ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

РОССИЙСКИЙ КАРДИОЛОГИЧЕСКИЙ ЖУРНАЛ

Russian Journal of Cardiology

SCIENTIFIC, PEER-REVIEWED MEDICAL JOURNAL

RUSSIAN SOCIETY OF CARDIOLOGY

IN ISSUE:

IN FOCUS:
Dyslipidemia. Atherosclerosis

№ 5 | 2020

РОССИЙСКОЕ КАРДИОЛОГИЧЕСКОЕ ОБЩЕСТВО

Russian Society of Cardiology

Scientific peer-reviewed medical journal

Mass media registration certificate № 017388 dated 06.04.1998

Periodicity — 12 issues per year
Circulation — 7 000 copies

The Journal is in the List of the leading scientific journals and publications of the Supreme Examination Board (VAK)

The Journal is included in Scopus, EBSCO, DOAJ

Russian Citation Index:
SCIENCE INDEX (2018) 3,054
Impact-factor (2018) 1,082

Complete versions of all issues are published: *www.elibrary.ru*

Instructions for authors: *https://russjcardiol.elpub.ru/jour/about/submissions#authorGuidelines*

Submit a manuscript: *www.russjcardiol.elpub.ru*

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Open Access

Printed: OneBook, Sam Poligraphist, Ltd. 129090, Moscow, Protopopovsky per., 6. www.onebook.ru

RUSSIAN JOURNAL OF CARDIOLOGY

№ 25 (5) 2020

founded in 1996

Editorial office:
115478, Moscow, a/ja 509
e-mail: cardiojournal@yandex.ru
Tel. +7 (985) 768 43 18

Publisher:
Silicea-Poligraf
e-mail: cardio.nauka@yandex.ru

https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-5

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3773

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Associations of polyphenols intake and the risk of dyslipidemia in the Siberian urban population

Batluk T. I., Denisova D. V., Berezovikova I. P., Shcherbakova L. V., Malyutina S. K., Ragino Yu. I.

Aim. To identify associations of polyphenols' (PP) consumption in general, as well as their classes with the risk of dyslipidemia in the Novosibirsk population aged 45-69 years.
Material and methods. In 2003-2005, as a part of the international project HAPIEE "Determinants of cardiovascular diseases in Eastern Europe: a multicenter cohort study", a population sample (n=9360) aged 45-69 years (mean age — 57,6 years) was examined in Novosibirsk. There were 4266 men and 5094 women. For the analysis of nutrition, a Food Frequency Questionnaire (FFQ) was used (141 product names). The content of PP and their classes was evaluated using the European database Phenol-Explorer 3.6. The food habits of the population were taken into account. The determination of total (TC) and high-density lipoprotein cholesterol (HDL-C) levels were carried out by enzymatic method. Hypercholesterolemia was established at TC >5,0 mmol/L (190 mg/dL). HDL-C <1,0 mmol/L in men and <1,2 mmol/L in women were considered as HDL-hypocholesterolemia. The concentration of low-density lipoprotein cholesterol (LDL-C) was calculated with the Friedewald formula (1972): TC-HDLC-TG/5. LDL-hypercholesterolemia was established at LDL-C <3,0 mmol/L.
Results. In comparison with the low PP consumption quartile, the odds for hypercholesterolemia in the highest consumption quartile for Other PP was 20% lower (OR 1,2, confidence interval (CI 1,01-0,14), p=0,033), for phenolic acids — 20% lower (OR 1,2 (CI 1,01-1,42), p=0,04) and for stilbenes — 37% lower (OR 1,37 (CI 1,15-1,64), p=0,001). The risk of HDL-hypocholesterolemia was lower in the quartile of high general PP consumption by 18% (OR 1,18 (CI 1,002-1,4), p=0,051), of phenolic acids by 32% (OR 1,32 (CI 1,11-1,57), p=0,001) and of other PP by 20% (OR 1,2 (CI 1,01-1,41), p=0,04). In comparison with the low PP consumption quartile, the odds for LDL-hypercholesterolemia in the high consumption quartile for Other PP decreased by 16% (OR 1,16 (CI 1,002-1,355), p=0,049), for lignans — by 33% (OR 1,33 (CI 1,14-1,56), p<0,001).
Conclusion. General intake of PP and their particular classes (phenolic acids, stilbenes, and Other PP) reduces the dyslipidemia risk in Siberian population.

Key words: polyphenols, blood lipids, population, dyslipidemia.

Relationships and Activities: the study was carried out as part of State Assignment № AAAA-A17-117112850280-2 and was supported by RF President grant for leading scientific schools (№ NS-2595.2020.7).

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Received: 01.03.2020
Revision Received: 02.04.2020
Accepted: 09.04.2020

For citation: Batluk T. I., Denisova D. V., Berezovikova I. P., Shcherbakova L. V., Malyutina S. K., Ragino Yu. I. Associations of polyphenols intake and the risk of dyslipidemia in the Siberian urban population. *Russian Journal of Cardiology.* 2020;25(5):3773. (In Russ.) doi:10.15829/1560-4071-2020-3773

Cardiovascular diseases keep the lead in the global mortality patterns [1]. The main causes of cardiovascular diseases (CVD) are non-modifiable (age, sex, family history) and modifiable (smoking, sedentary lifestyle, alcohol abuse, inappropriate diet) risk factors. The results of various multicenter studies show a high prevalence of CVD and their risk factors [2, 3]. For example, the observational study ESSE-RF revealed a high prevalence of hypercholesterolemia (HCE) in Russia — 57,6% (age group 25-64 years), with an increase to 74,5% in the age group 55-64 years [4].

Researchers from different countries pay great attention to studying the effect of diet on various cardiovascular risk factors, including changes in blood lipid levels. In recent years, interest has increased in assessing the impact of polyphenols' (PP) consumption on risk factors. Large population studies demonstrated that a high content of PP in the diet reduces blood lipids (NHANES, HAPIEE, Molisani, PREDIMED) [5-8]. Also, a PP rich diet influenced the lipid profile. For example, consumption of cocoa and cocoa-containing products (chocolate), olives and olive oil increases high-density lipoprotein cholesterol (HDL-C), while green tea lowers total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) [9-11].

Thus, most studies demonstrate a positive effect of PP consumption on blood lipids. The contribution of PP certain classes in the regions vary, depending on the geography and eating habits of the population, which also needs to be taken into account. However, there are still no large studies on the consumption of PP in Russia.

The aim of the study was to identify associations of polyphenols' (PP) consumption in general, as well as their classes with the risk of dyslipidemia in the Novosibirsk population aged 45-69 years.

Material and methods

As a part of the international project HAPIEE "Determinants of cardiovascular diseases in Eastern Europe: a multicenter cohort study", a population sample (n=9360) aged 45-69 years (mean age — 57,6 years) was examined in Novosibirsk. There were 4266 men and 5094 women. All participants signed informed consent. Local ethics committee approved this study. The levels of TC and HDL-C was determined by the enzymatic method using standard Biocon (Germany) kits using a biochemical analyzer Labsystem (Finland). HCE was established at TC >5,0 mmol/L (190 mg/dL). HDL-C <1,0 mmol/L in men and <1,2 mmol/L in women were considered as HDL-hypocholesterolemia. The concentration of LDL-C was calculated with the Friedewald formula (1972): TC-HDLC-TG/5. LDL-HCE was established at LDL-C <3,0 mmol/L.

Table 1

Consumption of various PP classes in groups with and without HCE

	Men				P (1-2)	Women				P (3-4)	P (1-3)	P (2-4)
	HCE- (1)		HCE+ (2)			HCE- (3)		HCE+ (4)				
	M (95% CI)*	Me (25%, 75%)	M (95% CI)*	Me (25%, 75%)		M (95% CI)*	Me (25%, 75%)	M (95% CI)*	Me (25%, 75%)			
Number of patients, n	722		3518			427		4623				
Total of polyphenols, mg	1283,4 (1236,1-1330,6)	1134 (869,2-1528)	1270,8 (1249,4-1292,1)	1118,8 (842,2-1537)		1196,7 (1137,9-1255,5)	1127 (799-1529,8)	1201,3 (1183,6-1219,1)	1064,9 (797,7-1441,5)			<0,001
Flavonoids, mg	865,5 (825-906,1)	716,3 (498,5-1108,5)	858,6 (840,2-876,9)	703,4 (494,4-1085,9)		843,8 (793,9-893,7)	748,1 (508,8-1099,6)	842,9 (827,8-857,9)	707,7 (494,7-1054,7)			
Phenolic acids, mg	277,4 (265,7-289,1)	267,4 (194,7-322,9)	272,6 (267,3-277,9)	254 (190,3-316,6)	0,045	231,8 (217-246,7)	215,7 (154,6-284,6)	235 (230,5-239,5)	203,9 (150-275,7)		<0,001	<0,001
Other polyphenols, mg	89,5 (87,2-91,8)	91,2 (72,3-109,2)	87,2 (86,2-88,3)	86,7 (66,1-107,1)	0,01	66,2 (63,3-69,1)	65,2 (43,2-86,9)	66 (65,1-66,9)	60,5 (44,6-84,2)		<0,001	<0,001
Lignans mg	43,1 (41,1-45,1)	39 (28,4-53,7)	45 (44,1-45,9)	39,5 (27,2-55,8)		47,7 (44,9-50,6)	43,5 (29,8-61,4)	50,4 (49,6-51,3)	44,5 (31-61,6)		0,003	<0,001
Stilbene mg	7,7 (7,4-8,0)	6,8 (6,7-12,1)	7,2 (7-7,3)	6,8 (6,7-7,1)	0,002	6,9 (6,6-7,2)	6,8 (6,7-7,1)	6,8 (6,7-6,9)	6,7 (6,8-7)			0,031

Note: p — Mann-Whitney U-test, * — data are standardized by age.

For the analysis of nutrition, a Food Frequency Questionnaire (FFQ) was used (141 product names). The content of PP and their classes was evaluated using the European database Phenol-Explorer 3.6. [13]. The eating habits of the population were taken into account. Dietary survey was not performed for 70 people due to technical reasons.

Statistical analysis was performed using the software package SPSS (v. 17). Normality of distribution was analyzed. We calculated age-standardized arithmetic mean value (M) and 95% confidence interval (CI). The data in the tables and text are presented as M (95% CI). Since the distribution of variables was non-normal, the medians (Me) and the interquartile range (25%, 75%) were calculated. Mann-Whitney U-test was used for the comparison of variation series of two independent groups. Risk was assessed by calculating OR (95% CI). Differences were considered significant at $p<0,05$.

Results

We divided all participants on the following groups: with HCE (HCE+) and without HCE (HCE-); HDL-hypocholesterolemia+ and HDL-hypocholesterolemia; LDL-HCE+ and LDL-HCE-.

We revealed that men without HCE had a higher content of phenolic acids, stilbenes and Other PPin the diet. The content of PP classes in diets of women with/without HCE was the same (Table 1). Sex differences were observed in the consumption of phenolic acids, Other PP, and lignans both in groups with and without HCE. The total amount of PP consumed was greater in men with HCE than in women.

The consumption of PP rich products characteristic of the Siberian population (cereals, pulses, white/brown bread, vegetables, potatoes, fresh fruits and berries, dried fruits, sweets (not including sugar), tea, coffee, alcohol, vegetable oil) was assessed. Men and women had different eating habits, which leads to differences in the consumption of most foods. It is worth noting that in men, the consumption of potatoes, white bread, brown bread, tea, as well as alcohol was significantly higher than in women, regardless of HCE. Women were more likely to eat fruits and berries were in all studied groups, in contrast to men ($p<0,001$). Alcohol consumption in HCE- men was 12,3 (10,9-13,7) ml/day, in HCE+ men — 12,8 (12,2-13,5) ml/day. In women, this parameter amounted to 2,3 (1,9-2,7) ml/day and 1,9 (1,8-2) ml/day, respectively ($p<0,001$).

To assess the HCE risk in relation to the consumption of PP and their certain classes, an odds ratio was calculated. We revealed that for the entire population, the odds of developing HCE in the high consumption quartile of other PP was 20% less than in the low consumption quartile: OR 1,2 (CI 1,01-

Table 2

Consumption of various PP classes in groups with and without HDL-hypocholesterolemia

	Men				P (1-2)	Women				P (3-4)	P (1-3)	P (2-4)
	HDL-hypocholesterolemia- (1)		HDL-hypocholesterolemia+ (2)			HDL-hypocholesterolemia- (3)		HDL-hypocholesterolemia+ (4)				
	M (95% CI)*	Me (25%, 75%)	M (95% CI)*	Me (25%, 75%)		M (95% CI)*	Me (25%, 75%)	M (95% CI)*	Me (25%, 75%)			
Number of patients, n	4019		222			4034		1015				
Total of polyphenols, mg	1275,2 (1255,2-1295,2)	1122,2 (847,6-1534,7)	1232,2 (1147,2-1317,3)	1110,3 (824,2-1566,2)		1207,2 (1188,2-1226,1)	1073,5 (804,7-1457,3)	1176,5 (1138,6-1214,3)	1051,6 (766,7-1420,2)		<0,001	0,045
Flavonoids, mg	860,4 (843,2-877,5)	706,6 (495,7-1087,6)	848,5 (775,5-921,6)	690,7 (490,3-1116,6)		846,6 (830,5-862,7)	712,1 (499,4-1064,6)	826,6 (790,5-860,7)	697,2 (485-1038,6)	0,04		
Phenolic acids, mg	274,6 (269,7-279,6)	257,3 (191,5-318,3)	251,1 (230-272,2)	243,7 (171,1-308,1)	0,046	237 (232,2-241,8)	206,7 (151,8-278,4)	225,7 (216,1-235,2)	201 (145,1-272,2)		<0,001	<0,001
Other polyphenols, mg	88 (87-88,9)	87,9 (68-107,3)	81,4 (77,4-85,5)	83,4 (54,7-106,8)	0,022	66,2 (65,3-67,2)	60,9 (44,9-85,2)	65,3 (63,4-67,1)	59,8 (43,6-83,3)		<0,001	<0,001
Lignans mg	44,7 (43,9-45,6)	39,5 (27,3-55,1)	43,8 (40,3-47,4)	39,1 (28,5-56,3)		50,3 (49,4-51,2)	44,4 (31-61,6)	49,8 (48-51,7)	44,3 (30,4-61,3)		<0,001	0,009
Stilbene mg	7,3 (7,1-7,4)	6,8 (6,7-7,3)	7,1 (6,6-7,7)	6,8 (6,7-7,5)		6,8 (6,7-6,9)	6,8 (6,7-7)	6,8 (6,6-7,1)	6,8 (6,7-7)			

Note: p — Mann-Whitney U-test, * — data are standardized by age.

Table 3

Consumption of various PP classes in groups with and without LDL-HCE

	Men				P (1-2)	Women				P (3-4)	P (1-3)	P (2-4)
	LDL-HCE- (1)		LDL-HCE+ (2)			LDL-HCE- (3)		LDL-HCE+ (4)				
	M (95% CI)*	Me (25%, 75%)	M (95% CI)*	Me (25%, 75%)		M (95% CI)*	Me (25%, 75%)	M (95% CI)*	Me (25%, 75%)			
Number of patients, n	932		3309			667		4382				
Total of polyphenols, mg	1262,3 (1220,7-1303,9)	1124 (853-1509,9)	1275,6 (1253,6-1297,7)	1120,6 (844,5-1542,7)		1184,2 (1137-1231,4)	1098,1 (803,6-1461,9)	1203,4 (1185,1-1221,6)	1064,2 (796,9-1449,4)			<0,001
Flavonoids, mg	846,5 (810,8-882,2)	707,9 (482,2-1081,8)	863,3 (844,4-882,3)	705,5 (499,9-1089,7)		829,8 (789,8-869,8)	732,5 (501,8-1061,4)	844,9 (829,4-860,4)	708,2 (494,5-1061,9)			
Phenolic acids, mg	276,5 (266,1-286,8)	262,3 (191-321)	272,5 (267-277,9)	254,8 (190,7-316,6)		321,1 (219-243)	210,9 (155,9-280,5)	235,3 (230,7-239,9)	204,1 (149,2-276,2)		<0,001	<0,001
Other polyphenols, mg	89,1 (87,1-91,1)	89,7 (70,4-108,3)	87,2 (86,1-88,2)	86,6 (66,1-107,1)	0,022	66,6 (64,2-68,9)	66,9 (46,4-85,9)	65,9 (65-66,8)	60,5 (44,5-84,2)		<0,001	<0,001
Lignans mg	42,6 (40,9-44,3)	38,2 (27,2-53,5)	45,3 (44,4-46,2)	39,7 (27,5-56)		49,5 (47,2-51,8)	44,3 (31,1-62,1)	50,3 (49,4-51,2)	44,4 (30,9-61,5)		<0,001	<0,001
Stilbene mg	7,5 (7,3-7,8)	6,8 (6,7-12,7)	7,2 (7-7,3)	6,8 (6,7-7,1)	0,046	7,1 (6,8-7,3)	6,8 (6,7-7,1)	6,8 (6,7-6,9)	6,8 (6,7-7)	0,024		

Note: p — Mann-Whitney U-test, * — data are standardized by age.

0,14), p=0,033. In the high consumption quartile of phenolic acids, it was also 20% less: OR 1,2 (CI 1,01-1,42), p=0,04. In the high consumption quartile of stilbenes, the risk of HCE was reduced by 37%: OR 1,37 (CI 1,15-1,64), p=0,001.

Sex differences in the odds of developing HCE were identified. For men in the high consumption quartile of stilbenes, the risk was reduced by 55%, compared with the low consumption quartile: OR 1,55 (CI 1,21-1,97), p<0,001; in the high consumption quartile of Other PP, it decreases by 28%: OR 1,28 (CI 1,02-1,6), p=0,034. For women, HCE risk was independent of PP amount consumed.

Table 2 presents data for groups with/without HDL-hypocholesterolemia.

Men with HDL-hypocholesterolemia consumed less phenolic acids and Other PP. HDL-hypocholesterolemia+ women were less likely to consume flavonoids compared to the HDL-hypocholesterolemia- group. Sex differences were observed in all groups regarding the consumption of both PP in general and their certain classes, except for flavonoids and stilbenes (Table 2).

HDL-hypocholesterolemia- men had higher consumption of white bread, vegetables, coffee and alcohol compared with HDL-hypocholesterolemia+. Women without HDL-hypocholesterolemia were more likely to consume coffee, alcohol and sweets, not including sugar.

Men consumed white bread, potatoes, sweets, not including sugar and alcohol significantly more than women, regardless of the presence of HDL-hypocholesterolemia. On the contrary, women preferred fruits, berries, dried and canned fruits.

In the highest consumption quartile of PP for the entire population, the risk of HDL-hypocholesterolemia was 18% lower than in the low consumption quartile: OR 1,18 (CI 1,002-1,4), p=0,051; for women — 23% lower: OR 1,23 (CI 1,02-1,5), p=0,035. In the high consumption quartile of phenolic acids for the entire population, the risk decreases by 32%: OR 1,32 (CI 1,11-1,57), p=0,001, for women — by 27%: OR 1,27 (CI 1,04 -1,54), p=0,021. In the high consumption quartile of Other PP for the entire population, risk decreases by 20%: OR 1,2 (CI 1,01-1,41), p=0,04.

Table 3 presents the data in groups with/without LDL-HCE. Regardless of LDL-HCE, men had a high consumption of Other PP (p<0,001), while women were more likely to consume lignans (p<0,001).

We detected a high consumption of white bread, potatoes and alcohol in all groups in men compared with women. Women were significantly more likely to consume fresh fruits and berries (205,4 (189,5-221,4) g/day and 230,1 (223,9-236,2) g/day in groups

without LDL-HCE and with LDL-HCE), compared with men (155,4 (144,5-166,3) g/day and 175,5 (169,7-181,3) g/day, respectively (p<0,001)).

The risk of LDL-HCE in the entire population was reduced by 16% in the high consumption quartile of other PP, compared with the low consumption quartile: OR 1,16 (CI 1,002-1,355), p=0,049. In men, the odds of fourth quartile of stilbene consumption decreased by 30% compared to the first quartile: OR 1,3 (CI 1,05-1,610), p=0,018; in women — by 31%: OR 1,31 (CI 1,038-1,66), p=0,024; in the entire population — by 33%: OR 1,33 (CI 1,14-1,56), p<0,001).

