New Markers of Coronary Heart Disease with Old Myocardial Infarction: Certain Variants of Relative Length of Telomeric Repeats

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ABSTRACT

One of the possible factors in the occurrence of coronary heart disease with myocardial infarction is oxidative stress. Oxidative stress intensifies the formation of free radicals, causing defects in proteins and nucleic acids. This can lead to their partial or complete destruction. For example, the result of such destruction of DNA molecules may be a decrease in the length of telomeric repeats in the chromosomes of cells in coronary heart disease.

Therefore, the aim of this work was to analyze the association of certain variants of the relative length of telomeric repeats (VRLTR) with coronary heart disease with old myocardial infarction (CHD with MI).

Keywords: relative length of telomeric repeats; coronary heart disease with myocardial infarction; percentage of the calibrator; oxidative stress; protective effect; chromosomes.

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New Markers of Coronary Heart Disease with Old Myocardial Infarction: Certain Variants of Relative Length of Telomeric Repeats

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ABSTRACT

One of the possible factors in the occurrence of coronary heart disease with myocardial infarction is oxidative stress. Oxidative stress intensifies the formation of free radicals, causing defects in proteins and nucleic acids. This can lead to their partial or complete destruction. For example, the result of such destruction of DNA molecules may be a decrease in the length of telomeric repeats in the chromosomes of cells in coronary heart disease.

Therefore, the aim of this work was to analyze the association of certain variants of the relative length of telomeric repeats (VRLTR) with coronary heart disease with old myocardial infarction (CHD with MI).

To measure the length of telomeric repeats, whole blood was collected, with the following DNA isolation from nuclear cells. The relative length of telomeric repeats was calculated based on the formula "2 to the power (-ΔCt)", where ΔCt = Ct of telomeres-Ct of albumin. In this case, Ct of telomeres is the threshold cycle of the telomeric repeat, and Ct of albumin is the threshold cycle of the albumin gene. The results of the relative length of telomeric repeats are presented as a percentage of the calibrator. DNA isolated from HeLa cell line was used as a calibrator.

By measuring variants of the relative length of telomeric repeats in the studied samples, an association of coronary heart disease with myocardial infarction with VRLTR-46, VRLTR-49, VRLTR-51, VRLTR-53 and VRLTR-56 was detected. At the same time, 6 of 21 variants of the relative length of telomeric repeats (VRLTR-63, VRLTR-65, VRLTR-68, VRLTR-70, VRLTR-71 and VRLTR-73) had a protective effect in coronary heart disease with myocardial infarction.

Therefore, in the present research work, we propose new markers of coronary heart disease with old myocardial infarction: certain variants of relative length of telomeric repeats.

Keywords: relative length of telomeric repeats; coronary heart disease with myocardial infarction; percentage of the calibrator; oxidative stress; protective effect; chromosomes.

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I. INTRODUCTION

One of the possible factors in the occurrence of coronary heart disease with myocardial infarction is oxidative stress [1-5]. Oxidative stress intensifies the formation of free radicals, causing defects in proteins and nucleic acids [6-10]. This can lead to their partial or complete destruction [11-15]. For example, the result of such destruction of DNA molecules may be a decrease in the length of telomeric repeats in the chromosomes of cells in coronary heart disease [16-20].

However, to date, there is no reliable data confirming the association of certain variants of telomeric repeat lengths with coronary heart disease with old myocardial infarction.

Telomeres are regions of chromosomal ends which contain tandem six-nucleotide repeats (TTAGGG) [21-25]. It is believed that they are intended for stable cell replication [26-30]. With each subsequent cell mitosis, the size of telomeric repeats decreases. Evidence has been obtained that a critical decrease in telomere size can cause degenerative changes in the cell followed by apoptosis [31-35].

