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CLINICAL, HEMODYNAMIC AND GENETIC ASPECTS OF THE DEVELOPMENT OF UNSTABLE VARIANTS ANGINA IN YOUNG MEN

Khasanjanova Farida Odilovna
assistant Professor of internal diseases №2 of Samarkand State medical Institute, Samarkand, Uzbekistan Address: Uzbekistan, Samarkand, Kozi-arik Street, house 450, Phone: +99897-892-11-54
E-mail: faridaxasanjanova@mail.ru
Khaydarova Dilrabo Davronovna
Assistant of the Department of Internal Diseases No. 2 of the Samarkand State Medical Institute, Samarkand, Uzbekistan Address: Uzbekistan, Samarkand, Abu Mansur Street Phone: +99897-914-43-45
E-mail:haydarova.1979@gmail.com
Muradova Raila Rustamovna
Assistant of the Department of Clinical Pharmacology of the Samarkand State Medical Institute, Samarkand, Uzbekistan Phone: +99891-553-52-26
E-mail: muradovarai@mail.ru
Nuralieva Rano Matyakubovna
Assistant of the Department of Clinical Pharmacology of the Samarkand State Medical Institute, Samarkand, Uzbekistan
E-mail:rano_nuralieva@mail.ru
Nasirova Dilangiz Akbarovna
student of the Medical and Pedagogical Faculty of Samarkand State University State medical institute, Samarkand, Uzbekistan
Phone: +99891-522-58-48
E-mail: Ndilangiz@gmail.com

Annotation

Recently, the prevalence of unstable variants of angina pectoris (NVS) among men at a young age has increased markedly. A significant role in the inflammation of the atherosclerotic plaque, which underlies the pathogenesis of NVS, is assigned to cytokines by the mediator. To date, the role of cytokine gene polymorphism in the development of NVS associated with inflammatory processes has been proven.

Object: The aim of the work is to study the clinical and hemodynamic and genetic aspects of the development of NVS in men at a young age on the basis of

clinical and hemodynamic parameters, genetic, biochemical markers and other risk factors.

Materials and methods: 100 patients with NVS were examined on the basis of the Samarkand branch of the Republican Scientific Center for Emergency Medical Care (SFRNCEMP) from 2018 to 2020. The patients were divided into 2 groups. The first group consisted of 70 young men. The second group consisted of 15 elderly men. This group of patients was a comparison group. The control group consisted of 15 practically healthy volunteers

Results: According to our results, it was found that young men, smokers who are overweight or obese, suffering from hypertension, having some form of dyslipidemia, as well as people with a hereditary predisposition to early development of cardiovascular pathology are primarily at increased risk of early development of NVS.

Conclusions: There is a fact that NVS in young people is still quite a rare event, in recent years there has been a steady increase in the frequency of its occurrence. Young men, smokers, and people with a hereditary predisposition to the early development of CVD are primarily at increased risk of early development of NVS. A better understanding of the main causes and mechanisms of the development of NVS in men at a young age is a serious task of modern cardiology. The ability to predict the risk of developing CVD in young men on the basis of traditional RFS, half of which are modifiable, opens up new prospects in the formation of a strategic approach to the management of young people with high risk.

Keywords: unstable angina variants, male, young age, interleukin gene, acute coronary syndrome.

Introduction

Cardiovascular diseases (CVD) ranks first in both economically developed and developing countries of the world in the structure of morbidity and mortality of the population [14]. According to many studies, recently there has been a continuous trend towards an increase in the number of young patients with unstable variants of angina pectoris (NVS), which is one of the variants of coronary heart disease (CHD) and this disease is an important socio-economic problem due to early disability and early mortality [5].

The incidence of NVS among young people (under 45 years of age), according to a number of foreign authors, ranges from 3 to 10% [1]. According to numerous studies, it has been proven that the incidence of CHD in men under 45 years of age is 1.4-1.5 times greater than in women of this age. Men with NVS at a young age have risk factors (FR) [3,4] that contribute to the early development and progression of atherosclerotic changes in the coronary arteries [6,7]. NVS, which manifested in men at a young age, differs from the elderly in the structure of the FR, clinical manifestations and prognosis of the disease.

Recently, in addition to traditional ffs of the development of CVD, a wider range of features associated with the early development of NVS has been considered. The most important risk factor for the development and progression of atherosclerosis, along with smoking [2, 15], arterial hypertension (AH) [1, 11], dyslipidemia, and obesity, is a genetic predisposition.

It is known that the pathogenesis of NVS is influenced by environmental factors that are realized against the background of genetic predisposition, so early detection of the hereditary nature and molecular mechanisms of NVS development is the basis of modern cardiology [13].

For the same reason, large-scale studies on genome-wide analysis of associations with CVD have recently been conducted all over the world, but due to the multifactorial nature of these pathologies, each ethnic group has its own specific range of genetic markers associated with an increased risk of developing a particular cardiovascular pathology. In clinical laboratory practice, pre-symptomatic diagnosis of NVS can be achieved through molecular genetic research of "predisposition genes" or candidate genes-polymorphic alleles compatible with birth and life, but under certain unfavorable conditions that contribute to the development of pathological conditions and diseases [18].