Discussion

This study identified associations between the consumption of PP, their certain classes and the risk of dyslipidemia in the Novosibirsk population: HCE, HDL-hypocholesterolemia and LDL-HCE. The data in the groups with/without HCE and with/without LDL-HCE obtained by us were partially consistent with the Moli-sani study, where high PP consumption was associated with lower levels of TC and LDL-C [8], and consistent with the meta-analysis of resveratrol consumption, which significantly reduced the concentration of TC and LDL-C in the blood [14]. However, there were conflicting data regarding resveratrol, where it did not affect the lipid profile [15]. It should also take into account the different stilbene sources (in particular, resveratrol) in the Novosibirsk population and in others. The main stilbene sources in Siberia for men and women are vegetables and fruits. In other populations, for example, in the Polish HAPIEE cohort, the main sources of stilbenes were alcohol (beer and wine), and in the SUN cohort, red wine and grapes [16, 17].

In people without/with HDL-hypocholesterolemia, PP in general, phenolic acids and Other PP make a greater contribution to reducing HDL-hypocholesterolemia risk. In the PREDIMED study, the level of HDL-C increased in parallel with an increase in the total urine excretion of PP [18]. However, methods for estimating the PP consumption varied. According to studies by Kim K, et al., Sohrab G, et al., an increase in the HDL-C levels was affected by the consumption of flavonoids [19, 20]. At the same time, our data did not correspond with the data of the A Nationwide Study (Polish WOBASZ II cohort): in men, a higher consumption of PP was significantly associated with low HDL-C levels (OR 1,410; 95% CI 1,080-1,842). According to the authors, the results can be explained by the eating habits of both sexes and the difference in normal ranges for HDL-C [21].

It is quite difficult to compare the results of studies with different aims. Many authors have studied specific products indicating their effect on the lipid profile. However, one cannot ignore that, although the products are sources of certain PP classes, they also contain other classes of PP and other substances. Other authors studied PP consumption in relation to the metabolic syndrome, which in turn included blood lipid parameters. A little number of researchers studied only consumption and a certain risk factor, as shown in our study.

Thus, associations of PP consumption and blood lipid profile in the Novosibirsk population were identified. Consumption of PP in general, and especially phenolic acids, stilbenes, and Other PP reduced the risk of dyslipidemia. Despite the fact that the obtained data were consistent with the other studies, there are many conflicting results for different populations, which suggests the need for further studies.

Relationships and Activities: the study was carried out as part of State Assignment № AAAA-A17-117112850280-2 and was supported by RF President grant for leading scientific schools (№ NS-2595.2020.7).

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3867

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Physical rehabilitation after acute myocardial infarction: focus on body weight

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Aim. To study the effectiveness of 1-year exercise training (ET) after acute myocardial infarction (AMI) during outpatient cardiac rehabilitation in patients with different body mass index (BMI).

Material and methods. The study included 312 patients after AMI, who were randomized into four groups depending on BMI: patients who used ET program with BMI <30 kg/m^2 (group 1 (n=78)) and BMI ≥30 kg/m^2 (group 2 (n=78)); patients who did not use ET program with BMI <30 kg/m^2 (group 3 (n=78)) and BMI ≥30 kg/m^2 (group 4 (n=78)). ET of moderate intensity (60% of the threshold value) was carried out 3 times a week for a year.

Results. In patients with obesity, ET was associated with decrease of blood pressure by 3,3/3,6% (p<0,01 for each) and BMI by 7,7% (p<0,001), while there was an increase by 4,2/3,6% (p<0,05 for each) and 2,1% (p<0,05), respectively, in obese patients without ET. In patients without obesity, ET was associated only with BMI decrease by 3,3% (p<0,01), while in patients without obesity and ET it did not change. Daily physical activity after ET increased regardless of BMI, and without ET it decreased in obese patients. ET was associated with the increase of duration and intensity of training in non-obese patients by 39,2% (p<0,001) and 47,1% (p<0,001), respectively; in obese patients — by 23,8% (p<0,001) and 26,5% (p<0,001), respectively. In control groups it has not changed. After ET, with any BMI, the levels of low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) decreased, and the high-density lipoprotein-cholesterol (HDL-C) increased. In the control groups, the concentration of TG increased, and with obesity there was also an increase in LDL-C and a decrease in HDL-C. Against the background of ET, the fibrinogen values decreased with any BMI, in contrast to the control groups. After 1-year ET, number of cardiovascular events (CVE) significantly decreased in non-obese patients by 37,5% (p<0,05) and in obese ones by 28,6% (p<0,05).

Conclusion. Long-term aerobic ET in patients with any BMI reduced cardiovascular risk factors and the risk of CVE. At the same time, with concomitant obesity, the maximum effect of cardiac rehabilitation was not achieved, which confirms the importance of controlling BMI in patients after AMI.

Key words: myocardial infarction, cardiac rehabilitation, exercise training, physical activity, obesity, body weight.

Relationships and Activities: none.

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Received: 28.04.2020
Revision Received: 05.05.2020
Accepted: 08.05.2020

For citation: Bubnova M. G., Aronov D. M. Physical rehabilitation after acute myocardial infarction: focus on body weight. *Russian Journal of Cardiology*. 2020;25(5):3867. (In Russ.) doi:10.15829/1560-4071-2020-3867

Cardiovascular diseases (CVD) is the leading cause of mortality in all countries of the world, including Russia. The development of CVD is closely linked to behavioral risk factors (RF), such as smoking, unhealthy diets, low physical activity, hypertension (HTN) and obesity. In all countries, the obesity epidemic has been observed over the past decade [1]. Among patients involved in cardiac rehabilitation, approximately 80% are overweight or obese [2]. The average body mass index (BMI) of rehabilitated patients over 10 years increased from 28,5 kg/m^2 to 30,1 kg/m^2 [3].

High efficiency of the cardiac rehabilitation programs based on systematic exercise training (ET) of moderate intensity has been proven to modulate cardiovascular RF, improve the quality of life (QOL), and reduce cardiovascular and all-cause mortality in patients with coronary artery disease (CAD) [4]. The beneficial effect of cardiac rehabilitation on the disease outcomes and the survival of patients with acute myocardial infarction (AMI) remains urgent in the period of active myocardial revascularization and therapy with statins and antiplatelet agents [5].

The negative effects of obesity on the CAD progression and the mortality risk after AMI have been demonstrated in studies [6, 7]. The question of the effectiveness of cardiac rehabilitation programs and systematic ET in obese patients remains open. This is especially true in the context of the obesity paradox. According to number of studies, patients with history of AMI and/or myocardial revascularization, suffering from peripheral atherosclerosis or heart failure (HF), had a U-shaped relationship between BMI and all-cause mortality risk (with a nadir in the range of BMI 26,5-<35 kg/m^2) [8-10]. The protective effect of large BMI values is obviously more often manifested in elderly patients with severe CVD and undernutrition [10].

The relationship of obesity with the prognosis in obesity paradox is affected, for example, by physical activity. According to the European Prospective Investigation into Cancer and Nutrition Study (EPIC) with 334,161 men and women (12,4-year follow-up), the negative impact of physical inactivity on patient mortality was more (almost 2 times) than high BMI (⩾30 kg/m^2) [11]. It should be noted that if patients after AMI and cardiac surgery are not involved in cardiac rehabilitation programs, the percentage of physically active ones among them remains low [12].

To aim was to study the effectiveness of 1-year ET after AMI during outpatient cardiac rehabilitation in patients with different BMI.

Material and methods

The study included 312 patients after AMI (>3 weeks) and percutaneous coronary interventions (PCI) at the age of <60 years for men and <55 years for women (mean age 52,1±3,9 years). All patients signed informed consent. There were following exclusion criteria: inadequately controlled HTN, aortic or left ventricular (LV) aneurysm with thrombosis, serious arrhythmias, NYHA class III-IV HF, BMI ⩾40 kg/m^2, moderate/severe diabetes and other severe comorbidities. This study was performed in accordance with the Helsinki declaration and Good Clinical Practice standards. The ethics committee approved this study.

Patients received standard drug therapy. They were randomized into four groups depending on BMI: experimental — patients who used ET program with BMI <30 kg/m^2 (group 1 (n=78)) and BMI ⩾30 kg/m^2 (group 2 (n=78)); control — patients who did not use ET program with BMI <30 kg/m^2 (group 3 (n=78)) and BMI ⩾30 kg/m^2 (group 4 (n=78)). To dynamically analyze certain parameters during rehabilitation, patients of the experimental group without obesity were divided into two subgroups depending on BMI: BMI <25 kg/m^2 (n=32) and 25,0-29,9 kg/m^2 (n=46). The follow-up period lasted 12 months.

Physical rehabilitation program included a set of gymnastic exercises of moderate intensity (60% of the threshold value according to cycle ergometer test (CET) by Aronov DM). There were group exercise classes (up to 10-12 people) lasting 60 minutes 3 times/week.

Clinical examination included collecting medical history, physical exam, measurement of blood pressure (BP), heart rate (HR) and BMI. Resting electrocardiography (ECG) was performed. CET using cycle ergometer (General Electric, USA) was performed until the generally accepted clinical or ECG stopping criteria (WHO, 1973, Aronov DM, 1995), or submaximal HR (Andersen KL, 1971) with the analysis of the duration (min) and power (W) of physical activity, resting and maximum HR (max) during CET (beats/min), resting double product (DP, CU) and DPmax. (Heart rate x systolic BP (SBP)/100), HR (beats x min) and DP (CU x min) growth during CET, the total physical work performed (A, kJ). Echocardiography was performed according to a standard method (Agilent, USA) with an assessment of the maximum anterior-posterior dimension of left atrium (LA, cm), LV end-diastolic dimension (EDD) and end-systolic dimension (ESD), LV ejection fraction (EF) by the Simpson's biplane method.

We determined levels of blood lipids (mmol/L): total cholesterol (TC), triglycerides (TG), high

Table 1

Characteristics of groups at the beginning of the study

Parameter	Experimental groups		Control groups		P	
	Group 1 Obesity- (n=78)	Group 2 Obesity+ (n=78)	Group 3 Obesity- (n=78)	Group 4 Obesity+ (n=78)	Group 1 vs Group 3	Group 2 vs Group 4
Age, years (M±m)	51,9±7,9	51,7±6,8	52,2±7,2	52,6±6,7	NS	NS
Men/Women, n (%)	73 (93,6)/5 (6,4)	75 (96,2)/3 (3,8)	74 (94,9)/4 (5,1)	73 (93,6)/5 (6,4)	NS	NS
History of AMI, n (%)	40 (51,3)	42 (53,8)	41 (52,6)	42 (53,8)	NS	NS
Hypertension, n (%)	35 (44,9)	52 (66,7)*	37 (47,4)	51 (65,4)*	NS	NS
Class I-II HF, n (%)	35 (44,9)	31 (39,7)	35 (44,9)	29 (37,2)	NS	NS
Type 2 diabetes, n (%)	3 (3,8)	11 (14,1)*	2 (2,6)	10 (12,8)*	NS	NS
SBP, mm Hg (M±m)	124,2±17,1	129,1±16,9	123,5±15,3	127,4±16,8	NS	NS
DBP, mm Hg (M±m)	82,1±11,0	85,3±10,3	80,2±9,1	84,2±10,4	NS	NS
Heart rate, bpm (M±m)	73,3±8,1	75,5±9,2	73,8±9,7	76,4±10,7	NS	NS
BMI, kg/m^2 (M±m)	26,6±1,6	32,2±1,6*	26,9±2,1	32,4±1,8*	NS	NS
LVEF, % (M±m)	57,5±8,8	55,6±9,4	57,3±8,7	56,7±9,0	NS	NS

Note: NS — not significant, * — p<0,05 — significance of differences between the groups "group 1 — group 2" and "group 3 — group 4".
Abbreviation: DBP — diastolic blood pressure, BMI — body mass index, LVEF — left ventriclular ejection fraction, AMI — acute myocardial infarction, SBP — systolic blood pressure, HF — heart failure.

density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) by Friedwald formula (WT Friedwald, et al. (1972)) with TG ⩽4,5 mmol/L. Using ACL coagulation analyzer (Instrumentation Laboratory, Italy), concentration of fibrinogen (g/L) and prothrombin index (%) was identified. Glucose levels (mmol/L) were assessed on an Airon-200 analyzer (Italy).

QOL was assessed was evaluated using questionnaire of Aronov DM and Zaitsev VP (1982) [13]. Daily physical activity was assessed using the ODA23+ questionnaire: <62 points — low physical activity; 62-84 points — moderate activity; >84 points — high activity. Patients kept diaries recording angina episodes.

We analyzed the total number of temporary disability days during the year. The primary endpoint included sudden cardiac death, recurrent AMI, and stroke.

Statistics. Analysis of the results was performed using the Statistical Analysis System (SAS, version 6.12). The mean and standard error (M±m) were calculated. For indicators measured on a nominal or ordinal scale, the frequency of detecting various gradations in percent was estimated. The significance of differences between groups was evaluated by Student's t-test for independent samples or paired t-test for dependent variables. For comparative analysis of more than two groups, analysis of variance (ANOVA) was used. Different proportions were compared using the chi-squared test. Differences were considered significant at p<0,05.

Results

Obese patients in both groups (groups 2 and 4) were initially more likely to suffer from HTN and type 2 diabetes than non-obese patients (groups 1 and 3) (Table 1). There were no significant differences between the experimental and control groups without (groups 1-3) and with obesity (groups 2-4).

Changes of cardiovascular RF. Office BP in patients prior to inclusion in the study were within <140/90 mm Hg. After 12 months in non-obese patients of the experimental and control groups, BP levels did not change. In obese patients of the experimental group, SBP significantly decreased by 3,3% (p<0,01) and diastolic BP (DBP) by 3,6% (p<0,01), while patients of the control group, on the contrary, had increase by 4,2% (p<0,05) and 3,6% (p<0,05), respectively.

With ET, a significant decrease in BMI was observed in patients with (by 7,7%, p<0,001) and without obesity (by 3,3%, p<0,01). Moreover, BMI did not change in trained patients with normal body weight (BMI <25,0 kg/m^2) and significantly decreased by 2,9% (from 27,1±1,4 to 26,3±1,5 kg/m^2, p<0,001) in trained patients with

Table 2

Changes of exercise tolerance before and after 1-year rehabilitation program in patients after AMI with different BMI

Parameter (M±m)	Точка исследования	Experimental groups			Control groups		
		Group 1 Obesity- (n=78)	Group 1 Obesity- (n=78)	P	Group 3 Obesity- (n=78)	Group 4 Obesity+ (n=78)	P
Physical activity, points	Initially	55,1±9,4	52,8±10,2	NS	53,2±11,4	51,5±11,3	NS
	12 months after	72,9±8,2	62,2±7,1	<0,05	57,1±9,5**	48,1±11,8*	NS
P		<0,001	<0,05		NS	<0,05	
Walking, km/day	Initially	4,0±1,8	3,6±1,3	NS	3,8±1,5	3,5±1,3	NS
	12 months after	5,8±1,1	4,4±1,3	<0,05	3,8±0,9*	2,8±1,1*	NS
P		<0,01	<0,05		NS	<0,05	
Power of physical activity, W	Initially	76,3±18,1	83,4±18,7	NS	80,2±20,1	87,1±17,9	NS
	12 months after	112,4±16,2	105,2±20,3	NS	85±18,9*	87±19,8*	NS
P		<0,001	<0,001		NS	NS	
Duration of physical activity, min	Initially	9,4±2,9	10,2±3,3	NS	9,8±2,9	10,6±3,1	NS
	12 months after	13,1±3,9	12,6±3,1	NS	10,4±3,9**	10,6±3,3*	NS
P		<0,001	<0,001		NS	NS	

Note: NS — not significant, * — p<0,01 — significance of differences between the groups “group 1 — group 3” and “group 2 — group 4”.

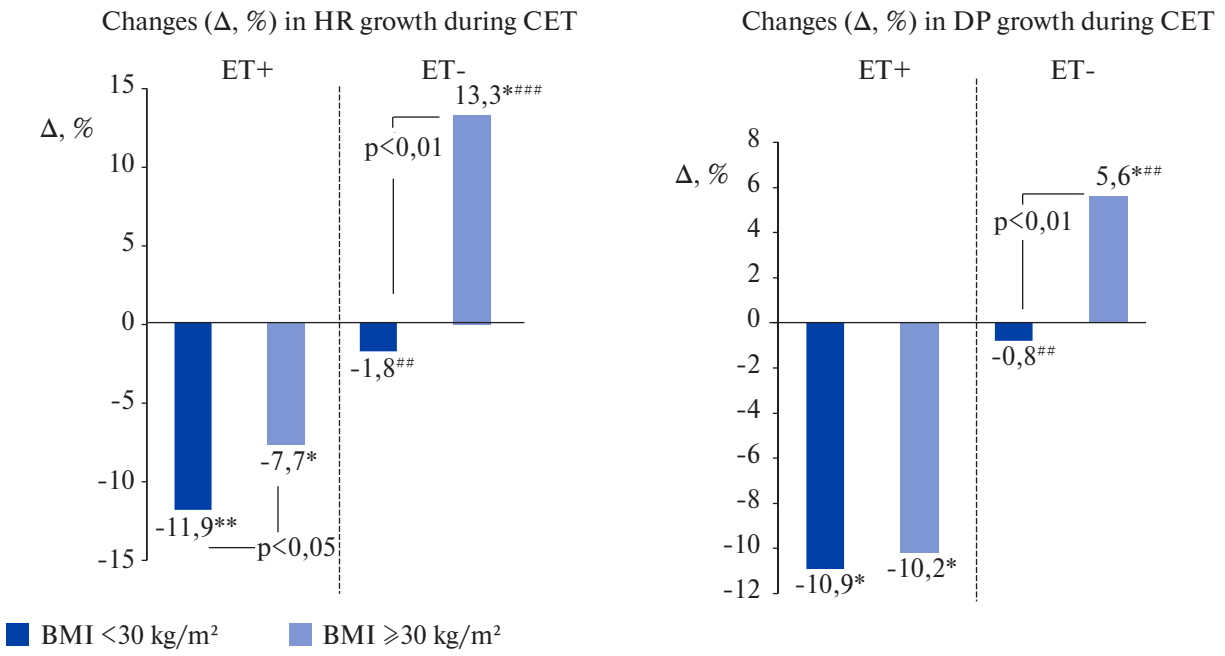

Figure 1. Changes (Δ, %) in HR and DP growth during CET in patients after AMI with/without 1-year regular ET with different BMI.
Note: * — P<0,05, ** — P<0,01 — in relation to initial value, # — P<0,05, ## — P<0,01, ### — P<0,001 — comparison of the experimental (ET+) group and the control group (ET-) among patients without obesity (BMI <30 kg/m^2) or with obesity (BMI ⩾30 kg/m^2); P<0,05, P<0,01 — intragroup comparison of non-obese (BMI <30 kg/m^2) and obese patients (BMI ⩾30 kg/m^2).

overweight (BMI 25,0-29,9 kg/m^2). In the control groups, BMI did not change in patients without obesity and significantly increased (by 2,1%, p<0,05, to 33,1±2,2 kg/m^2) in obese patients.