It has been noted that individuals who have very short telomeres have a higher risk of developing coronary heart disease [35-40]. Scientists from Scotland have shown that individuals with shortened telomeres have a threefold increased risk of death over the next decade [41]. Short telomeric repeat lengths have been found in elderly patients with cardiomyopathy [42]. Type 2 diabetes mellitus has been found to be significantly increased in individuals with short telomeres compared to individuals with long telomeres [43].

Meanwhile, it was found that the speed of decrease in the length of telomeric repeats is almost the same for different types of cells and tissues. Therefore, the use of human blood leukocytes, as the most accessible biological material for research, seems to be optimal [42, 43].

So, the main direction in the study of telomeres turned out to be the detection of the association between certain variants of shortened telomeres and certain human diseases. For this reason, it seems to be appropriate to include the analysis of telomeric repeat length variants into the biomarkers studied in coronary heart disease with myocardial infarction.

II. MATERIALS AND METHODS

To measure the length of telomeric repeats, whole blood was collected, with the following DNA isolation from nuclear cells. The DNA extraction kit "DNA-Extran1" (CJSC Synthol, Russia) was used. The length of telomeric repeats was determined by quantitative real- time polymerase chain reaction (RT-PCR) using a BIO-RADCFX 96 Real-Time System amplifier (Singapore). The study of each sample was repeated three times.

The relative length of telomeric repeats was calculated based on the formula "2 to the power (-ΔCt)", where ΔCt = Ct of telomeres-Ct of albumin. In this case, Ct of telomeres is the threshold cycle of the telomeric repeat, and Ct of albumin is the threshold cycle of the albumin gene. It should be noted that the albumin gene acted as an internal control against which the length of telomeric repeats was determined. The results of the relative length of telomeric repeats are presented as a percentage of the calibrator. DNA isolated from HeLa cell line was used as a calibrator.

Since there were no significant age differences between the samples of patients with coronary

heart disease who had suffered a myocardial infarction and conditionally healthy study participants, normalization of the length of telomeric repeats by age was not performed.

Statistical analysis of the relative length of telomeric repeats was carried out using the IBM SPSS Statistics 27.0 software package.

III. RESULTS AND DISCUSSION

In 300 DNA samples from samples of patients with coronary heart disease with old myocardial infarction (CHD with MI) and conditionally healthy study participants, variants of the relative length of telomeric repeats (RTL) were analyzed using real-time PCR.

Methods of clinical examination, high-resolution B-mode ultrasonography and DNA extraction were used. The criteria for inclusion in the sample of patients CHD with MI were-

1. Men and women aged 45 to 79 years.
2. Old myocardial infarction in the anamnesis.
3. Pathological Q waves with or without symptoms in the absence of non-ischemic causes. 4. Lack of exclusion criteria.
4. Voluntary consent to participate in the study.

The criteria for excluding patients CHD with MI were:

1. Age younger than 45 or older than 79 years.
2. Abnormal anatomical configuration of the neck and muscles; pronounced tortuosity and/or depth of the carotid arteries, and/or unusual locations of arterial branches.
3. Presence of oncological and other chronic diseases requiring regular drug therapy, except arterial hypertension.
4. Congestive heart failure (NYHA class III-IV).
5. Refusal to sign informed consent to participate in the study.

Based on clinical examination and ultrasonography data.

Two samples will be created consisting of-

1. 150 patients with coronary heart disease with old myocardial infarction;
2. 150 conditionally healthy study participants. An analysis of the average value of variants of relative length of telomeric repeats (VRLTR) in the blood leukocytes of study participants was carried out (Table 1). In Table 1, the results are presented as the mean value of the VRLTR and the standard error to the mean. According to the results presented in Table 1, the average value of VRLTR is significantly lower in patients with coronary heart disease with old myocardial infarction compared to conditionally healthy study participants (by 25.0%).