Links of genetic FR with predisposition to the disease are most often found in groups of patients exposed to some additional adverse external influences, such as, for example, improper lifestyle, stress, inactivity, smoking or other bad habits,

concomitant other diseases, unbalanced diet, medications, poor environmental conditions, infections, environmental pollution, etc. [10].

Many studies have shown the additive nature of the action of various genetic and environmental frs [8]. In this regard, active exposure to modifiable FR diseases in young people with a genetic predisposition may prevent the implementation of the impact of adverse genetic factors.

The analysis of molecular genetic markers associated with increased risk of HBC men at a young age, may provide an opportunity to take steps for early prevention of the disease in their carriers and, accordingly, will allow, if not to prevent the development of disease, then at least push back the timing of its occurrence or reduce the severity of the disease [9]. For this reason, the identification of candidate genes responsible for the development and course of NVS in young men is of scientific and clinical interest.

2 candidate genes were selected for the study, which, according to international databases, are associated with NVS: the pro-inflammatory interleukin 1β (IL-1β) C3953 (rs1143634) and anti-inflammatory interleukin-10 (IL-10) G1082A (rs1800896) gene.

The candidate gene, the il1β gene encoding interleukin 1, is a pro-inflammatory cytokine. IL-1β secreted by monocytes or lymphocytes, play a key role in attracting leukocytes to the endothelium, increase the binding of LDL with endothelium, alter the homeostatic properties of the endothelium, in the course of IL-1β may contribute to destabilization of atherosclerotic plaques by increasing the procoagulant activity of endothelial and metabolic disorders lipids (84).

IL-1β may play a role in atherothrombotic disease, contributing to the formation of atherosclerotic lesions, increasing vascular inflammation, and triggering the destabilization of atherosclerotic plaque, contributing to the formation of prothrombotic status.

Patients with NVS showed statistically significantly higher levels of IL-1β compared to healthy people.

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Another candidate gene in our study is the IL10 gene encoding interleukin 10, which is related to anti-inflammatory cytokines. IL10 is secreted by activated macrophages and T-helper cells of the second type. It performs many anti-inflammatory functions.

Many studies have shown that changing the level of IL10 not only mitigates the development of atherosclerosis, but also reduces tissue damage. It is believed that increasing its level provides a protective effect in the development of atherosclerosis. Identification of genetic factors and assessment of their contribution to the development of CVD are the main tasks of modern molecular cardiology. In this regard, genetic research devoted to the study of this disease is of particular relevance.

Objective: To study the clinical and hemodynamic and genetic aspects of the development of NVS in men at a young age on the basis of clinical and hemodynamic parameters, genetic, biochemical markers and other risk factors.

Material and methods: 100 patients with NVS were examined on the basis of the Samarkand branch of the Republican Scientific Center for Emergency Medical Care (SFRNCEMP) from 2018 to 2020. The patients were divided into 2 groups. The first group consisted of 70 young men. The second group consisted of 15 elderly men. This group of patients was a comparison group. The control group consisted of 15 practically healthy volunteers (Fig. 1).

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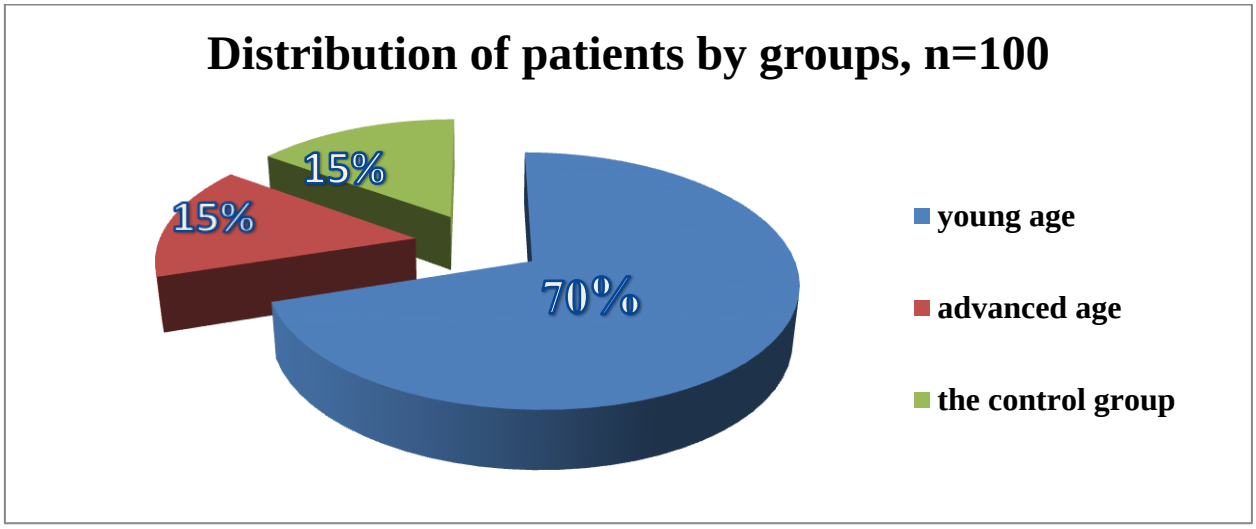
Fig.1

Distribution of patients by groups



Inclusion criteria: young men under 45 years of age and older men over 60 years of age with a confirmed diagnosis of NVS.