Initially, all patients had a low level of daily physical activity (Table 2). After 12 months of ET, it increased to an average level in obese patients (by 16,5%, p<0,05) and to a greater extent in non-

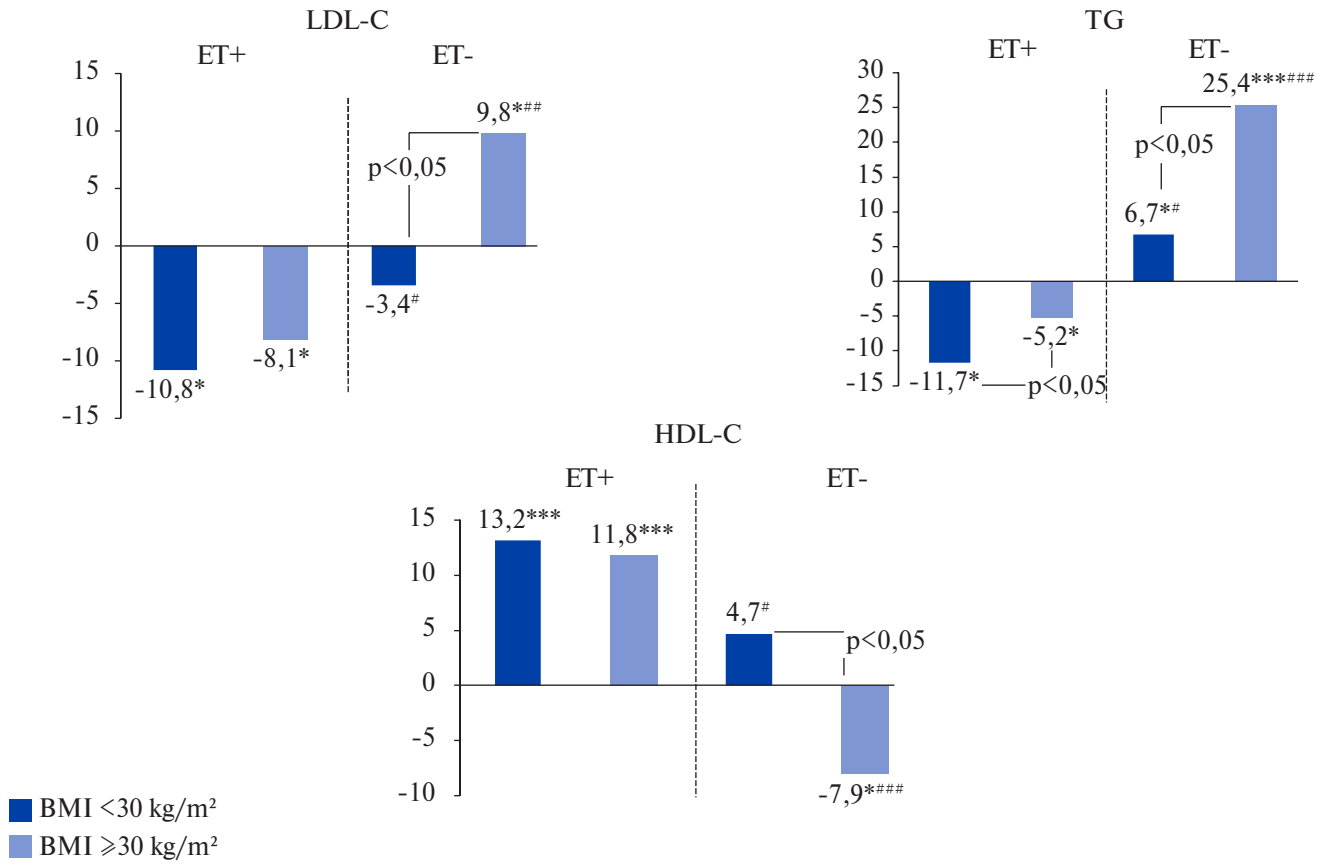

Figure 2. Changes (Δ, %) in blood lipids and lipoproteins in patients after AMI with/without 1-year regular ET with different BMI.
Note: * — P<0,05, ** — P<0,01 — in relation to initial value, # — P<0,05, ## — P<0,01, ### — P<0,001 — comparison of the experimental (ET+) group and the control group (ET-) among patients without obesity (BMI <30 kg/m^2) or with obesity (BMI ⩾30 kg/m^2); P<0,05, P<0,01 — intragroup comparison of non-obese (BMI <30 kg/m^2) and obese patients (BMI ⩾30 kg/m^2).

obese patients (by 32,3%, p<0,001). In control groups with obese patients, the level of physical activity did not change, while in obese patients it significantly decreased (6,1%, p<0,05). The distance traveled increased in non-obese patients by 1,8 km (p<0,01) and to a lesser extent in obese patients — by 0,8 km (p<0.05), whereas in control groups it did not change in non-obese patients and significantly decreased by 0,7 km (p<0,05) in obese patients.

Exercise tolerance changes. Patients included in the study did not initially differ in exercise tolerance having moderate results on CET (Table 2). After 12 months of ET, patients with both BMI <30 kg/m^2 and BMI ⩾30 kg/m^2 had a significant increase in exercise tolerance: power of physical activity increased by 47,1% (p<0,001) and 26,5% (p<0,001), respectively (p<0,005 between groups), and the duration by 39,2% (p<0,001) and 23,8% (p<0,001; p<0,01 between groups) This was accompanied by a significant increase in the total physical work in non-obese patients by 63,3% (p<0,001) and in obese ones by 46,8% (p<0,001; p<0,05 between groups).

There was a decrease in average HR and DP growth during CET (Figure 1). Load threshold on CET was increased in non-obese patients by 13,7% (p<0,05) and obese ones by 10,6% (p<0,05) without significant differences between them.

In untrained patients without obesity, the studied indicators of exercise tolerance did not change (Figure 1). However, obese patients, on the contrary, needed more oxygen and an increase in hemodynamic load (HR and DP growth during CET) to achieve initial values.

Changes of echocardiography. No initial differences in echocardiographic parameters between groups were found. With 1-year ET, there was a small but significant decrease in LV ESD in patients without obesity by 3,9% (p<0,05) and with obesity by 3,2% (p<0,05). LVEF increased by 7,3% (p<0,01) and 5,7% (p<0,01), respectively. EDD and LA dimension did not changed. In trained patients with a BMI <25 kg/m^2, LVEF increased by

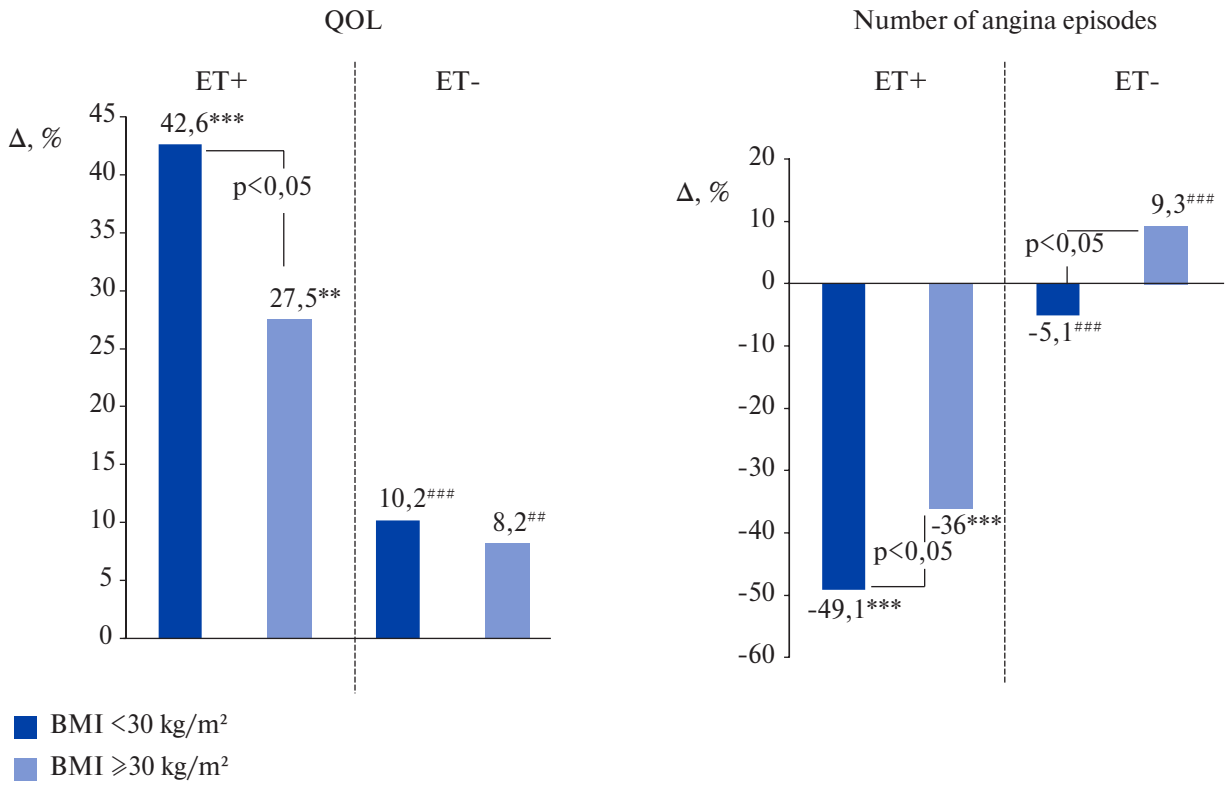

Figure 3. Changes (Δ, %) in QOL and number of angina episodes in patients after AMI with/without 1-year regular ET with different BMI.
Note: * — P<0,05, ** — P<0,01 — in relation to initial value, # — P<0,05, ## — P<0,01 , ### — P<0,001 — comparison of the experimental (ET+) group and the control group (ET-) among patients without obesity (BMI <30 kg/m^2) or with obesity (BMI ⩾30 kg/m^2); P<0,05, P<0,01 — intragroup comparison of non-obese (BMI <30 kg/m^2) and obese patients (BMI ⩾30 kg/m^2).

7,8% (p<0,05) and with a BMI of 25,0-29,9 kg/m^2 — by 6,7% (p<0,05).

Without ET, patients without and with obesity did not have favorable echocardiographic changes after 12 months. On the contrary, obese patients had a slight increase in LA dimension (by 4,1%, p<0,05).

Changes of atherothrombogenic parameters. Blood glucose levels in all groups was within normal limits and did not changed for 12 months. After ET, the fibrinogen concentration significantly decreased: in patients without obesity — by 18,9% (from 3,7±1,1 g/L to 3,0±0,4 g/L, p<0,05) and with obesity — by 21,6% (from 3,7±1,3 g/L to 2,9±0,5 g/L, p<0,05). In control groups, such positive dynamics were not recorded (without obesity — from 3,7±1,2 g/L to 3,5±0,8 g/L; with obesity — from 3,6±0,8 g/L to 3,8±0,6 g/L, respectively). The prothrombin index increased only in the control groups equally: in patients without obesity by 8,1% (p<0,05) and with obesity by 8,6% (p<0,01).

All trained patients had a favorable change in lipid panel: LDL-C and TG levels significantly decreased; HDL-C concentrations increased (Figure 2). In control group with non-obese patients, only the TG concentration increased moderately, and with obese patients, the levels of LDL-C and TG increased and HDL-C decreased (Figure 2).

Changes of QOL and clinical state. In both experimental groups, QOL parameters improved, especially significant in patients with BMI <30 kg/m^2 (Figure 3). In two control groups, QOL was not changed.

In trained patients with any BMI, a decrease in the number of angina episodes was observed, but was more pronounced in non-obese subjects (Figure 3). Moreover, in trained patients with normal body weight, the number of angina episodes decreased by 54,6% (p<0,001) and with overweight — by 43,5% (p<0,001). In the control groups, obese patients had significantly more angina episodes than non-obese ones.

The total number of temporary disability days in trained non-obese patients was 162 (2,1 per 1 patient) and obese ones — 250 (3,2 per 1 patient); in the control groups — 258 (3,3 per 1 patient) and 384 days (4,9 per 1 patient), respectively. With ET, the number of temporary disability days decreased in patients without obesity by 96 days

(by 1,1 per 1 patient, p<0,05) and with obesity by 134 days (by 1,7 per 1 patient, p<0,05). Moreover, patients with obesity had higher total number of temporary disability days than non-obese patients in experimental (by 88 days totally or 1,1 per 1 patient) and control groups (by 126 days totally or 1,6 per 1 patient). The total number of temporary disability days in trained patients with BMI <25 kg/m^2 was 187 days (2,4 per 1 patient) and with BMI of 25,0-29,9 kg/m^2 — 132 days (1,7 per 1 patient).

After 12-month ET, the primary endpoint in patients without obesity was recorded in 2 cases and with obesity — in 4 cases, and in the control groups, respectively, in 8 and 9 cases. Due to an exacerbation of CAD, there were 8 hospitalizations in trained patients without obesity and 11 in obese patients, and 8 and 12 hospitalizations in non-trained patients, respectively. The total number of all cardiovascular events (CVE) (primary endpoint + hospitalization) was 10 in trained patients without obesity and 15 with obesity; in the control groups, 16 and 21, respectively. With ET, there were reduction of all CVE in patients without obesity (comparison of the experimental and control groups) by 37,5% (p<0,05) and in patients with obesity by 28,6% (p<0,05). The total number of all CVE in trained patients with a BMI <25 kg/m^2 amounted to 7 events and with a BMI of 25,0-29,9 kg/m^2, only 3 events.

Discussion

This randomized clinical trial demonstrated the beneficial effects of 1-year outpatient physical rehabilitation program in patients after AMI/PCI with different body mass. At the same time, the study revealed some features of this results.

The involvement of obese patients in the ET program made it possible to effectively control cardiovascular RF. Thus, in patients with obesity, the levels of SBP (by 4,2 mm Hg) and DBP (by 3,1 mm Hg) significantly decreased against their increase in non-trained patients. This is consistent with a meta-analysis which showed that aerobic ET in sedentary obese people is able to lower SBP by an average of 3,4-7,4 mm Hg, and DBP by 2,4-5,8 mm Hg [14].

Studies with patients involved in ET program demonstrated a decrease in body mass already by 12-24 weeks [2, 15]. In our obese patients, aerobic ET reduced BMI by an average of 7,7%, and in patients without obesity by 3,3%. The extent of ET reduction depends on the load level: the higher this level, the more a decrease in BMI [16]. It has been proven that weight loss during ET in patients with overweight or obesity occurs due to a decrease in white (visceral) adipose tissue with an increase in lean mass [17]. If patients after AMI are not involved in cardiac rehabilitation programs, it is difficult to effectively control body weight and the opposite effect can be observed, as in the current study.

Patients' participation in ET programs increased their daily physical activity in obese patients by 16,5% and in non-obese patients by 32,3%. In non-trained obese patients, the level of daily physical activity continued to decline. Since sedentary lifestyle adversely affects the survival of patients after AMI, close attention should be paid to increasing the level of daily physical activity [18].

A positive aspect of ET was an increase in exercise tolerance with economical heart operation and lower energy consumption due to a decrease in the hemodynamic response to the load and myocardial oxygen demand (HR and DP growth during CET). Moreover, the training effect in patients without obesity was more pronounced. Clinically, ischemic threshold elevation was expressed by a reduction in angina episodes during daily living activities in obese patients (by 36%) and to a greater extent in patients without obesity (by 49,1%). Regular ET has been shown to improve the coronary endothelial function with an increase in the coronary and collateral flow reserve due to the stimulation of angiogenesis [19]. Such changes can be noticeable after 1-3 months, depending on the intensity of training.

An increase in exercise tolerance, as well as a decrease in the number of angina episodes with regular ET in patients after AMI, is of great importance for improving survival. So, a 15% (1 standard deviation) increase in aerobic fitness was associated with a ~18% lower risk of MI 30 years later [20]. In the present study, the increase in power of physical activity during CET after a 1-year ET was 47,1% in patients without obesity (p<0,001) and 26,5% with obesity (p<0,001). According to the Prospective Observational Longitudinal Registry of Patients With Stable Coronary Artery Disease (CLARIFY) with 20,400 subjects, persistence of angina episodes in patients with CAD can increase the risk of cardiovascular death and nonfatal MI by 66% and AMI by 66% [21].

After a 1-year period without ET, the initial physical performance required a higher oxygen-cost hemodynamic reaction, clinically manifested by the larger number of angina episodes.

Regular 1-year ET is able to restrain LV remodeling processes with increase in its contractile function regardless of the initial body weight, in contrast to the control groups.

Regular ET, causing positive metabolic changes in skeletal muscle and adipose tissue, eliminates the vis-

ceral fat negative effects, which increase cardiometabolic risk. After the completion of a 1-year physical rehabilitation, patients with any BMI had lower levels of LDL-C and TG, and higher HDL-C levels. Such positive effects in lipid metabolism with weight loss and improved exercise tolerance after cardiac rehabilitation/regular ET in obese patients were reported in other studies [2, 22]. A decrease in fibrinogen concentration after ET in patients with any BMI is a favorable fact, since hyperfibrinogenemia is a marker of thrombus formation and inflammation. In contrast, obese patients not involving in cardiac rehabilitation programs had atherothrombogenic changes in blood.

This study included working-age patients. Therefore, the number of temporary disability days was assessed. The involvement of patients after AMI in a rehabilitation program allowed reducing the number of temporary disability days: with obesity (BMI $\geqslant$30 kg/m^2) by 49 days; without obesity (BMI <30 kg/m^2) by 90 days.

In patients with obesity of both groups, CVE developed more often than in patients without obesity. Participation of non-obese patients after AMI in a 1-year rehabilitation program reduced the incidence of all CVE (primary endpoint + hospitalization) by 1,6 times, and in patients with obesity — by 1,4 times. According to study by Doimo S, et al., the participation of patients after AMI/PCI (n=839) in cardiac rehabilitation programs led to a 1,7-fold decrease in the risk of CVE + hospitalization compared to non-participants (p<0,001) [23].

Conclusion

Outpatient cardiac rehabilitation program, based on regular ET of moderate intensity, showed a comprehensive positive effect on obese patients after AMI. This proves the need for more active involvement in the rehabilitation programs of obese patients with high atherothrombogenic risk. It has been shown that with concomitant obesity it is not possible to achieve the maximum effect of cardiac rehabilitation. Since concomitant obesity can worsen the rehabilitation prognosis, control of body weight is a priority for patients with CAD. Obese patients should be assigned to a special group, and their rehabilitation should be based on an individually selected loads. Moreover, the duration of rehabilitation programs should be long in order to obtain the best clinical effect.

Relationships and Activities: none.

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-1-3579

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Arterial stiffness as a factor of structural and functional cardiac remodeling in obesity

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Aim. To analyze the association of parameters characterizing the degree of arterial stiffness and echocardiographic criteria for cardiac remodeling in patients with abdominal obesity. **Material and methods.** The study included 194 patients (men aged 46 to 55 years (49,0±2,3 years)), without hypertension (24-hour average blood pressure (BP) 117,5±5,5/73,0±4,1 mmHg), diabetes and cardiovascular diseases, with abdominal obesity (waist circumference >94 cm, body mass index 31,3±3,5 kg/m^2). Lipids and glucose concentrations were evaluated, and glomerular filtration rate was estimated using the CKD-EPI equation. We conducted 24-hour monitoring of blood pressure and arterial stiffness parameters (aortic pulse wave velocity (PWV), augmentation index (AIx) and systolic BP in the aorta), and echocardiography. **Results.** Left ventricular (LV) hypertrophy was detected in 14 (7,2%) patients, LV diastolic dysfunction — in 36 (18,6%) patients. The correlation of the average aortic PWV and the AIx with the LV mass index and the left atrial volume was shown. Patients with a high aortic PWV exceeding the 75th percentile of distribution (8,2 m/s) were characterized by a higher incidence of hypertrophy (18,8% vs 4,9%, p<0,01) and LV diastolic dysfunction (50,0% vs 12,3%, p<0,001). Patients with/without LV hypertrophy and diastolic dysfunction were characterized by higher values of average 24-hour aortic PWV, AIx and systolic BP in the aorta. According to the regression analysis, the predictors of LV diastolic dysfunction were age, waist circumference, aortic PWV, and AIx.

Conclusion. The relationship of parameters characterizing the degree of arterial stiffness, primarily, aortic PWV and echocardiographic parameters of the structural and functional cardiac remodeling in obese patients was revealed. Patients with a high aortic PWV (>8,2 m/s for men aged 46-55 years) are characterized by a higher prevalence of LV hypertrophy and diastolic dysfunction, as well as left atrial dilatation. This association is probably a reflection of one of the many pathogenesis links of HF and supraventricular cardiac arrhythmias in obese patients.

Key words: arterial stiffness, left ventricular hypertrophy, left ventricle diastolic dysfunction, obesity.

Relationships and Activities: none.

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Received: 30.19.2019
Revision Received: 01.12.2019
Accepted: 08.12.2019

For citation: Druzhilov M. A., Kuznetsova T. Yu. Arterial stiffness as a factor of structural and functional cardiac remodeling in obesity. *Russian Journal of Cardiology*. 2020;25(1):3579. (In Russ.) doi:10.15829/1560-4071-2020-1-3579

A large number of metabolic, neurohumoral and hemodynamic disorders in obesity, even in patients without associated diseases and medical conditions, lead to remodeling of cardiac structure and function, manifested in various patterns, including left ventricular (LV) concentric hypertrophy, left atrial (LA) dilatation, LV diastolic and systolic dysfunction [1].

Various pathophysiological pathways of this association are actively studied. The results of papers have demonstrated the dominate importance of abdominal visceral and ectopic (epicardial) obesity [2, 3], hyperactivation of sympathoadrenal and renin-angiotensin-aldosterone systems, selective leptin and insulin resistance [3, 4], chronic inflammation due to excessive secretion of pro-inflammatory adipocytokines, neprilysin hypersecretion, leading to more intense removal of circulating natriuretic peptides [5], decreasing adiponectin levels and the development of adiponectin resistance [6].

In addition, remodeling of cardiac structure and function is associated with increased arterial stiffness [7]. Currently, the related pathophysiological pathways are being specified, among which the dysfunction of smooth muscle cells and changes in its proportions with extracellular matrix are of major importance [8].

At present, the gold standard for assessing arterial stiffness is the definition of carotid-femoral pulse wave velocity (PWV) [9]. An alternative easy-to-use indicator, characterized by a high correlation with carotid-femoral PWV, is the aortic PWV [10]. In addition, an increase in the augmentation index, as well as the level of central blood pressure (BP), may indirectly indicate an increased vascular stiffness [11].

In obesity, large elastic artery remodeling due to dysfunctional adipose tissue and dysadipokinemia develops faster than the "normal" aging process [12]. We also demonstrated the relationship of visceral obesity, verified by echocardiography with determination of epicardial fat thickness, and parameters characterizing arterial stiffness [13].