Analysis of variants in the relative length of telomeric repeats in samples of patients with CHD with MI and conditionally healthy study participants was carried out using nonparametric statistics using the Wilcoxon rank test (Table 2) with further correlation analysis of mutations detected using the Wilcoxon test (Table 3). It should be noted that VRLTR have designations depending on their relative length in percents to the calibrator. The range of values for variants of the relative length of telomeric repeats in the studied samples ranged from 31% to 80%, in relation to the calibrator.

Table 1: Analysis of the Average Value of Variants of the Relative Length of Telomeric Repeats in the Blood Leukocytes of Study Participants

Samples of Study Participants	Mean Relative Length of Telomeric Repeats	Standard Error to the mean	Reliability of Results
Patients with coronary heart disease with old myocardial infarction	51	1.1	$p \leq 0.001$
Conditionally healthy study participants	68	1.4	$p \leq 0.05$

Table 2: Analysis of Variants of the Relative Length of Telomeric Repeats in Samples of Patients with Coronary Heart Disease with Old Myocardial Infarction (CHD With MI) and Conditionally Healthy Study Participants using the Wilcoxon Rank Test

Variants of the Relative Length of Telomeric Repeats	Type of Rank	Number of Ranks	Mean Rank	Sum rank
VRLTR -31	Negative	2	3.11	3.18
	Positive	2	1.27	1.65
	Neutral	3		
VRLTR -32	Negative	1	3.15	4.17
	Positive	2	2.56	4.58
	Neutral	4		
VRLTR -33	Negative	2	2.16	3.18
	Positive	2	2.05	3.16
	Neutral	3		
VRLTR -34	Negative	2	1.43	1.72
	Positive	1	2.26	2.26
	Neutral	4		
VRLTR -35	Negative	2	2.04	2.17
	Positive	2	1.12	1.21
	Neutral	3		
VRLTR-36	Negative	2	2.08	3.06
	Positive	3	3.14	4.08
	Neutral	2		
VRLTR-37	Negative	2	2.02	3.27
	Positive	2	3.02	4.09
	Neutral	3		
VRLTR-38	Negative	2	2.16	2.48
	Positive	3	2.29	2.87
	Neutral	2		
VRLTR-39	Negative	2	3.05	4.21
	Positive	1	4.83	4.83

	Neutral	4		
VRLTR-40	Negative	2	2.30	3.11*
	Positive	4	1.51	6.41*
	Neutral	1		
VRLTR-41	Negative	1	4.22	4.22*
	Positive	2	3.78	8.63*
	Neutral	3		
VRLTR-42	Negative	2	4.18	6.03
	Positive	2	3.05	4.97
	Neutral	3		
VRLTR-43	Negative	2	2.75	3.18*
	Positive	4	3.21	6.69*
	Neutral	1		
VRLTR-44	Negative	1	2.19	2.19*
	Positive	2	2.87	4.81*
	Neutral	4		
VRLTR-45	Negative	3	2.11	3.94
	Positive	1	3.16	3.16
	Neutral	3		
VRLTR-46	Negative	2	3.17*	7.30*
	Positive	4	5.32*	21.33*
	Neutral	1		
VRLTR-47	Negative	1	3.98	3.98*
	Positive	2	4.01	8.04*
	Neutral	3		
VRLTR-48	Negative	3	5.35	6.24
	Positive	2	4.14	6.45
	Neutral	2		
VRLTR-49	Negative	2	1.10*	2.24*
	Positive	4	2.21*	8.96*

	Neutral	1		
VRLTR-50	Negative	4	3.11	5.03
	Positive	2	2.15	3.15
	Neutral	1		
VRLTR-51	Negative	2	2.08*	6.18*
	Positive	4	6.16*	12.36*
	Neutral	1		
VRLTR-52	Negative	2	3.25	3.98
	Positive	1	4.08	4.08
	Neutral	4		
VRLTR-53	Negative	2	2.60*	7.84*
	Positive	3	5.45*	16.75*
	Neutral	2		
VRLTR-54	Negative	4	6.71	7.56
	Positive	1	4.12	4.12
	Neutral	2		
VRLTR-55	Negative	2	1.50	2.11
	Positive	2	2.15	2.94
	Neutral	3		
VRLTR-56	Negative	2	2.50*	5.09*
	Positive	4	5.04*	20.24*
	Neutral	1		
VRLTR-57	Negative	3	3.64	4.14
	Positive	3	5.16	6.12
	Neutral	1		
VRLTR-58	Negative	3	5.16	6.28
	Positive	2	3.11	3.54
	Neutral	3		
VRLTR-59	Negative	4	2.28*	5.56
	Positive	2	1.14*	4.27

