:10.1007/s10557-016-6711-0.