The aim of this study was to analyze the association of parameters characterizing the arterial stiffness and echocardiographic criteria for cardiac remodeling in patients with abdominal obesity. This study was performed in accordance with the Helsinki declaration. The medical ethics committees of the Ministry of Health of the Republic of Karelia approved this study. All patients signed informed consent.

Material and methods

The study included 194 patients (men aged 46 to 55 years (49,0±2,3)) without hypertension (mean BP — 117,5±5,5/73,0±4,1 mm Hg), diabetes and cardiovascular diseases, with abdominal obesity (waist circumference >94 cm, body mass index 31,3±3,5 kg/m^2). Patients did not receive any antihypertensive, lipid-lowering and antidiabetic drugs.

The study included 194 patients (men aged 46 to 55 years (49,0±2,3 years)), without hypertension (24-hour average blood pressure (BP) 117,5±5,5/73,0±4,1 mm Hg), diabetes and cardiovascular diseases, with abdominal obesity (waist circumference >94 cm, body mass index 31,3±3,5 kg/m^2). Patients did not receive any antihypertensive, lipid-lowering and antidiabetic drugs. Lipids and glucose concentrations were evaluated, and glomerular filtration rate was estimated using the CKD-EPI equation. We conducted 24-hour monitoring of blood pressure and arterial stiffness parameters (aortic pulse wave velocity (PWV), augmentation index (AIx) and systolic BP) (BPlab MnSDP-3 monitor, Vasotens 24 software, OOO Petr Telegin, Russia), and echocardiography (Logiq 5P Premium, General Electric, USA).

LV mass was calculated by the formula of American Society of Echocardiography (ASE). LV mass was indexed to height^{2,7} (LV mass/height^{2,7}). LV hypertrophy was considered LVMI ⩾50 g/m^{2,7} [14]. The relative wall thickness index (RWT) was calculated as RWT=(IVSd+PWTd)/LVIDd (with IVS: inter-ventricular septum; PWT: posterior wall thickness; LVID: LV internal diameter; d, in diastole). LA volume was calculated using an ellipsoid model, and then indexed to the body surface area and to height^{2,7}. LV diastolic function was investigated using pulsed-wave and tissue Doppler imaging. We calculated the average early diastolic mitral annular velocity, the early diastolic transmitral flow velocity and their ratio, the tricuspid regurgitation peak velocity, the transmitral flow deceleration time and the ratio of early to late filling velocity of LV. LV diastolic dysfunction was verified in accordance with guidelines of American Society of Echocardiography and the European Association of Cardiovascular Imaging [15].

Statistical processing was carried out using software packages Statistica 10, SPSS 22. The data are presented as the mean and standard deviation, as well as the frequencies. A correlation analysis was performed with the calculation of the Pearson's linear correlation coefficient (r) and related significance by the t-test. Group comparability was analyzed using the two-tailed Student's t-test and the Pearson's chi-squared test. Binary stepwise logistic regression was used. The differences were considered significant at $p<0,05$.

Results

Table 1 presents the main characteristics of subjects. Impaired fasting glycemia and impaired glucose

Table 1

The main characteristics of the patients

Parameter	Value
Age, years	49,0±2,3
Body mass index, kg/m^2	31,3±3,5
Body mass index ⩾30 kg/m^2, %	63,9
Body mass index 25-29, kg/m^2, %	36,1
Waist circumference, cm	104,8±7,3
Prediabetes, %	14,4
Impaired lipid metabolism, %	93,8
Average 24-hour SBP, mm Hg	117,5±5,5
Average 24-hour DBP, mm Hg	73,0±4,1
LV mass index, g/m^{2,7}	40,8±7,0
LV hypertrophy, %	7,2
LA volume, ml	44,6±7,3
Indexed LA volume, ml/m^2	21,5±3,2
Indexed LA volume, ml/m^{2,7}	10,2±1,9
LV diastolic dysfunction, %	18,6
Aortic pulse wave velocity, m/s	7,4±0,8
Average 24-hour aortic SBP, mm Hg	107,7±5,3
Average 24-hour augmentation index, %	-33,6±16,8

Abbreviations: DBP — diastolic blood pressure, LV — left ventricle, LA — left atrium, SBP — systolic blood pressure.

Table 2

Echocardiographic parameters of the structural and functional cardiac remodeling with/without high aortic pulse wave velocity

Parameter	Aortic PWV >8,2 m/s (n=32)	Aortic PWV <8,2 m/s (n=162)
LV mass index, g/m^{2,7}	45,1±7,0**	39,9±6,7**
LV relative wall thickness index	0,42±0,03*	0,40±0,04*
LV hypertrophy, %	18,8*	4,9*
Indexed LA volume, ml/m^2	23,1±3,0*	21,2±3,1*
Indexed LA volume, ml/m^{2,7}	11,0±1,9*	10,0±1,9*
LV diastolic dysfunction, %	50,0**	12,3**

Note: * — p<0,01, ** — p<0,001.
Abbreviations: LV — left ventricle, LA — left atrium, PWV — pulse wave velocity.

tolerance were detected in 28 patients (49,4%), various dyslipidemia types — in 182 (93,8%) patients.

The average 24-hour aortic PWV, systolic BP, and augmentation index were 7,4±0,8 m/s, 107,7±5,3 mm Hg and -33,6±16,8%, respectively. The 75th percentile for aortic PWV was 8,2 m/s. LVMI, LV volume and indexed volume were 40,8±7,0 g/m^{2,7}, 44,6±7,3 ml and 21,5±3,2 ml/m^2 (10,2±1,9 ml/m^{2,7}), respectively. LV hypertrophy was revealed in 14 (7,2%) patients. The LV ejection fraction by Simpson's rule exceeded 60% in all patients; LV diastolic dysfunction was detected in 36 (18,6%) cases.

To assess the relationships of arterial stiffness and echocardiographic parameters of cardiac remodeling, a correlation analysis was performed. The Pearson's linear correlation coefficient for aortic PWV with LVMI and indexed LA volume (ml/m^{2,7}) was 0,32 (p<0,001) and 0,31 (p<0,001), for aortic systolic

Table 3

Arterial stiffness parameters in subgroups of patients with/without left ventricular hypertrophy and diastolic dysfunction

Parameter	LVH+ (n=14)	LVH- (n=180)	LVDD+ (n=36)	LVDD- (n=158)
Aortic pulse wave velocity, m/s	8,1±0,2***	7,3±0,8***	8,0±0,5***	7,2±0,7***
Average 24-hour aortic SBP, mm Hg	110,9±3,4**	107,4±5,3**	110,3±4,1***	107,1±5,3***
Average 24-hour augmentation index, %	-22,4±22,0*	-34,5±16,5*	-21,7±16,7**	-36,3±15,7**

Note: * — p<0,05, ** — p<0,01, *** — p<0,001.
Abbreviations: LVH — left ventricular hypertrophy, LVDD — left ventricular diastolic dysfunction, SBP — systolic blood pressure.

Table 4

Results of the regression analysis of LV diastolic dysfunction predictors

Predictor	Unstandardized coefficient	Standardized coefficient	p
Age	0,263	0,101	<0,01
Waist circumference	0,068	0,034	<0,05
Aortic PWV	1,427	0,384	<0,001
Augmentation Index	0,03	0,015	<0,05
Constant	-31,74	7,469	<0,001

Abbreviations: PWV — pulse wave velocity.

BP — 0,20 (p<0,01) and 0,15 (p<0,05), for the augmentation index — 0,31 (p<0,001) and 0,49 (p<0,001), respectively.

As shown in Table 2, patients with a "high" aortic PWV exceeding the 75th percentile of distribution (n=32) were characterized by a higher LVMI (45,1±7,0 g/m^{2,7} vs 39,9±6,7 g/m^{2,7}, p<0,001), LV relative wall thickness index (0,42±0,03 vs 0,40±0,04, p<0,01), indexed LA volume (23,1±3,0 ml/m^2 vs 21,2±3,1 ml/m^2, p<0,01; 11,0±1,9 ml/m^{2,7} vs 10,0±1,9 ml/m^{2,7}, p<0,01). This subgroup was characterized by a higher incidence of LV hypertrophy (18,8% vs 4,9%, p<0,01) and LV diastolic dysfunction according to echocardiography (50,0% vs 12,3%, p<0,001).

We carried out a comparative analysis of arterial stiffness parameters in subgroups with/without LV hypertrophy and LV diastolic dysfunction (Table 3). Patients with LV hypertrophy had a higher average 24-hour aortic PWV (8,1±0,2 m/s vs 7,3±0,8 m/s, p<0,001), average augmentation index (-22,4±22,0% vs -34,5±16,5%, p<0,05) and average 24-hour aortic systolic BP (110,9±3,4 mm Hg vs 107,4±5,3 mm Hg, p<0,01). A similar data was observed in patients with/without LV diastolic dysfunction: 8,0±0,5 m/s vs 7,2±0,7 m/s (p<0,001), -21,7±16,7% vs — 36,3±15,7% (p<0,01) and 110,3±4,1 mm Hg vs 107,1±5,3 mm Hg (p<0,001), respectively.

The risk of LV diastolic dysfunction in patients with abdominal obesity was evaluated by binary logistic regression analysis. Clinical and laboratory data, 24-hour BP monitoring indicators, aortic PWV, augmentation index and systolic BP were studied as predictors (Table 4). The components of the mathematical model were age, waist circumference, aortic PWV and augmentation index: -31,74+0,263*age+0,068*waist circumference+1,427*aortic PWV+0,03*augmentation index. Moreover, aortic PWV was characterized by the highest standardized regression coefficient (0,384, p<0,001). The significance level of the Hosmer-Lemeshow test was 0,76, which indicates adequate goodness of fit.

Discussion

Various epidemiological studies and their meta-analyzes confirmed the independent role of obesity in the pathogenesis of cardiac remodeling and heart failure, and based on the results of experimental and clinical studies, numerous underlying etiopathogenetic pathways have been identified [1, 3]. There is more and more evidence for the presence of neurohormonal imbalance in patients with visceral obesity,

which becomes the subsequent basis for cardiac pathology [5].

To assess the association of arterial stiffness and echocardiographic parameters, we specifically included obese patients without hypertension, diabetes and any cardiovascular diseases in order to exclude the contribution of comorbidities. Moreover, in 7,2% and 18,6% of cases, LV hypertrophy and diastolic dysfunction were detected, which emphasizes the independent role of obesity in their development.

Probably, pathophysiological pathways that specify the processes of cardiac and vascular remodeling in obese patients are common. Reflection of the latter is excessive arterial stiffness. At the same time, the developing vascular wall changes are already becoming an independent component in the pathogenesis of further cardiac remodeling.

In our studies, we repeatedly analyzed the relationship of obesity, verified by various criteria, including ectopic (epicardial) visceral obesity, with arterial stiffness [12, thirteen].

In this study, we demonstrated the association of vascular and cardiac remodeling parameters in obese patients. The performed correlation analysis revealed correlation of aortic PWV and augmentation index with indexed LV mass and LA volume. It was shown that patients with a high aortic PWV are more likely to have LV hypertrophy and diastolic dysfunction, and both remodeling and LV hypertrophy are concentric in nature. The results of binary logistic regression analysis showed the leading role of arterial stiffness parameters in assessing the likelihood of echocardiographic signs of LV diastolic dysfunction in a patient with abdominal obesity.

The data obtained allow to consider arterial stiffness parameters, as a possible additional predictor that broadens indications for echocardiography. At the same time, understanding the etiopathogenesis of structural and functional cardiac impairment in obesity will allow to develop both pharmacological and non-pharmacological methods for preventing the development and progression of cardiac disease.

Conclusion

The relationship of parameters characterizing the degree of arterial stiffness, primarily, aortic PWV and echocardiographic parameters of the structural and functional cardiac remodeling in obese patients was revealed. Patients with a high aortic PWV (>8,2 m/s for men aged 46-55 years) are characterized by a higher prevalence of LV hypertrophy and diastolic dysfunction, as well as LA dilatation. This association is probably a reflection of one of the many pathogenesis links of HF and supraventricular cardiac arrhythmias in obese patients.

Relationships and Activities: none.

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3825

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Assessment of neovascularization in atherosclerotic carotid sinus plaques using quantitative contrast-enhanced ultrasound perfusion imaging

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Aim. To assess the prospects of using quantitative contrast-enhanced ultrasound perfusion imaging of atherosclerotic carotid sinus plaques.

Material and methods. The study included 5 men and 1 woman (59-76 years old, median 72) with symptomatic coronary sinus atherosclerosis. The inclusion criterion was history of ischemic stroke due to internal carotid artery lesion (NASCET ≥60%). We performed contrast-enhanced ultrasound perfusion imaging of the carotid arteries, endarterectomy, studying pathomorphology of the removed plaque with the calculation of the neovascular density and the total number of neovessels with a diameter <40 μm. Neovascularization was assessed by quantitative contrast-enhanced ultrasound 20 seconds after the 1 ml infusion of Sonovia (Bracco, Italy) and subsequent application of the flash. The analysis of dynamics of ultrasonic signal intensity in the atherosclerotic plaque was carried out by creating the curves of the ultrasonic signal intensity (dB)/time (s) over 3 segments of the cross section of the internal carotid artery long axis. The automatic calculation of the intensity dynamics took into account the parameter values in the studied areas within 20 s after the flash. The calculated coefficients (A, B, β) of the exponential equation for 3 atherosclerotic segments were recorded.

Results. Perfusion and neovascularization were assessed in 27 segments of atherosclerotic plaques. The correlation relationships between the ultrasonic parameters of plaque perfusion and the severity of neovascularization were assessed according to the histological data. Significant correlations of the β coefficient exponential curve and histological parameters characterizing the prevalence of "young" vessels (<40 microns) in the atherosclerotic plaque were revealed. Spearman's R for the density of neovessels was 0,54; for the number of neovessels with a diameter <40 μm — -0,66 (p<0,01).

Conclusion. Diagnosis of atherosclerotic plaque neovascularization becomes possible to quantify, assessing not only the presence of neovascular vessels, but also the perfusion intensity. The novel approach replaces the qualitative and semi-quantitative method for calculating the number of carotid plaques neovessels *in vivo*.

Key words: carotid stenosis, perfusion, neovascularization, quantitative analysis.

Relationships and Activities: none.

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Received: 04.04.2020
Revision Received: 06.05.2020
Accepted: 13.05.2020

For citation: Ermakova O. A., Umnov I. N., Bobrov A. L., Kitaichev K. V., Chirsky V. S., Plaminsky D. Yu. Assessment of neovascularization in atherosclerotic carotid sinus plaques using quantitative contrast-enhanced ultrasound perfusion imaging. *Russian Journal of Cardiology*. 2020;25(5):3825. (In Russ.) doi:10.15829/1560-4071-2020-3825

The idea that *vasa vasorum* is involved in the pathophysiology of atherosclerosis was firstly described in studies by W. Köester (1876) and M. Winternitz (1938), which showed that the atherosclerotic segments of the coronary arteries had a rich vascular network from adventitia to intima [1, 2]. As atherosclerosis progresses, a decrease in oxygen diffusion reduces the nutrition of arterial wall. Physiological compensation causes an intima-media thickening that exceeds the oxygen diffusion threshold, causing ischemia and subsequent activation of the continuous release of angiogenic growth factors [3]. The absence of pericytes in the new vessels is accompanied by the diffusion of potentially harmful plasma components (oxidized low-density lipoprotein cholesterol, glucose, advanced glycation end-products, inflammatory cells) into the extracellular intima matrix, which increases the volume of atherosclerotic plaque [4].

Deposition of plasma components further reduces the oxygen diffusion to the vascular wall, causing a continued increase in angiogenesis. Ultimately, the plaque is enveloped by external membrane. Neovascularization inside plaques becomes a sign of symptomatic atherosclerosis [5]. New capillaries of the vascular wall (neo-vessels) are already detected in type II plaques. They originate mainly from adventitia, less often from the lumen of the major vessel; the spread of blood vessels to the intima is a sign of vascular malformation and is associated with risk of plaque ulceration [6]. Formation of microvessels in plaque, on the one hand, is a sign of reparation; on the other hand, vessels in the surface plaque layer destabilizes it, increasing the risk of ulceration and rupture [7].

A direct and indirect assessment of vascular wall perfusion, as well as direct visualization of neovessels, can provide assessing the response to antiatherosclerotic therapy and improve risk stratification. There are three levels of blood flow assessment inside an atherosclerotic affected vascular wall: vascular, interstitial and cellular. The vascular level can be assessed using optical coherence tomography and contrast-enhanced ultrasound. The interstitial level can be studied using contrast-enhanced magnetic resonance imaging. Cellular perfusion is characterized by active metabolic processes between the capillary and the structural components of the plaque. There are still no methods for assessing cellular perfusion of atherosclerotic plaques. Contrast-enhanced ultrasound seems to be the most accessible and non-invasive method for studying the perfusion of atherosclerotic plaques in the aorta and major arteries.

The aim was to assess the prospects of using quantitative contrast-enhanced ultrasound perfusion imaging of atherosclerotic carotid sinus plaques

Material and methods

The pilot open-label uncontrolled study with 1 woman and 5 men (59-76 years of age, median — 74 years) with symptomatic hemodynamically significant atherosclerotic lesion of bifurcation of the common and internal carotid arteries (CA) was performed. Local ethics committee approved this study. All patients signed informed consent. There were following inclusion criteria: previous carotid ischemic stroke >6 months prior to examination, corresponding to a significant atherosclerotic lesion (NASCET ⩾60%) of internal CA. All subjects underwent contrast-enhanced ultrasound of CA using Logiq E9 Ultrasound System (GE, USA) with the assessment of internal CA stenosis using the NASCET approach [8]. Characteristics of perfusion in atherosclerotic plaque were studied.

A quantitative assessment of perfusion in atherosclerotic plaques was performed by dynamically assessing the intensity of ultrasound waves as they travel through tissue after an intravenous bolus injection of 1 ml Sonovia (Bracco, Italy) followed by 0,9% sodium chloride bolus injection (5 ml). Sonography was performed by generating cross-sectional long-axis image of internal CA in the plaque area, as well as in the proximal and distal vessel segments without atherosclerotic lesions of at least 5 mm wide each. Video clips were recorded after adequate filling of the vessel with contrast agent. Perfusion was evaluated after applying a high-energy ultrasonic pulses (flash) destroying the bubbles of contrast agent followed by visualization of the vessel. Quantitative calculation of the ultrasonic intensity of 5 areas was carried out using specialized software for tissue intensive curve analysis.

The software of the ultrasound system automatically analyzed the changes in intensity of the ultrasonic signal and built up scatter diagrams of the acoustic intensity values before and after applying a flash for each analyzed segment. In addition, the exponential equation for the dependence of the estimated parameter with time was calculated. The dynamics curve of the signal intensity value was built up within 20 seconds after applying flash. The exponential equation was as follows: $y=A(1-e-\beta t)+B$, where y is acoustic intensity of the signal; t — time; A, B, β — coefficients of the exponential equation. Exponential coefficients (A, B, β) of the acoustic intensity for 20 seconds were recorded for three atherosclerotic segments, proximal and distal areas CA lumen. For each measurement series, the data were presented graphically as 5 dynamical curves of acoustic intensity. The coefficients obtained for each of the analyzed segments were given in the table (Figure 1).