	Neutral	1		
VRLTR-60	Negative	3	3.16	4.12
	Positive	2	5.41	5.98
	Neutral	1		
VRLTR-61	Negative	2	1.14	1.50*
	Positive	3	2.01	3.00*
	Neutral	2		
VRLTR-62	Negative	2	3.33	4.51
	Positive	2	2.50	3.57
	Neutral	3		
VRLTR-63	Negative	4	5.08*	20.46*
	Positive	2	2.24*	5.11*
	Neutral	1		
VRLTR-64	Negative	2	2.19	3.74
	Positive	2	3.11	4.26
	Neutral	3		
VRLTR-65	Negative	4	4.06*	16.28*
	Positive	2	2.02*	4.11*
	Neutral	1		
VRLTR-66	Negative	1	1.32	1.32
	Positive	2	1.54	2.18
	Neutral	4		
VRLTR-67	Negative	2	2.37	2.94
	Positive	2	3.68	4.01
	Neutral	3		
VRLTR-68	Negative	4	4.25*	17.48*
	Positive	2	2.16*	4.34*
	Neutral	1		
VRLTR-69	Negative	1	1.15	1.15
	Positive	2	1.34	1.68

	Neutral	3		
VRLTR-70	Negative	4	6.12*	25.56*
	Positive	2	2.11*	4.26*
	Neutral	2		
VRLTR-71	Negative	4	6.18*	26.83*
	Positive	2	2.01*	4.04*
	Neutral	1		
VRLTR-72	Negative	3	3.06	4.10
	Positive	2	2.34	3.72
	Neutral	2		
VRLTR-73	Negative	4	4.17*	16.71*
	Positive	2	2.08*	4.18*
	Neutral	1		
VRLTR-74	Negative	1	1.16	1.16
	Positive	2	1.19	1.82
	Neutral	3		
VRLTR-75	Negative	1	2.96	2.96
	Positive	1	3.76	3.76
	Neutral	3		
VRLTR-76	Negative	4	2.38	9.56*
	Positive	2	2.04	4.71*
	Neutral	1		
VRLTR-77	Negative	2	3.24	4.59
	Positive	1	3.22	3.22
	Neutral	3		
VRLTR-78	Negative	3	5.33	8.35
	Positive	3	5.62	7.68
	Neutral	1		
VRLTR-79	Negative	3	7.23	21.80*
	Positive	1	3.15	3.15*

	Neutral	3		
VRLTR-80	Negative	4	6.18*	8.81
	Positive	2	3.07*	5.94
	Neutral	1		

*Note: * is more than two-fold difference between positive and negative rank value.*

According to the Wilcoxon rank test, 21 variants of the relative length of telomeric repeats were detected to be associated with coronary heart disease with myocardial infarction: VRLTR-40, VRLTR-41, VRLTR-43, VRLTR-44, VRLTR-46, VRLTR-47, VRLTR-49, VRLTR-51, VRLTR-53, VRLTR-56, VRLTR-59, VRLTR-61, VRLTR-63, VRLTR-65, VRLTR-68, VRLTR-70, VRLTR-71, VRLTR-73, VRLTR-76, VRLTR-79 and VRLTR-80.