In three patients, ultrasound revealed concentric atherosclerotic plaques of internal CA. Two patients

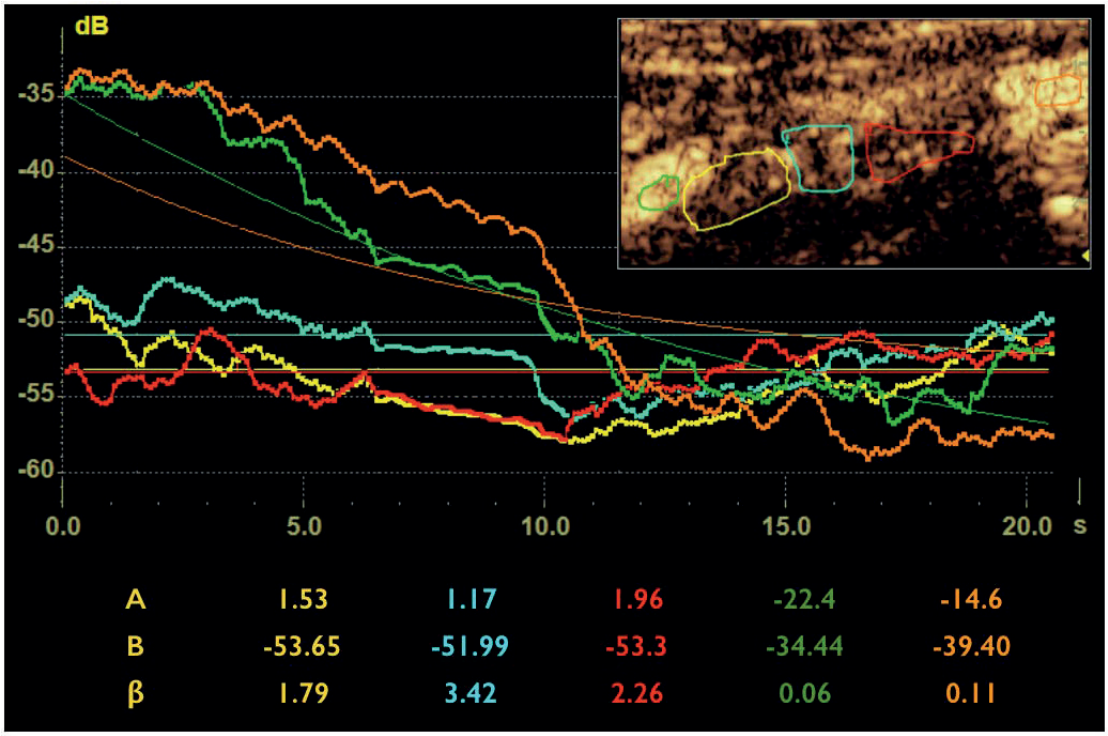

Figure 1. An example of a TIC analysis results in patient M. with symptomatic hemodynamically significant stenosis of the right internal CA.
Note: at the top right is a scan of a longitudinal section of the internal carotid artery during contrast-enhanced ultrasound. Five areas for evaluating the acoustic intensity were allocated. The orange and green areas correspond to the proximal and distal parts of the internal CA. The red, turquoise and yellow areas correspond to the proximal, middle and distal parts of the atherosclerotic plaque. The center presents graphs of the dynamics of the acoustic intensity in the studied areas for 20 seconds after flash. The curve colors correspond to the colors of the areas shown on the scan. Thin curves is modeling the exponential dependence of the acoustic intensity on the estimated areas of the same color. Below are the coefficients of the equation for each of the 5 areas.

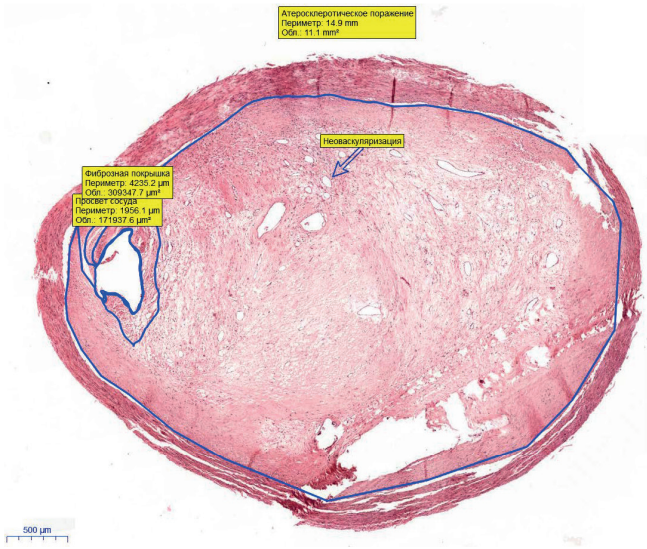

Figure 2. Morphology of the atherosclerotic plaque of patient M. with symptomatic hemodynamically significant stenosis of the right internal CA.
Note: All-vessel density was 84,782 $\mu m^2/cm^2$. Vessels with a diameter of <40 µm predominate; their cross-section number was 97 versus 24 for vessels with a diameter of ⩾40 µm. At the same time, the vessel density with a diameter of <40 µm was only 27492 $\mu m^2/cm^2$ (32%).

had plaque of the posterior wall, one — the anterior wall of the internal CA. In the case of concentric lesion, front and back of the plaque in the central, proximal and distal segments were analyzed.

Within 2 weeks after examination, each patient underwent endarterectomy. Morphological characteristics of removed atherosclerotic plaques was studied with an assessment of neovascularization in cross sections at 3 levels (distal, central and proximal) calculating 2 parameters: neovascularization density in a plaque, total number of neovessels with a cross-section diameter of more and less than 40 µm (Figure 2). In total, an analysis of 27 segments of atherosclerotic plaques was performed.

Statistical analysis was performed with Spearman's rank correlation coefficient using the Statistica 8.0 software package (StatSoft, USA). The data obtained are presented as median, maximum, minimum value, Spearman's rank correlation coefficients. Differences were considered significant at $p<0,05$.

Results

The data of 6 patients with symptomatic hemodynamically significant lesions of the carotid sinus were

Table 1

The values of the correlation coefficients (R, Spearman) between the estimated plaque perfusion and ultrasound and histological parameters of the stenotic area of the internal CA

	A		B		β
The degree of stenosis of internal CA (NASCET)	-	p>0,05	-	p>0,05	-
Peak systolic blood flow	-	p>0,05	-	p>0,05	0,44
Neovessel density	-	p>0,05	-	p>0,05	0,54
The number of neovesels with a diameter of ⩾40 μm	-	p>0,05	-	p>0,05	-
The number of neovessels with a diameter of <40 μm	-	p>0,05	-	p>0,05	-0,66
Density of neovessels with a diameter of ⩾40 μm	-	p>0,05	-	p>0,05	0,57
Density of neovessels with a diameter of <40 μm	-	p>0,05	-	p>0,05	-

Note: Significant correlation coefficients are presented.

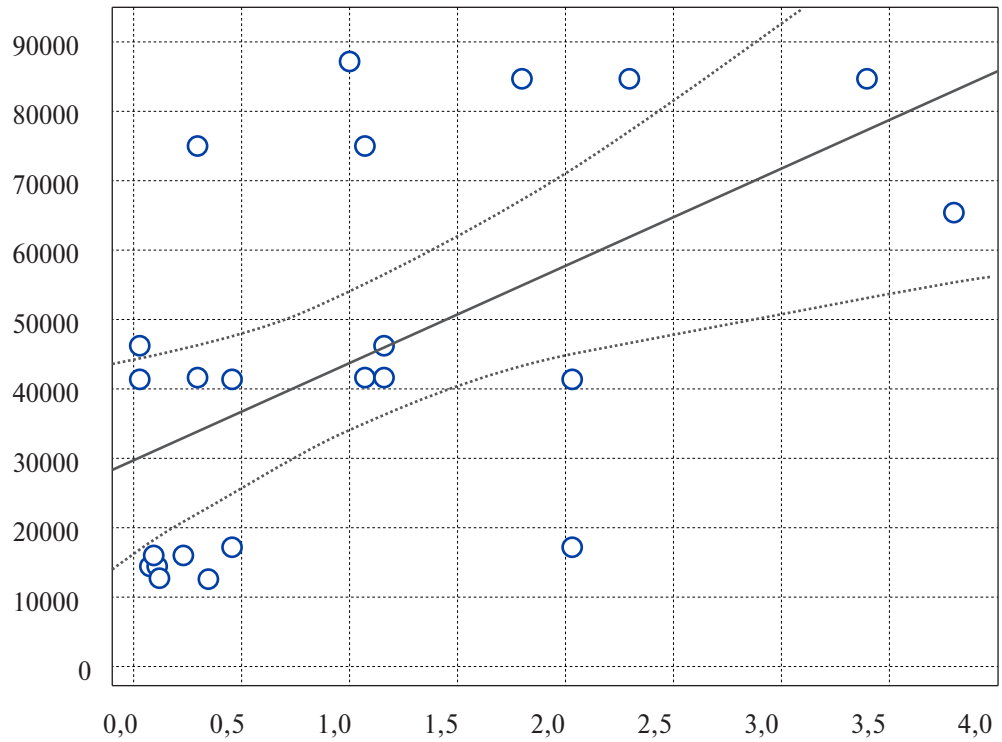

Figure 3. Correlation analysis. Scatterplot matrix of acoustic intensity in segments of atherosclerotic plaques and β coefficient of the exponential equation. Spearman R=0,54; p=0,008.

analyzed. Perfusion and morphology parameters of 27 segments of atherosclerotic plaques were evaluated. The median degree of stenosis was 75% (70-80%). The median peak systolic velocity in the internal CA was 250 cm/s (230-507 cm/s). The median density of plaque neovascularization was 41676 $\mu m^2/cm^2$ (12711-87334 $\mu m^2/cm^2$). The median number of vessels with a diameter of <40 μm amounted to 107 (55-189). The median number of vessels with a diameter of ⩾40 μm amounted to 25 (11-62). The median neovascularization density of atherosclerotic plaque by vessels with a diameter of <40 μm was 10165 $\mu m^2/cm^2$ (7647-27491 $\mu m^2/cm^2$), and by vessels ⩾40 μm — 32695 $\mu m^2/cm^2$ (643-74558 $\mu m^2/cm^2$).

The correlation between the ultrasonic parameters of plaque perfusion and the level of neovascularization was studied according to histology of the material taken during endarterectomy, the estimated severity of stenosis and the peak systolic flow velocity in internal CA (Table 1). Significant correlations of

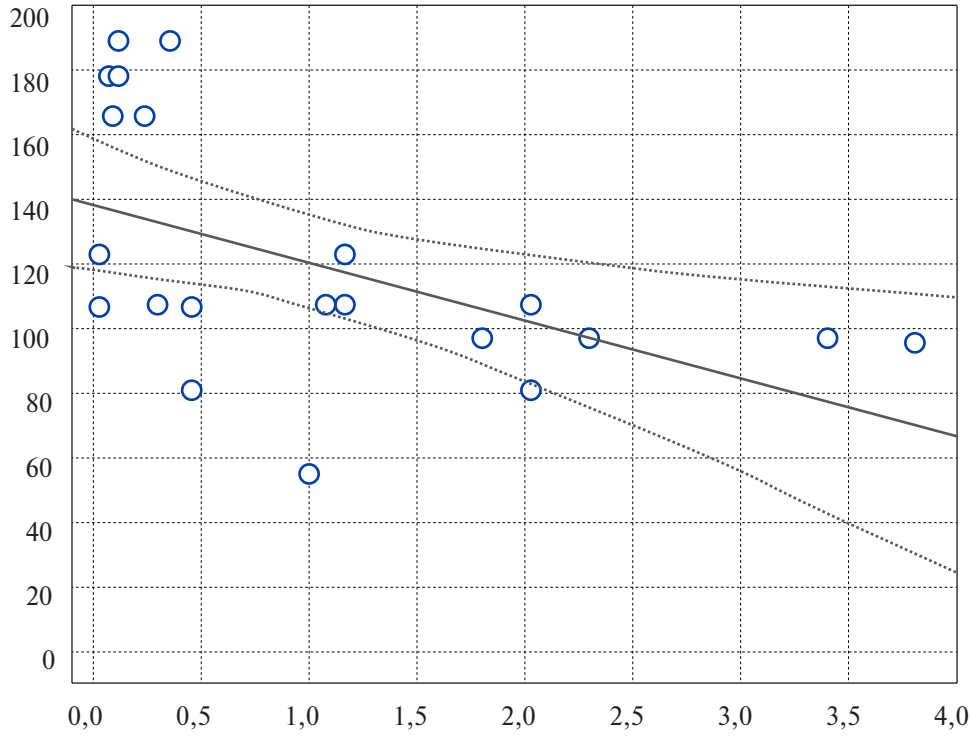

Figure 4. Correlation analysis. The scatterplot matrix of the number of neovessels with a diameter of <40 μm and β coefficient of the exponential equation. Spearman R=-0,66; p<0,001.

the β coefficient exponential curve of dependence of the acoustic intensity on time and the peak systolic flow velocity in the internal CA, neovascularization density and the number of neovessels with a diameter of <40 μm were revealed (Figs. 3, 4). The relationship between the β coefficient and the number of neovessels with a diameter of ⩾40 μm was not significant.

Discussion

The data obtained confirm the usefulness of quantitative perfusion contrast-enhanced ultrasound to assess the severity of plaque neovascularization in carotid sinus. Among the parameters of the exponential equation, significant correlations were obtained only for the β coefficient. β coefficient had a direct moderate correlation with all-vessel density of plaque tissue and neovessels with a diameter of ⩾40 μm, inverse moderate correlation with the number of neovessels with a diameter of <40 μm. Additionally, a moderate direct relationship between the β coefficient and peak systolic velocity in the internal CA was revealed as a parameter characterizing the severity of stenosis.

The first data showing a significant relationship between neovessels of an atherosclerotic plaque and cardiovascular events was presented in 2010 by Hellings W, et al. [9]. The authors examined 818 patients with symptomatic atherosclerosis of CA and previous endarterectomy. A morphology of removed carotid plaques was assessed for neovascularization, calcification, connective tissue and lipid degeneration. Follow-up was carried out for 3 years after endarterectomy. Authors assessed cardiovascular mortality, surgery, number of non-fatal myocardial infarction and strokes. Kaplan-Meier survival analysis was performed for two groups of patients with mildly and highly expressed morphological manifestations of atherosclerosis in removed plaques. It turned out that high plaque vessel density was associated with increased risk of developing endpoints (odds ratio (OR) 1,4 (1,1-1,9)). At the same time, the severity of calcification, connective tissue and lipid degeneration was not associated with a significant increase in the risk of cardiovascular events.

A number of further studies evaluated the severity of neovascularization by the semi-quantitative method by counting the number of microvessels visualized during a contrast-enhanced investigation [10]. Most researchers believe that the severe neovascularization, the higher the cardiovascular risk [9, 11-13]. The division of vessels into "small" (<20 μm) and "large" (>40 μm), however, can change the prospective assessment of atherosclerosis course. It is hypothesized that the predominance of "small" neovessels indicates a high activity of atherosclerotic (or even

inflammatory) process. "Large" vessels indicate a high reparative potential and stabilization of the plaque [12].

The first publications on the quantitative assessment of plaque perfusion and morphology were presented only in 2014 [11, 14]. The technique involved cross-section contrast-enhanced scanning and assessing the absolute values of acoustic intensity in the artery lumen, as well as the central and peripheral parts of the plaque. The study showed that the maximum values of acoustic intensity were recorded in the artery lumen, the minimum — in the central part of the plaque. In symptomatic patients, the ultrasound intensity in the peripheral plaque area is significantly higher (10,8±3,7 dB) than in asymptomatic (7,7±2,4 dB, $p<0,01$).

The method for quantifying neovascularization presented in this study is a novel approach. Firstly, it is proposed to use the short-term increase in the mechanical index (flash) to destroy all the bubbles of contrast agent. This provides equalizing the acoustic intensity in all segments and an assessment over the next 20 seconds of changes in filling the contrast agent. Secondly, the acoustic intensity is estimated not by absolute values, but by the exponential coefficients of the equations created as a result of dynamical observation of filling with a contrast agent. The method allows to simplify the assessment of results and to eliminate the influence of random errors during investigation.

Morphological assessment of atherosclerotic lesions of CA, carried out by a number of authors, show that almost every plaque has signs of neovascularization [12]. The number, dimension and density of neovessels are determined by many factors, among which age and the severity of systemic microinflammation are most important. However, there is no generally accepted point on the negative impact of neovascularization on the course of atherosclerosis. Probably, the predominance of "small" vessels is a reflection of intensive angiogenesis due to microinflammation and the active formation of atherosclerotic plaque. Large-diameter vessels are more often found closer to the adventitia. Detection of such vessels can be associated with a stable course of atherosclerosis. It is vessels of large diameter ($\geqslant$100 μm) that can be well visualized during contrast-enhanced ultrasound. The severity of neovascularization by small-diameter neovessels is better assessed by the novel quantitative approach presented in this study [15]. Interrelation of the processes of neovessel formation in atherosclerotic plaque, as well as their potential negative impact on vascular complications, remains to be further studied.

Unfortunately, our study is limited by the relatively small sample size, which do not allow us to evaluate all forms of atherosclerotic lesions in the common and internal CA, taking into account its severity, the plaque stability, the course of dyslipidemia, other cardiovascular diseases and related complications, the age, constitutional and gender differences of patients. Ultrasonic sections do not fully consist with morphology data. However, taking into account the potential benefits and simplicity of obtaining data on the plaque perfusion in CA, further testing a novel diagnostic approach and accumulating statistical data is an important problem.

Conclusion

Diagnosis of atherosclerotic plaque neovascularization becomes possible to quantify, assessing not only the presence of neovascular vessels, but also the perfusion intensity. The novel approach replaces the qualitative and semi-quantitative method for calculating the number of carotid plaques neovessels *in vivo*. A direct moderate correlation was found between the severity of plaque neovascularization in the carotid sinus according to morphological data and the intensity of blood supply according to contrast-enhanced ultrasound. Dynamic perfusion contrast-enhanced ultrasound of the carotid sinus provides quantifying the severity of plaque neovascularization and identifying areas of plaques with a maximum neovessel density.

Relationships and Activities: none.

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3735

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Comparative analysis of adrenergic reactivity of erythrocytes in patients with myocardial infarction depending on the severity of coronary obstruction

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Aim. To study the parameters of beta-adrenergic reactivity of membrane (β-ARM) of erythrocytes in patients with myocardial infarction with nonobstructive coronary arteries (MINOCA) and single-vessel CAD.

Material and methods. The study included 40 patients with MI (experimental group — 19 patients; control group — 21 patients). Three patients (15,7%) with diagnosed acute myocarditis were excluded from the analysis. Levels of β-ARM were determined upon admission, on the 2nd, 4th and 7th day after MI. The normal range of β-ARM were <20 CU.

Results. In a significant proportion of patients, β-ARM values were two times higher than normal values. The median β-ARM in the experimental group at admission was 41,7 (29,0; 61,5) CU, on the day 1 — 48,6 (38,5; 57,3) CU, day 4 — 49,4 (39,0; 63,3) CU, day 7 — 53,5 (35,2; 67,7) CU. In the control group, the median β-ARM at admission was 52,5 (25,4; 64,5) CU, day 1 — 51,6 (28,3; 56,9) CU, day 4 — 48,5 (34,9; 61,2) CU, day 7 — 45,1 (32,2; 68,9) CU. Static analysis of β-ARM at all follow-up periods did not show differences between the groups by median level (p>0,05). The curves of β-ARM median changes show its multidirectional dynamics in the studied groups. During the hospitalization, in the group of patients with MINOCA there was a downward trend in β-ARM. In the control group, there was a tendency to increase of β-ARM. A statistically significant correlation of β-ARM with the ejection fraction (r=0,83, p=0,0007) and a moderate correlation between the β-ARM level on the 4th day and GRACE risk (r=0,55, p=0,03) in patients of the control group were revealed.

Conclusion. β-ARM values in patients with MINOCA were doubled, and this increase was comparable to levels in patients with obstructive CAD. During the hospitalization, the β-ARM levels did not significantly change, despite the use of beta-blockers.

Key words: nonobstructive coronary artery atherosclerosis, myocardial infarction with nonobstructive coronary arteries, beta-adrenergic reactivity of erythrocytes.

Relationships and Activities: The study was carried out as a part of the theme of fundamental scientific research № AAAA-A15-115123110026-3.

ID trial: ClinicalTrials.gov (NCT03572023).

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Received: 02.02.2020
Revision Received: 17.04.2020
Accepted: 20.04.2020

For citation: Vorobyova D. A., Rebrova T. Yu., Afanasyev S. A., Ryabov V. V. Comparative analysis of adrenergic reactivity of erythrocytes in patients with myocardial infarction depending on the severity of coronary obstruction. *Russian Journal of Cardiology*. 2020;25(5):3735. (In Russ.) doi:10.15829/1560-4071-2020-3735

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) is important and common clinical problem, which became clear after the introduction of invasive coronary angiography (ICA) into routine practice. According to large registers of acute myocardial infarction (AMI), the incidence of MINOCA is 5-15% [1-3]. An increasing number of studies on MINOCA did not provide comprehensive answers about the mechanisms of ischemia and its consequences.

It is known that hyperactivation of the sympathoadrenal system (SAS) is considered as one of the key causes of impaired cardiovascular homeostasis in patients with AMI [4]. Pathological activation of SAS causes a quantitative and functional change in adrenergic receptors, contributing to desensitization of cell membranes to stress mediators and hormones [5]. This is accompanied by a significant decrease in beta-adrenergic receptor (β-AR) density on the membrane of cardiomyocytes. With a reduced amount of β-AR and the action of catecholamines, myocardial oxygen demand increases and against the background of microvascular changes, vasospasm, non-obstructive atherosclerosis, it can contribute to AMI, characteristic of patients with MINOCA [6, 7].

At present, there is no unified method for assessing the activity of SAS, therefore, both direct and indirect approaches are used. Direct methods include the determination of blood mediators and hormones of SAS. These approaches are highly specific and sensitive, but at the same time labor-intensive and expensive. Indirect methods are as follows: assessment of the activity of enzymes for catecholamine synthesis and deactivation, determining the levels of electrolytes in blood and cortisol in saliva, as well as other methods [8]. In addition, one of such indirect methods is the determination of β beta-adrenergic reactivity of membrane (β-ARM) of erythrocytes. It is based on the fact that by binding to β-AR on the erythrocyte membrane, adrenergic agonists and blockers can alter the activity of hyposmolar hemolysis of these cells [4]. This method was developed and implemented by R. I. Stryuk and I. G. Dlusskaya, who for the first time studying adrenergic reactivity in patients with hypertension (HTN), revealed a 2-fold increase in β-ARM compared to the normal values. The authors concluded that values of β-ARM >20 CU can be used as an objective quantitative criterion for the hyperadrenergic type of HTN, and the β-ARM method can be considered a systemic indicator of adrenergic reactivity of the body [4]. This indicator characterizes both the sensitivity of cell membranes to catecholamines and the functional state of adrenergic receptors, which can dynamically alter with changes in SAS.

Previously, it was shown that β-ARM values were significantly increased in the early period after infarction in patients with AMI with obstructive coronary arteries [9, 10]. However, there are no data on the changes of β-ARM during and after AMI. In addition, a comparative assessment of adrenergic receptors in patients with MINOCA and AMI with single-vessel coronary stenosis is of interest. The central hypothesis that was tested in this study was that higher adrenergic reactivity is one of the leading factors for MINOCA.

The aim was to study the parameters of beta-adrenergic reactivity of membrane (β-ARM) of erythrocytes in patients with myocardial infarction with nonobstructive coronary arteries (MINOCA) and single-vessel coronary artery disease (CAD).

Material and methods

The non-randomized, open-label, controlled study was performed (ClinicalTrials.gov Identifier: NCT03572023. Ethics committee of the Cardiology Research Institute of Tomsk National Research Medical Centre approved this study (№ 164 of 11.23.2017). All patients signed informed consent.

The experimental group included patients over 18 years old with acute coronary syndrome (ACS) and non-obstructive CAD (intact coronary arteries or stenosis <50%) according to ICA performed within 24 hours from ischemia onset, with high and intermediate risk categories on the GRACE Score. The control group included patients over 18 years old with ACS, high and intermediate risk categories on the GRACE Score and obstructive single-vessel CAD (stenosis ⩾75%) according to ICA performed within 24 hours from ischemia onset. Patients with history of coronary revascularization were excluded from the study.

B-ARM was determined by assessing the osmotic fragility of erythrocytes after β-AR blockade *in vitro* by selective β-blocker using the BETA-ARM reagent kit (AGAT, Russia). Analysis of β-ARM was performed upon admission, on the 2nd, 4th and 7th day after AMI. Normal values of β-ARM are in the range from 2,0 to 20,0 CU, which reflects the high osmotic fragility of erythrocytes. An increase in β-ARM is a result of desensitization of β-AR on erythrocyte membranes. A decrease in the number of binding sites on the erythrocyte membrane leads to an increase in hyposmolar hemolysis. In addition, β-ARM values exceed 20 CU.

Dynamic measurement of cardiac enzymes was carried out upon admission, on the 2nd, 4th and 7th day from the ischemia onset. Conventional echocardiography was performed on the 4th day using the VIVID E9 ultrasound system (GE Healthcare).

Statistical analysis was carried out using the STATISTICA 10 software package. Hypothesis of a normal distribution was tested using the Shapiro-

Table 1

Clinical and anamnestic characteristics of patients

	MINOCA	Single-vessel lesion	p-value
Number of patients, n %	19 (100)	21 (100)	
Men, n (%)	7 (33,3)	17 (80,9)	0,04
Age, Me (Q25; Q75)	66 (51;71)	60 (56;68)	0,22
Hypertension, n (%)	15 (78,9)	16 (76,1)	0,83
Dyslipidemia, n (%)	15 (78,9)	17 (80,9)	0,62
Obesity, n (%)	13 (68,4)	11 (52,3)	0,30
Heredity*	9 (47,3)	12 (57,1)	0,35
Smoking, n (%)	8 (42,1)	16 (76,1)	0,11
Type 2 diabetes, n (%)	-	4 (19,0)	0,18
GFR, ml/min/1,73 m^2, Me (Q25; Q75)	69 (54,0;83,0)	79 (65,0;89,0)	0,17
History of angina, n (%)	11 (57,8)	6 (28,5)	0,04
History of stroke, n (%)	1 (5,2)	2 (9,5)	0,60
Peripheral atherosclerosis, n (%)	5 (26,3)	7 (33,3)	0,62
Time of admission to the hospital, min, Me (Q25; Q75)	390 (143;900)	180 (98;240)	0,02
STEMI, n (%)	12 (63,1)	19 (90,4)	0,03
GRACE score (Q25; Q75)	2,5 (2,0;9,0)	2,3 (2,0;5,0)	0,42
Prehospital TLT, made/effective	4 (21,0)/3 (15,7)	11 (52,3)/7 (33,3)	0,002

Note: * — positive family history for cardiovascular disease.
Abbreviations: GFR — glomerular filtration rate, TLT — thrombolytic therapy, MINOCA — myocardial infarction with non-obstructive coronary arteries.

Wilk test. Quantitative traits are presented as medians (Me) and quartiles (Q25; Q75). Qualitative traits are presented as n (%) (n — absolute number; % — relative percentage value). Nominal data were analyzed using the Pearson's chi-squared test and the Fisher's two-tailed exact test (expected frequencies <5). Due to the fact that the studied values were not normally distributed, the nonparametric Mann-Whitney U-test was used to assess the differences in the independent samples. To assess the significance of differences in the dependent samples, the nonparametric Friedman's test was used. To evaluate the correlation between the variables, the nonparametric Spearman's test was used. Multiple regression and logistic analyzes were performed. Differences were considered significant at $p<0,05$.

Results

The study included 40 patients with ST-segment elevation MI (STEMI) and non-STEMI (NSTEMI) (19 patients with MINOCA and 21 patients with MI with obstructive CAD). The median age of patients in the experimental and control groups was 66,0 (54; 71) and 60 (56; 68) years, respectively.

After a differential diagnosis, 3 (15,7%) patients with acute myocarditis diagnosed with magnetic resonance imaging and endomyocardial biopsies, were excluded from the study. Among them, one patient had a combination of myocarditis and pulmonary embolism.

The main clinical and anamnestic characteristics of patients of both groups are presented in Table 1. There were significant differences in gender, history of angina, diabetes, time of admission, and prehospital thrombolytic therapy (TLT).

All patients in the hospital received ACS therapy according to national guidelines: dual antiplatelet therapy (Cardiomagnyl; Clopidogrel/Ticagrelor), low-molecular-weight heparins, beta-blockers, statins, ACE inhibitors or sartans.

An analysis of examination data revealed that patients with MINOCA had significantly lower values of creatine phosphokinase (CPK), CPK-myocardial band (MB) on the 1^{st} and 4^{th} day and troponin I on the 1^{st}, 4^{th} and 7^{th} day compared with the control group. A higher level of C-reactive protein (CRP) was determined on the 1^{st} day in the experimental group. According to echocardiography, levels of end-diastolic and end-systolic volume, the left ventricular (LV) local contractility index were significantly higher in patients with MI with obstructive CAD. Examination data of the studied groups are presented in Table 2.

Table 2

Data of investigations

Parameter	MINOCA	Single-vessel lesion	p-value
CPK, u/l, at admission	309,5 (150,0;752)	350,5 (250,5;673)	0,46
CPK, u/l, 1 day	308,5 (140,5;614,0)	1178,5 (588,0;2409,0)	<0,001
CPK, u/l, 4 days	127 (60,0;353,0)	333,5 (139,5;653,5)	0,02
CPK, u/l, 7 days	85 (51,0;138,0)	97,0 (72,0;180,0)	0,24
CPK-MB, u/l, upon admission	38,5 (26,0;88,5)	45,9 (26,5;96)	0,56
CPK-MB, u/l, 1 day	31,0 (13,7;71,3)	173,5 (60,1;260,5)	<0,001
CPK-MB, u/l, 4 days	18,9 (12,0;23,6)	36,4 (19,5;59,5)	0,002
CPK-MB, u/l, 7 days	15,7 (12,0;19,0)	16,4 (11,8;22,1)	0,69
Troponin I, ng/ml, 1 day	0,65 (0,2;6,0)	4,9 (1,0;25,2)	0,01
Troponin I, ng/ml, 4 days	0,5 (0,08;1,9)	0,7 (0,5;4,4)	0,057
Troponin I, ng/ml, 7 days	0,09 (0,02;0,2)	0,4 (0,2;0,9)	<0,001
Cholesterol, mmol/L	4,5 (3,7;5,8)	4,5 (3,9;4,9)	0,43
TG, mmol/l	1,3 (0,9;2,5)	1,7 (1,1;2,0)	0,55
HDL, mmol/l	1,2 (0,9;1,4)	1,1 (1,1;1,3)	0,99
LDL, mmol/l	2,7 (2,1;3,4)	2,6 (2,2;2,8)	0,37
LDL/HDL	2,8 (1,6;3,0)	2,1 (1,8;2,3)	0,31
CRP, mg/l, 1 day	24,5 (3,8;42,0)	4,9 (4,1;27,3)	0,29
CRP, mg/l, 4 days	16,0 (4,8;20,0)	4,8 (3,9;17,9)	0,29
CRP, mg/l, 7 days	5,3 (3,4;10,0)	3,9 (3,5;12,4)	0,86
LV EDV, ml	95,0 (76,0;106,0)	101 (91,0;122,0)	0,11
LV ESV, ml	34,0 (28,0;45,0)	43,0 (35,0;53,0)	0,06
LCII, score	1,0 (1,0;1,2)	1,2 (1,2;1,5)	0,04
LVEF, %	60,0 (45,0;60,0)	56,0 (50,0;60,0)	0,51

Abbreviations: INLS — local contractility impairment index, EDV — end-diastolic volume, EDV — end-systolic volume, CPK — creatine phosphokinase, LV — left ventricle, HDL — high density lipoproteins, LDL — low density lipoproteins, CRP — C-reactive protein, TG — triglycerides, EF — ejection fraction, LCII — local contractility impairment index.

We found that in 85% of patients, the values of β-ARM were 2 times higher than normal values (Figure 1). Static analysis of β-ARM at all follow-up periods did not reveal significant differences between the groups by median level (p>0,05). The curves of changes in β-ARM medians during observation, presented in Figure 2, show its multidirectional dynamics. During hospitalization, patients with MINOCA had a downward trend in β-AWP, while patients with MI with obstructive CAD — an upward trend.

Correlation analysis revealed a moderate correlation between the level of β-ARM on the 4th day and the GRACE score (r=0,55, p=0,03) in patients with MI with obstructive CAD. In patients with MINOCA, a close correlation of β-ARM with the left ventricular ejection fraction (LVEF) was obtained (r=0,78, p=0,0007). The revealed correlation in patients with MINOCA was confirmed by multiple regression analysis, which were obtained by step-by-step inclusion of cardiovascular risk factors: age, sex, smoking, heredity; GRACE score, time of admission to the hospital; examination parameters: serum levels of CPK, CPK-MB, troponin I, CRP, end-diastolic volume, end-systolic volume, LV local contractility index and LVEF. It was revealed that the β-ARM level is correlated with age, heredity, risk (GRACE score), LVEF, and levels of myocardial necrosis markers:

Equation 1

– β-ARM level on the 4th day = -43,09 — 0,54 * GRACE score — 27,5 * heredity — 2,35 * CPK-MB, 4th day + 9,6 * troponin I, 4th day + 2,3 * LVEF.

Equation 2

– β-ARM level on the 7th day = -64,2 — 0,57 * age — 1,22 * CPK-MB, 7th day + 13,2 * troponin I, 7th day + 2,7 * LVEF.

Discussion

Before comparing β-ARM between groups, it was important to compare their clinical, history and exami-

nation characteristics. So, the median age of patients in the experimental group was 66 years, which is higher than in patients with MI with obstructive CAD. There were significantly lower number of men in the experimental group (43,7%), p=0,02. According to the analysis of risk factors, patients with MINOCA did not have diabetes, but statistically more often had a history of angina (62,5%), and for other risk factors, there were no differences, p>0,05. It was also found that 62,5% of patients with MINOCA had ST-segment elevation ACS, in contrast to the control group, where there were 90,4% of such patients (p=0,01), which is consistent with a higher frequency of prehospital TLT in the control group (p=0,007). However, according to the GRACE score, patients of both groups had a moderate cardiovascular risk, p=0,26 (Table 1). Attention is drawn to the low level of cardiac enzymes in patients with MINOCA, which indicates a small area of necrosis. These data are consistent with significant differences in the local contractility impairment index (p=0,007) (Table 2). We also revealed significant differences in CRP levels in patients with MINOCA on the first day after AMI (p=0,05), which may indicate a more aggressive atherosclerosis with plaque destabilization [11].

Thus, patients with MINOCA were older, later admitted to hospital, had a lower number of risk factors and a less pronounced increase in serum myocardial necrosis markers. This suggests a more favorable course of MI and less neurohormonal reactivity both during and after the hospitalization.

Based on the obtained data and theoretical assumptions, one would expect that the β-ARM data would be different in the studied groups. However, this hypothesis was not confirmed: β-ARM values were comparable, p>0,05. The medians of β-ARM in both groups were doubled (Figure 1), which generally corresponds to adrenergic hyperactivity and is characterized by an increase in SAS activity, and also indicates protective desensitization of β-AR in response to a change in their autonomic regulation due to AMI. Similar data were found in patients with AMI with obstructive atherosclerosis with different clinical course, however, β-ARM parameters were studied only on the 1st day from the index event [9]. The authors found the relationship of β-ARM with the clinical features of ST-segment elevation AMI. Thus, patients with complicated AMI had low β-ARM (β-ARM ⩽20 CU), which indicates a high risk of recurrent events due to the high sensitivity of β-AR to catecholamines. An increase in β-ARM (>20 CU), on the contrary, was a favorable prognostic factor. This indicates that the protective role of desensitization is activated, the amount of β-AR is reduced and this is manifested in various systems and organs, including the cardiac muscle [8]. At the same time,

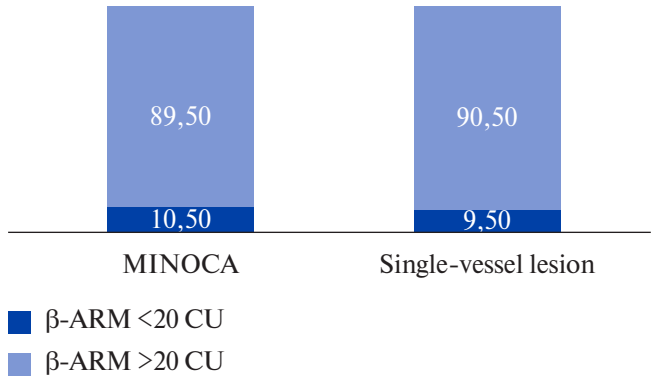

Figure 1. Patients with β-ARM <20 CU and >20 CU, %.

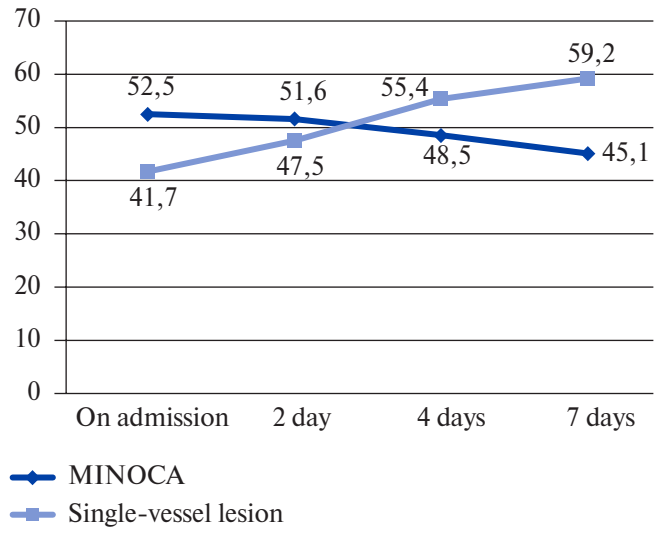

Figure 2. Changes of β-adrenergic reactivity of erythrocyte membranes in the studied groups.

the results of other studies confirm the hypothesis that prolonged stimulation with catecholamines during myocardial ischemia reduces the β-AR amount, ensures maintenance of the cardiac contractility, and is a criterion for a favorable prognosis in the period after MI [10, 12]. These data are consistent with the correlation of β-ARM with LVEF confirmed by multiple regression analysis, which is revealed in our study. The higher the β-ARM and LVEF, the more favorable prognosis in post-MI period in patients with MINOCA.

We revealed moderate correlation between the β-ARM level on the 4th day and the GRACE score in patients with MI with obstructive CAD. This can also be associated with the prognosis, since the GRACE score is an indicator of the prognosis after MI.

Changes of β-ARM medians in patients of both groups, presented in Figure 2, shows it multidirectionality, despite the fact that there were no signifi-

cant differences (p>0,05). In the group of patients with obstructive CAD, there was a trend towards an increase in β-ARM, while patients with MINOCA were more likely to have a β-ARM decrease. There is evidence in studies that long-term beta-blocker use leads to a decrease in β-ARM as a result of a decrease in β-AR desensitization [8, 13]. In the present study, 85% of patients took beta-blocker from the admission to the hospital, however, the upward trend of β-ARM was observed only in the control group, which is probably associated with the restoration of blood flow after myocardial revascularization, a decrease in stress mediators and hormones, partial desensitization of β-AR as a result of taking beta-blockers. Lack of significant changes in β-ARM parameters in patients with MINOCA is associated with continued activation of SAS and a decrease in the β-AR number, which in turn causes less binding of β-AR to β-blocker and is manifested by hyposmolar hemolysis of erythrocytes. Preserved hypersympathicotonia is probably associated with other pathogenetic mechanisms affecting this indicator. To answer questions about how long hypersympathicotonia preserves and how it is associated with a long-term prognosis, whether beta-blocker in patients with MINOCA reduces the effect of catecholamines, further large studies with a long-tern follow-up period is necessary.

Conclusion

During hospitalization, β-ARM values in patients with MINOCA were doubled, and this increase was comparable to levels in patients with obstructive CAD. Within the follow-up period, the β-ARM levels did not significantly change, despite the use of beta-blockers, which indicates the continued long-term desensitization of adrenergic receptors under the action of catecholamines.

Relationships and Activities. The study was carried out as a part of the theme of fundamental scientific research № AAAA-A15-115123110026-3.

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3874

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

Antiarrhythmic drug therapy after atrial fibrillation ablation: data of the ESC-EHRA registry

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Aim. Catheter ablation (CA) is an effective approach for rhythm control in atrial fibrillation (AF), however antiarrhythmic therapy (AAT) remains important. There is a lack of data about long-term AAT use after CA. This study evaluates AAT after CA for AF.

Material and methods. In 2012-2016, EURObservational Research Programme of Atrial Fibrillation Ablation Long-Term (EORP AFA L-T) registry was conducted, which included 476 Russian patients (57,1% — men; mean age — 57,1±8,7 years). The follow-up after CA was 12 months (available in 81,9% of patients). The use of AAT was evaluated prior to hospitalization, during hospitalization for CA, as well as at 3, 6 and 12 months of follow-up.

Results. Prior to CA, 439 (92,2%) patients received AAT. During CA, 459 (96,4%) patients were treated with AAT. After CA, AAT was used by 463 (97,3%), 370 (94,8%), and 307 (78,7%) patients at 3, 6 and 12 months of follow-up, respectively. There was no arrhythmia recurrence in 187 (47,9%) subjects. Among these patients, 40 (21,4%) received class IC or III AAT. The peak of AAT use was found for class IC agents within 3 months after CA (P<0,05), while for other drugs this trend was not observed. There were no factors associated with AAT usage in patients without arrhythmia recurrence after CA. A positive correlation of arrhythmia non-recurrence with a minimum number of previously used antiarrhythmic agents was revealed (RR=0,85; 95% CI 0,73-0,98; P=0,03).

Conclusion. The frequency of AAT use after AF ablation is significantly reduced. However, there is a cohort of patients without documented arrhythmia recurrence still receiving AAT, which requires special attention of physicians. There were no clinical predictors of continued AAT in subjects without arrhythmia recurrence.

Key words: atrial fibrillation, antiarrhythmic therapy, registry, catheter ablation.