During a correlation analysis, for 5 of the 21 detected VRLTR variants, highly significant differences were found between samples of patients with CHD with MI and conditionally healthy study participants (Table 3). In particular, an association of coronary heart disease with old myocardial infarction with variants of the relative length of telomeric repeats VRLTR-46, VRLTR-49, VRLTR-51, VRLTR-53 and VRLTR-56 was identified. At the same time, 6 of 21 variants of the relative length of telomeric repeats (VRLTR-63, VRLTR-65, VRLTR-68, VRLTR-70, VRLTR-71 and VRLTR-73) had a protective effect in coronary heart disease with old myocardial infarction.

IV. CONCLUSION

In the present research work, we propose new markers of coronary heart disease with old myocardial infarction: certain variants of relative length of telomeric repeats (VRLTR). These markers in the studied samples were presented as percentages of the calibrator. DNA isolated from HeLa cells was used as a calibrator.

By measuring variants of the relative length of telomeric repeats in the studied samples, an association of coronary heart disease with myocardial infarction with VRLTR-46, VRLTR-49, VRLTR-51, VRLTR-53 and VRLTR-56 was detected. At the same time, 6 of 21 variants of the relative length of telomeric repeats (VRLTR-63, VRLTR-65, VRLTR-68, VRLTR-70, VRLTR-71 and VRLTR-73) had a protective effect in coronary heart disease with myocardial infarction.

Table 3: Correlation of Variants of the Relative Length of Telomeric Repeats with Coronary Heart Disease with Old Myocardial Infarction

Number	Variants of the relative length of telomeric repeats	Correlation coefficient	Asymptomatic significance (two-sided)
1	VRLTR-40	0.211	0.101*
2	VRLTR-41	0.302	0.064*
3	VRLTR-43	0.287	0.071*
4	VRLTR-44	0.218	0.096*
5	VRLTR-46	0.609	0.001**
6	VRLTR-47	0.305	0.068*
7	VRLTR-49	0.591	0.002**
8	VRLTR-51	0.610	0.001**
9	VRLTR-53	0.554	0.003**
10	VRLTR-56	0.621	0.001**
11	VRLTR-59	-0.312	0.056*
12	VRLTR-61	-0.306	0.068*
13	VRLTR-63	-0.608	0.001**
14	VRLTR-65	-0.615	0.001**
15	VRLTR-68	-0.425	0.043**
16	VRLTR-70	-0.554	0.036**
17	VRLTR-71	-0.482	0.031**
18	VRLTR-73	-0.542	0.042**
19	VRLTR-76	-0.244	0.076*
20	VRLTR-79	-0.267	0.071*
21	VRLTR-80	-0.326	0.054*

*Note: * is highly significant correlation of mutations with CHD with MI (p≤0.05);*
*** is correlation of mutations with coronary heart disease with myocardial infarction at the level of significance p≤0.1.*

Author Contributions

Conceptualization, M.A.S.; methodology, M.A.S.; validation, A.I.R. and M.D.S.; formal analysis, M.A.S. and M.D.S.; investigation, M.A.S., N.A.D., M.D.S. and A.I.R.; resources, A.Yu.P., T.I.K., I.A.S., D.F.B. and A.V.Ch.; data curation, M.A.S, N.A.D. and M.D.S.; Writing – Original Draft Preparation, M.A.S., M.D.S., N.A.D., A.I.R., P.P. and D.M.; Writing – Review & Editing, V.P.K., M.A.P. and A.Yu.P.; Project Administration, A.N.O. and V.N.S; Funding Acquisition, A.N.O.

All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was performed in accordance with the principles outlined in the Declaration of Helsinki of 1975 and its revised version of 2013. The study protocol was approved by the Institute for Atherosclerosis Research Committee on Human Research, Moscow, Russia, protocol No. 078-15 of September, 08, 2015.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data availability statements

The datasets presented in this article are not readily available because the data are part of an ongoing study of patients with cardiovascular diseases from Russia.

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Conflict of interests

The authors declare no conflict of interests. The material for the investigation has never been published before.

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