Relationships and Activities. The Committee of EURObservational Research Programme was supported by the following companies: Abbott Vascular Int. (2011-2014), Amgen Cardiovascular (2009-2018), AstraZeneca (2014-2017), Bayer AG (2009-2018), Boehringer Ingelheim (2009-2019), Boston Scientific (2009-2012), The Bristol Myers Squibb and Pfizer Alliance (2011-2019), Daiichi Sankyo Europe GmbH (2011-2020), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014-2017), Edwards (2016-2019), Gedeon Richter Plc. (2014-2016), Menarini Int. Op. (2009-2012), MSD-Merck & Co. (2011-2014), Novartis Pharma AG (2014-2017), ResMed (2014-2016), Sanofi (2009-2011), SERVIER (2009-2018).

Acknowledgments. The authors are grateful to the Registry Executive Committee and the EORP Oversight Committee, as well as Elin Folkesson Lefrancq, Viviane Missiamenou, Cecile Laroche and Professor Aldo P. Maggioni. A complete list of registry co-executors is given in Appendix 1.

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Received: 30.04.2020
Revision Received: 15.05.2020
Accepted: 18.05.2020

For citation: Korobchenko L.E., Bayramova S.A., Kharats V.E., Kachalkova O.N., Dmitriev A.Yu., Batalov R.E., Morgunov D.P., Silin I.A., Aleksandrovskiy A.A., Kryzhanovskiy D.V., Romanov A.B., Pokushalov E.A., Lebedev D.S., Kuznetsov V.A., Kolunin G.V., Zamanov D.A., Chetverikov S.Yu., Yashin S.M., Popov S.V., Ivanitsky E.A., Gorkov A.I., Mamchur S.E., Bazaev V.A., Mikhaylov E.N. Antiarrhythmic drug therapy after atrial fibrillation ablation: data of the ESC-EHRA registry. *Russian Journal of Cardiology*. 2020;25(5):3874. (In Russ.) doi:10.15829/1560-4071-2020-3874

Atrial fibrillation (AF) is the most common sustainable arrhythmia in clinical practice. The complex therapy of AF includes the prevention of thromboembolic events, conservative and interventional treatment aimed at improving the rhythm and preventing the AF recurrence. A number of randomized clinical trials [1-4] showed that pulmonary vein isolation was more effective than antiarrhythmic therapy (AAT) in rhythm control. AAT remains an important component of AF treatment in most patients, both aimed at catheter ablation and those who do not have indications for interventional treatment.

Earlier studies have shown that a history of AAT before catheter ablation can be a predictor of cardiac ablation outcomes [5]. At the same time, according to expert opinion and official guidelines [6, 7], in the first 3 months after ablation, AAT is indicated for the prevention of early recurrence of AF. The decision to continue therapy is based on AF recurrence, as well as the individual characteristics of a patient [8].

The clinical guidelines indicate AAT withdrawal after catheter ablation if there is no documented AF recurrence. However, in actual practice, the frequency of AAT use after ablation, the type of preferred AAT and its duration remain unstudied.

To obtain relevant data on catheter ablation (CA) for AF in 2012-2016, a registry observational study was conducted on the management of patients hospitalized for CA (EORP Atrial fibrillation ablation long-term registry = EORP AFA LT). As a part of the Russian Society of Cardiology, data from 13 hospitals of Russia were included in the study.

The aim of this study was to assess the characteristics and changes of AAT in the preoperative, perioperative and long-term periods after AF ablation in Russia.

Material and methods

Registry. The EORP AFA L-T registry was a prospective international multicenter project. The registry organizers did not provide for specific prescriptions for drug therapy and diagnostic procedures for patients. It was carried out according to current guidelines and local clinical practice.

The inclusion criteria were the age >18 years and hospitalization for AF ablation.

The registry included data from 106 cardiology centers from 27 countries, including 13 Russian institutions.

In total, 3742 patients were included in the registry, of which 476 were Russian patients (study group). The main clinical characteristics of patients were presented in a previous publication [9].

Catheter ablation and follow-up. AF ablation included pulmonary vein isolation. At the discretion of the operator, an additional substrate modification was performed in the left and/or right atrium.

After AF ablation, patients were monitored for 12 months with rhythm control and in-person recurrence

Table 1

Applied dosages of AAT

	Ic			III	
	Propaphenone	Lappaconitine hydrobromide (Allapinin)	Ethacyzin	Amiodarone	Sotalol
Dosages (mg/day)	150-600 (450)	25-160 (75)	100	100-600 (200)	40-640 (160)

Note: the ranges of prescribed dosages and the median daily dose in brackets for the entire observation period are indicated. The protocol of the register did not provide for the separation of the beta blockers and CCB groups by individual drugs.

Table 2

The frequency of using various AAT during the follow-up period

	Before hospitalization (476 subjects in total)	During hospitalization for AF CA (476 subjects in total)	3-month follow-up period (476 subjects in total)	6-month follow-up period (390 subjects in total)	12-month follow-up period (390 subjects in total)
Number of patients received AAT	439 (92,2%)*	459 (96,4%)	463 (97,3%)	370 (94,8%)*	307 (78,7%)*
Ic	134 (28,2%)	145 (30,3%)	148 (31,1%)	112 (28,7%)	27 (6,9%)*
• Propaphenone	94 (19,7%)	104(21,8%)	106 (22,3%)	79 (20,3%)	26 (6,7%)*
• Allapinin	37 (7,8%)	40 (8,4%)	41 (8,6%)	31 (7,9%)	0*
• Etatsizin	3	1	1	2	1
III	254 (53,3%)	297 (62,4%)*	298 (62,6%)	237 (60,8%)	130 (33,3%)*
• Amiodarone	156 (32,8%)	172 (36,1%)	167 (35,1%)	135 (34,6%)	49 (12,6%)*
• Sotalol	97 (20,6%)	124 (26,1%)*	130 (27,3%)	102 (26,2%)	81 (20,8%)
beta-blockers	217 (45,6%)	199 (41,8%)	183 (38,4%)	176 (45,1%)*	180 (46,2%)
CCB	43 (9%)	49 (10,3%)	42 (8,8%)	36 (9,2%)	36 (9,2%)
Ic+III	23 (4,8%)	28 (5,9%)	23 (4,8%)	18 (4,6%)	1 (0,3%)*

Note: * — P<0,05.

Abbreviations: AAT — antiarrhythmic therapy, CA — catheter ablation, AF — atrial fibrillation, CCB — non-dihydropyridine calcium channel blockers.

detection (surface ECG, Holter monitoring), by telephone or using implantable monitors. Recurrence was considered to be any documented episodes of atrial tachyarrhythmia lasting more than 30 seconds.

The exclusion criterion was feedback failure until the end of the follow-up period.

The primary endpoint was the AAT frequency in patients on follow-up visits at 3, 6, and 12 months.

Secondary endpoints were the change or continuation of AAT, the AAT continuation for 12 months in patients without AF recurrence.

Clinical indicators and accepted therapy were entered into the electronic database before hospitalization, during hospitalization for AF ablation, immediately after CA, after a 3-month (blinded) period and at a 12-month visit; if necessary, unscheduled visits were carried out and taken into account.

In the early postoperative period, complications of AF ablation were evaluated.

Antiarrhythmic therapy. The electronic database included data on the intake of a wide range of drugs for the treatment of cardiovascular diseases, including AAT, therapy for hypertension (HTN), hypercholesterolemia, heart failure, as well as anticoagulant therapy. AAT was carried out using class IC (Propafenone, Lappaconitine hydrobromide (Allapinin), Diethylaminopropionylethoxycarbonylaminophenothiazine (Etatsizin)) and class III (Amiodarone, Sotalol) antiarrhythmic agents, as well as beta blockers and non-dihydropyridine calcium channel blocker (CCB). The applied dosages of class IC and III agents are shown in Table 1. The drugs were prescribed by physician caring for patient.

Statistical analysis. Continuous variables are presented as mean±standard deviation. Frequencies are presented as a percentage of the absolute number. The relationship was assessed using a Pearson correlation coefficient for a normal distribution and Spearman's correlation coefficient for non-normal distribution. To compare the normally distributed mean values, we used Student's t-test, while for non-normally distributed values — Mann-Whitney U test. For frequency comparison, the Pearson's chi-squared

Table 3

AAT use before hospitalization

	Without AAT (n=33)	1 AAA (n=252)	2 AAAs (n=160)	3 AAAs (n=22)	4 AAAs (n=4)
Free from relapse	12 (36,4%)	113 (44,8%)*	56 (35,0%)	8 (36,4%)	1 (25,0%)
CAD	2 (6,1%)	53 (21,0%)*	65 (40,6%)	9 (40,9%)	2 (50,0%)
HF	14 (42,4%)	82 (32,5%)*	70 (43,8%)	13 (59,1%)	1 (25,0%)
HTN	9 (27,3%)	105 (41,7%)*	46 (28,8%)	6 (27,3%)	2 (50,0%)
Ic	-	54 (21,4%)*	68 (42,5%)	10 (45,5%)*	4 (100,0%)
• Propaphenone	-	42 (16,7%)*	44 (27,5%)	7 (31,8%)*	4 (100,0%)
• Allapinin® [Lappaconitine hydrobromide]	-	12 (4,8%)*	24 (15,0%)	3 (13,6%)	2 (50,0%)
III	-	115 (45,6%)*	112 (70%)*	22 (100,0%)	4 (100,0%)
• Amiodarone	-	57 (22,6%)*	82 (50,0%)	15 (68,2%)	2 (50,0%)
• Sotalol	-	58 (23,0%)	30 (18,8%)	7 (31,8%)	2 (50,0%)
beta-blockers	-	76 (30,2%)*	119 (74,4%)	19 (86,4%)	4 (100,0%)
CCB	-	7 (2,8%)*	21 (13,1%)	14 (63,6%)	4 (100,0%)

Note: * — P<0,05.

Abbreviations: AAA — antiarrhythmic agent, CAD — coronary artery disease, HF — heart failure, HTN — hypertension, CCB — calcium channel blockers.

Table 4

AAT and comorbidity

	CAD (n=132)	HTN (n=167)	HF (NYHA ⩾2) (n=184)	Comorbidity free (n=30)
Ic	51 (38,6%)	74 (44,3%)	79 (42,9%)	16 (53,3%)
III	110 (83,3%)*	124 (74,3%)	144 (78,3%)	20 (66,7%)
beta-blockers	93 (70,5%)	108 (64,7%)	137 (74,5%)*	19 (63,3%)
CCB	32 (24,2%)	30 (18,0%)	37 (20,1%)	5 (16,7%)

Note: * — P<0,05.

Abbreviations: CAD — coronary artery disease, HF — heart failure, HTN — hypertension, CCB — calcium channel blockers, NYHA — New York Heart Association.

test was used. Analysis of AAT administration predictors was carried out using multinomial logistic regression. The differences were considered significant at P<0,05.

Results

Clinical characteristics of patients. The study included 476 people of the Russian population (men — 57,1%; mean age — 57,1±8,7 years). Paroxysmal AF was the most common — 67,2%, persistent AF — 19,7%, long-standing persistent AF — 11,1%; in 9 patients (1,9%), the type of AF was not verified. A visit 12 months after ablation was performed in 392 (84,4%) patients. Among patients, there were following comorbidities: HTN — 167 (35,1%); NYHA class ⩾II heart failure (HF) — 184 (38,7%), of which 6 patients had reduced left ventricular ejection fraction (LVEF<50%); coronary artery disease (CAD) — 132 (27,7%).

Postoperative complications were recorded in 22 (4,6%) patients and most often (n=13) were associated with approach to the femoral vessels (hematomas and pseudoaneurysms).

Antiarrhythmic therapy. Before hospitalization, the majority of patients (n=439; 92,2%) received AAT. In the future, there was a peak AAT use in the 3-month period after the AF ablation (n=463; 97,3%) and a further slight decrease to 370 (94,8%) in the 6-month period and to 307 (78,7%) by the 12-month visit. Moreover, 27 (6,9%) patients received class IC AAT, 130 (33,3%) — class III, 180 (46,2%) — beta-blockers, and 36 (9,2%) — CCB. The frequency of using various AAT during the follow-up period is presented in Table 2.

AF recurrence. Early AF recurrence (within the first 3 months after ablation) was recorded in 102 (30,8%) patients. Within the remaining follow-up period, arrhythmia recurrence was reported in 125

(32,1%) patients. The administration of propafenone in the postoperative period was associated with the course without early recurrence (Po=0,17, P=0,04).

In patients who continued AAT, AF recurrence was recorded in 203 (52,1%) cases. At the same time, the highest recurrence rate was observed in patients with an initially paroxysmal AF — 69,5%, persistent AF — 19,2%, and long-standing persistent AF — 11,3% (P<0,01).

There were no significant associations of AF recurrence with specific antiarrhythmic agents.

Out of 307 (78,7%) patients who continued the prescribed AAT, 187 (47,9%) did not have AF recurrence during the entire follow-up period. Of these, 5 (2,7%) patients continued to take class IC agents, 35 (18,7%) patients — class III (7 — Amiodarone and 28 — Sotalol). In addition, 92 (49,2%) patients continued to take beta-blockers and 18 (9,6%) patients — CCB. However, indications for using these drugs were not described in the database. At the same time, all 187 patients had comorbidities (75,4% — HTN; 41,7% — NYHA class ⩾2 HF; 31,6% — CAD). Univariate regression analysis did not reveal significant predictors of AAT continuation in patients without AF recurrence among the following clinical parameters: gender, age, AF type, early and late recurrence of arrhythmias in the postoperative period, and comorbidities. In this regard, multivariate regression analysis was not performed.

AAT use before hospitalization. Before hospitalization, patients took a different number of antiarrhythmic agents (Table 3). The largest group consisted of patients taking one antiarrhythmic agent (n=252). These patients had the highest rate of freedom from arrhythmia recurrence by a 12-month period: 44,8% vs 35,0%, P=0,049 (group of one and two antiarrhythmic agents, respectively: 44,8% vs 36,4%, P>0,05 (group of one agent and without AAT, respectively); 36,4% vs 25,0% (group of three and four agents, respectively). A lower recurrence rate was found in the subgroup with one ineffective antiarrhythmic agent compared to the subgroup with a large number of drugs used (RR=0,85; 95% CI 0,73-0,98; P=0,03).

AAT and comorbidity. As expected, AAT differed depending on comorbidities of patients (Table 4). Thus, a group of patients with CAD received the largest number of class III agents and CCB before and during hospitalization (P<0,01). Patients with HF had the highest rate of taking beta-blockers. Patients without structural heart disease used class IC agents more often (P<0,05).

HTN correlated with a rarer use of Allapinin at all follow-up stages (Po=-0,150; P<0,05).

Discussion

Several important results were obtained. The use of AAT decreases 3 months after AF ablation, which corresponds with current recommendations. Nevertheless, there remains a category of patients with continuing AAT up to 12 months or more without documented AF recurrence. It is important that our study did not reveal clinical factors associated with prolonged AAT without indications.

A large proportion of patients continued AAT in the postoperative period, which may be due to their subjective signs even without documented arrhythmia recurrence on ECG. It can be assumed that the true recurrence rate could be underestimated, and continued therapy is associated with complaints. On the other hand, as shown in previous results, in some patients post-operative arrhythmias were detected using implantable cardiac monitors, which is associated with more reliable identification of asymptomatic and short-term arrhythmias [8]. Nevertheless, the fact of the common AAT use, including in patients without documented arrhythmia recurrence, requires attention and informing specialists caring for patients after ablation.

The lowest recurrence rate was found in patients with a minimal number of AAT in history (1 agent), which indicates the likely need for an earlier decision to conduct ablation, rather than continuing to select AAT after the first failure. This conclusion is consistent with official indications for AF ablation [1, 2].

During the first three months after ablation, there was a peak in the use of class IC agents with a subsequent decrease in their prescription. This indicates the preferred use of these drugs for prophylaxis in the first months of the postoperative period in patients without structural heart disease.

Over the past 15-20 years, the narrative of AAT in AF has changed, which reflects clinical guidelines for the management of AF [6, 10, 11]. To date, conservative therapy remains first-line approach. However, the use of AAT in patients after AF ablation is less standardized. AAT is associated with a risk of complications, therefore, their use should be considered individually, and the need to continue or withdrawal should be made every time when consulting patients. For example, in case of early arrhythmia recurrence (first 3 months after ablation), AAT is justified. In approximately 40% of cases, such arrhythmia recurrences are not recorded in long-term period, and AAT can be canceled [12]. Thus, assessing the need for therapy at each visit and informing patients can help reduce the frequency of use of unnecessary therapy and reduce the risk of its complications.

Clinical trials comparing AF ablation and AAT showed that AAT use in the 3-month postablative period significantly reduces the risk of early recur-

rence. However, long-term administration of AAT did not show a significant advantage in rhythm control [3, 13, 14].

The POWDER-AF study compared the efficacy of long- (1 year) and short-term (3 months) AAT. The study showed a lower incidence of symptomatic arrhythmia recurrence (2,7% vs 21,9%, P<0,001) and reablation (1,4% vs 19,2%, P<0,01) in the long-term AAT group; quality of life did not differ between groups. However, there were few patients with organic heart disease (9%), which does not reflect actual clinical practice [8]. Further clinical studies are needed for a comprehensive analysis of this.

Study limitations. Limitations include the voluntary participation of specialists in the study, non-standardized AAT protocols, and intermediate patient observations. The main limitations of the Register were published earlier [9, 15].

Conclusion

The frequency of AAT after AF ablation is significantly reduced. However, there is a cohort of patients without documented arrhythmia recurrence still receiving AAT. There were no clinical predictors of continued AAT in subjects without arrhythmia recurrence. Clinicians need to be better informed of approaches to AAT after AF.

Acknowledgments. The authors are grateful to the Registry Executive Committee and the EORP Oversight Committee, as well as Elin Folkesson Lefrancq, Viviane Missiamenou, Cecile Laroche and Professor Aldo P. Maggioni. A complete list of registry co-executors is given in Appendix 1.

Relationships and Activities. The Committee of EURObservational Research Programme was supported by the following companies: Abbott Vascular Int. (2011-2014), Amgen Cardiovascular (2009-2018), AstraZeneca (2014-2017), Bayer AG (2009-2018), Boehringer Ingelheim (2009-2019), Boston Scientific (2009-2012), The Bristol Myers Squibb and Pfizer Alliance (2011-2019), Daiichi Sankyo Europe GmbH (2011-2020), The Alliance Daiichi Sankyo Europe GmbH and Eli Lilly and Company (2014-2017), Edwards (2016-2019), Gedeon Richter Plc. (2014-2016), Menarini Int. Op. (2009-2012), MSD-Merck & Co. (2011-2014), Novartis Pharma AG (2014-2017), ResMed (2014-2016), Sanofi (2009-2011), SERVIER (2009-2018).

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https://russjcardiol.elpub.ru
doi:10.15829/1560-4071-2020-3904

ISSN 1560-4071 (print)
ISSN 2618-7620 (online)

COVID-19 infection after recent heart transplantation: a case report

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History of heart transplantation in combination with immunosuppressive therapy and acute viral respiratory infection overlay makes the patient difficult to manage. In case of COVID-19, the setting is complicated by unknown pathogenesis, including its effect on blood, coagulation system, and lung tissue. Current case report discusses the 60-year-old patient with a COVID-19 infection occurred in the immediate postoperative period after heart transplantation.

Key words: SARS-CoV-2, 2019-nCoV, immunosuppression, coronavirus, atypical pneumonia, hypercoagulation, atrial thrombosis, heart failure.

Relationships and Activities: none.

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Received: 12.05.2020
Revision Received: 14.05.2020
Accepted: 18.05.2020

For citation: Vechorko V. I., Gordeev I. G., Gubareva E. V., Ryndyaeva E. V., Averkov O. V. COVID-19 infection after recent heart transplantation: a case report. *Russian Journal of Cardiology*. 2020;25(5):3904. (In Russ.) doi:10.15829/1560-4071-2020-3904

The pandemic of novel coronavirus infection SARS-CoV-2 (Covid-19) required a review of current standards, including the standards and protocols for the management of various pathologies. Being a viral respiratory infection with an unknown pathogenesis, Covid-19 is especially dangerous for patients with comorbidities and immunodeficiency. Such patients, of course, include people after transplantations. According to study by Pereira, et al. (2020) with a cohort of 90 such patients, sixteen patients died (18% overall, 24% of hospitalized, 52% of ICU). The authors concluded that transplant recipients with COVID-19 appear to have more severe outcomes, although testing limitations likely led to undercounting of mild/asymptomatic cases [1]. Of course, heart recipients are at particular risk [2].

In Russia, according to anti-epidemic measures, the treatment of patients with a suspected or established COVID-19 is carried out in specialized hospitals. O. M. Filatov City Clinical Hospital № 15 in Moscow is a general hospital with a priority area of cardiology, which was completely redesigned to fight infection. We offer a case report of a patient after a recent (less than a month) heart transplantation hospitalized with COVID-19.

Clinical case

A 60-year-old patient was admitted with complaints of fever up to 38,5° C, shortness of breath, weakness, and a tingling under the shoulder blades. He was delivered by the ambulance team from home 4 days after being discharged from another hospital, where he received an orthotopic heart transplantation due to ischemic cardiomyopathy.

These complaints appeared the day after discharge. The patient has a history of myocardial infarction (9 years ago) and hypertension. The epidemiological history was positive: an employee of transplantology center had a positive test for SARS-CoV-2. The patient came to Moscow from another region for surgical intervention.

The patient takes chronic medications: Methylprednisolone 4 mg/day, Tacrolimus 3 mg/day, Mycophenolate mofetil 2 g/day, Trimethoprim/sulfamethoxazole 480 mg/day, Amlodipine 2,5-5 mg/day.

Upon admission to the hospital, the patient had a moderate state and normal consciousness. The body weight was normal. There were a respiratory rate of 22 per minute, spontaneous breathing, SpO_2 of 90%. Blood pressure was 121/80 mm Hg, heart rate — 115 per minute. The heartbeat was regular, without pulse deficit.

According to multi-slice computed tomography (Figure 1), there were bilateral multisegmental areas of ground glass opacity and consolidation, mainly in the subpleural sections (right lung — 15%, left — 10%). The lumen of the trachea, the main and segmental bronchi remained constant.

Bronchi were not narrowed; the bronchial walls were thickened. Diaphragm, mediastinum, and pleural cavities were without pathological findings. There was a pericardial fluid with a diameter of up to 32 mm. Mediastinal lymph nodes were not enlarged (up to 9 mm). Report: CT pattern of bilateral multisegmental pneumonia, high level of suspicion COVID-19 infection, moderate severity (CT1). Hydropericardium.

According to the first echocardiography (upon admission), the heart chambers had normal sizes and contractility. Left ventricular (LV) walls were thickened. Mild mitral and tricuspid regurgitation. Grade 1 LV diastolic dysfunction. There were large hydropericardium (up to 3,2 cm). Diastolic collapse of the right atrium and right ventricle. Visceral pericardial layer had depositions.

Three days later, a repeated echocardiogram (Table 1) (Samsung Medison HS60-RUS) showed left atrial dilatation. The left ventricle was D-shaped. LV walls were thickened. Grade 1 mitral and tricuspid regurgitation was identified. LV local and global systolic function were not impaired. Pericardium was without findings. In left atrial appendage, a mobile echo-bright formation 27x11 mm in size, probably a thrombus, was visualized. During the week, its size changed to 27x11 mm. It was decided to not use transesophageal echocardiography. The electrocardiogram is shown in Figure 2.

There were following laboratory findings: hemoglobin level of 77 g/l (hypochromic anemia, anisocytosis), which changed to 100 g/l after blood transfusion; absolute ($0,7\times10^9$/L, followed by a decrease to $0,3\times10^9$/L) and relative lymphopenia; an increase in C-reactive protein level to 70 mg/L and a further decrease to 22 mg/L; an increase in D-dimer level to 800 ng/ml; an increase in procalcitonin level to 0,5 ng/ml, followed by a decrease to 0,1 ng/ml.

The initial diagnosis of COVID-19 infection was made according to clinical, investigational, and epidemiological criteria, and was subsequently confirmed by repeated polymerase chain reaction (PCR) with an interval of 2 days.

The treatment was carried out using the following medications: IV azithromycin, IV ampicillin/sulbactam, intranasal interferon-alpha; therapy with tacrolimus, mycophenolate mofetil, methylprednisolone was continued. Anticoagulants were used: initially — enoxaparin (0,4 ml/day); after detecting left atrial appendage thrombus — rivaroxaban (20 mg/day), subsequently switched with warfarin.

Pericardiocentesis was performed — serous-hemorrhagic fluid of 960 ml was evacuated (hemorrhagic effusion with lymphoid reaction, single mesothelial

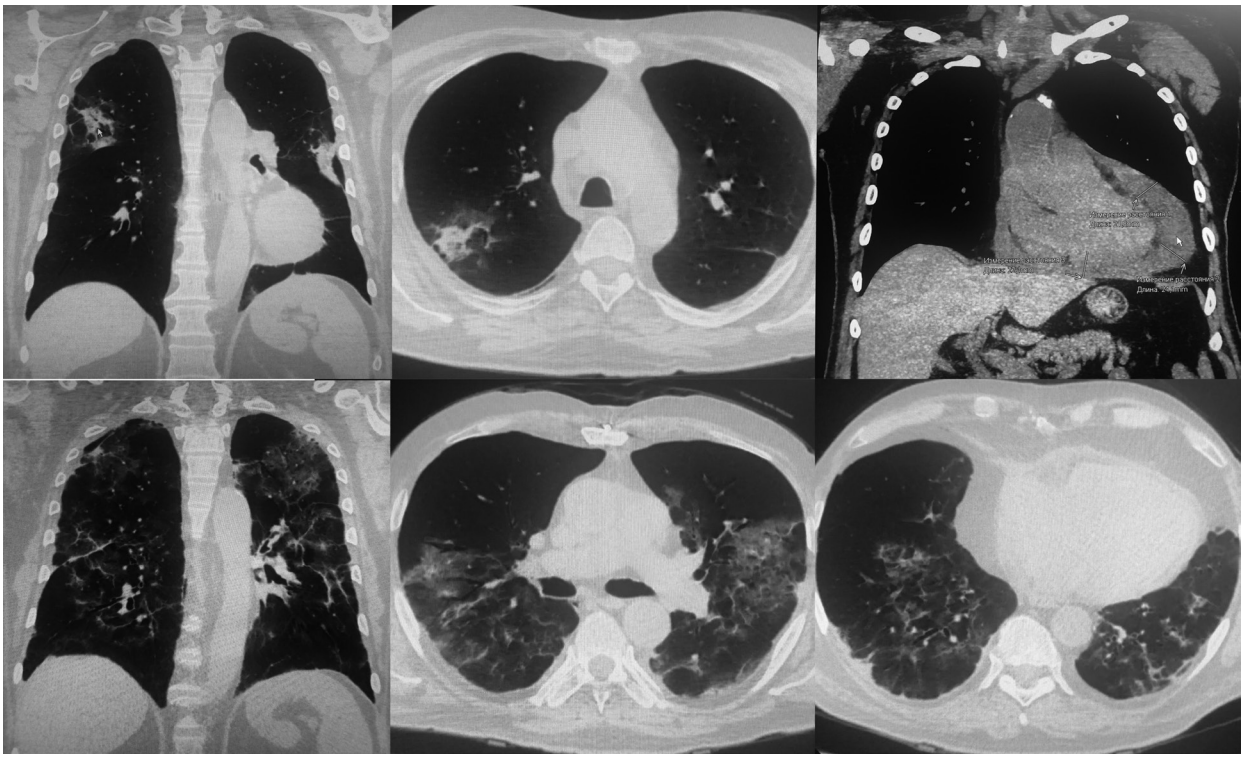

Figure 1. Lung and cardiac computed tomography scan.

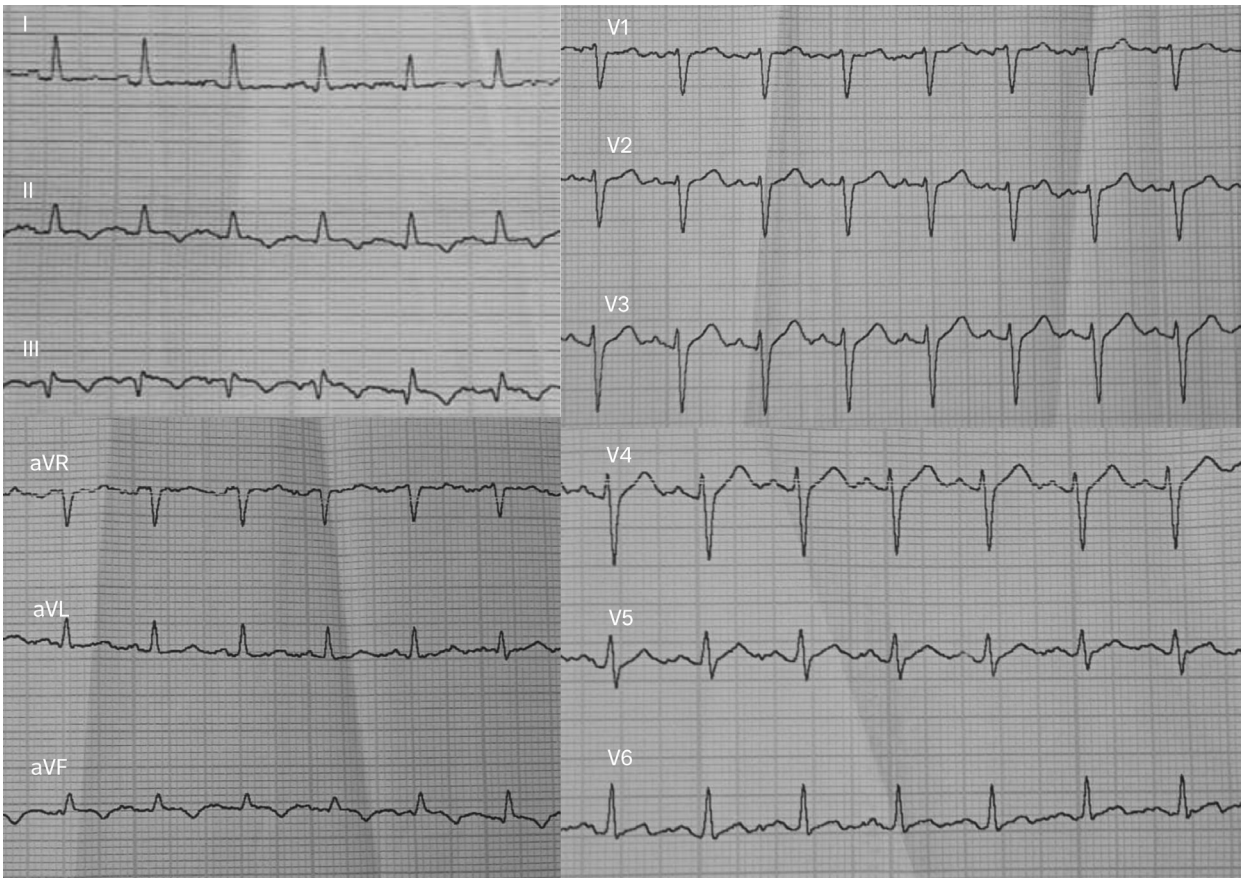

Figure 2. Electrocardiogram.

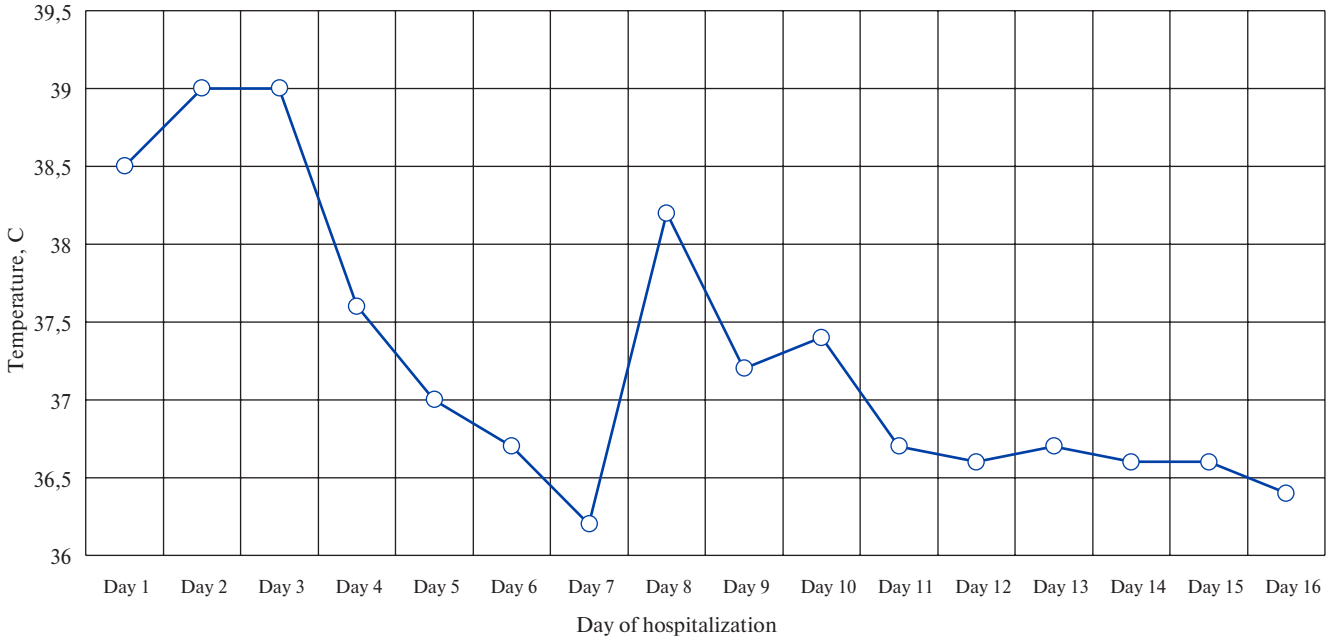

Figure 3. Temperature curve.

Table 1

Echocardiographic data after pericardiocentesis

Parameter	Value	Standard
Aortic annulus, mm	25	до 40
Aortic valve opening, mm	21	15-26
Left atrial size, mm	36x56	30-40
LV EDV, ml	64	67-155
LV ESV, ml	27	22-58
LVEF (Simpson biplane), %	57	52-74
Diastolic thickness of IVS, mm	13	6-11
Diastolic thickness of LVPW, mm	11	6-11
Effective stroke volume, ml	36	-
Right ventricle, ml	27	<33
Right atrial size, mm	28x34	28-40
Pulmonary artery diameter, mm	18	-
Aortic valve: leaflets are not thickened. Vmax — 1,2 m/s, PGr — 6,6 mm Hg. Aortic insufficiency is not detected. Aortic root — 3,7 cm.		
Mitral valve: leaflets are not thickened. Mitral insufficiency — grade 1. Vmax — 0,9 m/s, PGr — 3,9 mm Hg.		
Tricuspid valve: leaflets are not thickened. Tricuspid insufficiency — grade. Vmax — 0,6-0,9 m/s		
Pulmonary valve: insufficiency — grade 1. Vmax 0,9 m/s, PGr 3,3 mm Hg.		
The inferior vena cava is not dilated, collapses with inspiration >50%.		
Abnormally located LV chords. In left atrial appendage, a mobile echo-bright formation 27x11 mm in size, probably a thrombus, is visualized.		

Abbreviations: EDV — end-diastolic volume, ESV — end-systolic volume, LV — left ventricle, EF — ejection fraction, IVS — interventricular septum, LVPW — left ventricular posterior wall, Vmax — maximum flow rate, PGr — pressure gradient.

cells). The drainage was removed, further accumulation of fluid according to echocardiography was not found.

During treatment, the state of the patient was stable, the fever decreased with an episode of febrile temperature return (Figure 3). There was no shortness of breath; SpO_2 — 95% (oxygen insufflation of 6 l/min). Hemodynamics was stable.

To continue treatment, the patient was transferred to a specialized institution dealing with patients after

heart transplantation. At discharge, there was an improvement in the form of body temperature normalization, a decrease in C-reactive protein and procalcitonin levels. Anticoagulant therapy with warfarin was administered under the control of INR.

Diagnosis upon transferring:

Primary diagnosis: I25.5 Ischemic cardiomyopathy. Postinfarction cardiosclerosis. Implantation of IABP. Removal of IABP. Orthotopic heart transplantation. Stage 2A heart failure (Strazhesko-Vasilenko Classification), NYHA class II.

Competing diagnosis: U07.1 COVID-19 infection (identified virus). SARS-CoV-2 smears are twice positive.

Comorbidities: I11.9 Stage 3 hypertension, very high risk.

Complications of the primary disease: J12.8 Community-acquired bilateral multisegmental viral pneumonia. Grade II respiratory failure. I31.3 Exudative pericarditis. Pericardiocentesis, pericardial drainage. Drainage removal. I51.3 Left atrial appendage thrombus.

Discussion

This patient had a combination of several pathological processes: immunosuppression, infection against its background, early period after recent major surgical intervention, cardiac disease. An additional complicating factor was the development of left atrial thrombosis, which increase the risk of embolism. Actually, the association of the infectious inflammatory process with the increase in blood coagulation has long been known. However, unknown mechanisms of COVID-19 infection and recent heart transplant heart makes the management of this patient unusual.

In a study by Li F, et al. (2020), there was a first experience of managing such patients in January-February 2020. The first case, a 51-year-old man with a history of heart transplantation in 2003, initially SpO_2 of 99%, without shortness of breath, body temperature of 38,5° C, with characteristic CT changes — ground glass opacity. Then COVID-19 infection was confirmed by PCR test. Apparently healthy patient was discharged after 1-month hospitalization, but with persistent residual changes in lung CT scan. The second patient, a 43-year-old man, was quarantined due to the 2019-nCoV positive test. Then he was hospitalized, but was discharged 2 weeks later due to the double negative PCR test. These authors indicate that the development of the disease and the clinical characteristics of heart recipients differ little from the common ones [3].

Holzhauser L, et al. reported the experience of managing two COVID-19 patients with a transplanted heart (2020). First case is a 59-year-old African-American woman who underwent heart transplantation in 2012 due to non-ischemic cardiomyopathy, also suffering from diabetes, hypertension and chronic kidney disease. The clinical state was severe, with an arterial pH of 7,3, pCO_2 of 32 mm Hg, pO_2 of 64 mm Hg with FiO_2 of 0,8. The condition remained serious. On the seventh day of hospitalization, it was decided to not use extracorporeal membrane oxygenation due to comorbidity profile, age, unfavorable prognosis. On the tenth day, the family was informed of the futility of further treatment and it was discontinued. The second case is a 75-year-old man who underwent heart transplantation in 2000 due to ischemic cardiomyopathy. He admitted in a moderate severity condition. Within 4 days before hospitalization there was a cough, fever up to 38,6° C, diarrhea, weakness and loss of appetite. Upon admission, SpO_2 was 99%. The clinical course worsened on the fifth day: there was a need for oxygen insufflation, single administration of tocilizumab, methylprednisolone. His condition improved and on the eighth day he was discharged. The authors noted that in heart recipients, the immune response to viruses and the transplant-vs-host interaction, against which the infection develops, should be divided. This requires more careful management in order to overcome the response to the virus and avoid cytokine release syndrome [4].

Ren ZL, et al. (2020) summarizes data on heart recipients in context of COVID-19 pandemic. The study included 87 patients, of which 57 had an unfavorable epidemiological history. All preventive and quarantine measures were performed. Four patients had signs of acute respiratory infection, of which 3 had negative PCR test (4^{th} — unknown). According to retrospective assessment of clinical and laboratory data, 21% of patients had lymphopenia. Five patients had an episode of hepatic failure, 6 — renal failure. The authors concluded that in context of COVID-19 pandemic, patients with a transplanted heart, being at high risk, take adequate precautions and do not characterized by an increased danger [5].

In our example, the patient had an increased risk of thrombosis and embolism. For the pathogenesis of SARS-CoV-2 infection, blood coagulation characteristics have been shown [6], but they have yet to be studied. According to study by Panigada M, et al. (2020), a severe inflammatory response triggers changes in blood coagulation, which can be explained by disseminated intravascular coagulation syndrome. However, the authors did not show an increase in the number of platelets. There was an increase in levels of fibrinogen, D-dimer, factors VIII and von Willebrand, which does not characteristic of it, but can partially explain the risk of thromboembolism [7].

The coagulation system is influenced by other regulatory systems, including the sympathetic nervous system, and in case of cardiac disease and heart failure, this effect is enhanced [8]. It should be noted that patients after transplantation of organs, in particular, the heart, have features of the immune system and the related mechanisms of inflammation, and, accordingly, hemostasis. The possible direct effect of SARS-CoV-2 on the coagulation system is not excluded. The widespread use of anticoagulants is effective in patients hospitalized with COVID-19 infection. However, It should be taken into account that only vitamin K antagonists are non-selective anticoagulants that can affect many components of hemostasis. They require control of dose and drug interactions [9, 10]. The risk of thrombotic events is by no means the only one in patients with transplanted organ and COVID-19, but one of the most important.

Conclusion

The spread of a novel infection requires a review of all current recommendations. Perhaps a new situation will entail a revision of the risk factor model and biosocial relationships of the disease development [11]. With the accumulation of data on COVID-19 pathogenesis, the features of managing patients with a different underlying disease will become clear. It is important to remember that humanity is not safe from new pandemics. In parallel with the study of a novel COVID-19 infection as such, it is necessary to develop ideas about working in suspense.

Relationships and Activities: none.

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