Exclusion criteria: men under 45 years of age who have been excluded from the diagnosis of NVS/ACS, men who refused to participate in the study, a serious and unstable condition of the patient that makes it difficult to conduct the survey, acute cerebral circulation disorder, the presence of acute or chronic diseases in the acute stage.

In all patients, clinical and anamnestic data were evaluated, standard general clinical and biochemical studies, including lipid metabolism indicators, and fasting glucose was evaluated. In addition to standard electrocardiography (ECG) in 12 leads, all patients underwent echocardiography (EchoCG) on the Mindray device in accordance with the recommendations of the American Association of Echocardiography in M - and B - modes, height and weight were measured with the calculation of body mass index (BMI). The ESH/ESC (2015) and RKO/WHO (2014) recommendations were used for the diagnosis of NVS.

When collecting anamnesis in men with NVS, we found out the presence of CHD (previously suffered myocardial infarction (MI), angina pectoris of tension or rest), the presence of risk factors (atherosclerosis of other vascular areas, hypertension, smoking, diabetes, obesity). When questioning the patient paid

attention to the period preceding the development of the NAF, as well as the factors behind the development of this disease (excessive exercise, infection, emotional stress), find out information about the early manifestation of CVD in next of kin.

The leading complaint in individuals with unstable angina is pain behind the sternum. For a more detailed description of anginal pain, the following criteria were used: features of the pain syndrome, intensity of the pain attack, frequency of pain attacks, duration of the pain attack, tolerance to physical activity, the effect of nitroglycerin, non-narcotic or narcotic analgesics; vegetative manifestations, hemodynamic disorders.

For the diagnosis of NVS, the following clinical groups are characteristic: patients after a prolonged anginal attack at rest, lasting more than 15 minutes, without taking nitroglycerin; patients with severe angina pectoris that first occurred in the last 28-30 days, persons who have destabilized the pre-existing SS with the appearance of characteristics inherent in at least III FC according to the classification of the Canadian Association of Cardiology or attacks of pain at rest.

The diagnosis of post-infarction cardiosclerosis was made on the basis of anamnestic data, ECG and EchoCG data.

Statistical processing of the results was carried out using the statistical software packages Arlequin 2006 (version 3.5.2.2.), Excel 2017, SISA. Data storage and primary processing were performed in a Microsoft Excel 2010 database using the Statistica 10 program. The data were expressed as follows: mean (M) ± standard deviation (m). To determine the statistical significance of differences in continuous values depending on the type of distribution, the Student's t criterion (for parametric distribution) and the Kolmogorov-Smirnov criteria, and the Mann-Whitney U criterion (for nonparametric distribution) were used. Percentages are based on the Chi-square criterion. The level of statistical significance was taken corresponding to p0. 05.

Results of the study: The groups of patients studied were comparable in age. The average age of the examined patients in the first group of patients with NVS was 37.3±8.2 years, in the comparison group-67±5.2 years, and in the control group – 25.1±5.1 years. 22 (31.4%) patients in the first group were diagnosed with progressive angina pectoris, 13 (18.5%) – with first – onset angina pectoris, 9 (12.8%) patients with AMI, 13 (18.5%) – acute coronary syndrome with ST-segment elevation (STEMI), 12 (17.4%) - ACS with ST-segment depression (STEMI).

Thrombolytic therapy in patients with STEMI was performed in 8 (11.4%) cases. 30 (2.8%) people had burdened heredity according to KVZ. 11 (15.7%) patients previously had post-infarction cardiosclerosis (PICS), CABG was performed in 2 (2.8%) patients. The analysis of concomitant diseases revealed that 32 (45.7%) patients had arterial hypertension (AH), 8 (11.4%) - type 2 diabetes millitans. Most of the patients in the main group were smokers – 43 (61.4%). 39 (55.7%) patients were overweight, I st – 7 (10%), II st – 9(12.8%) patients were obese.

Table-1.

Clinical and anamnestic data of examination of patients

Indicators	NVS patients young age, n=70	Patients with NVS elderly, n=15
Age	37,3±8,2	67±5,2
Progressive angina pectoris of tension	22 (31,4%)	13 (86,6%)
First-time angina pectoris	13 (18,5%)	-
AMI	9 (12,8%)	-
Acute coronary syndrome with segment elevation ST	13 (18,5%)	2 (13,3%)
Acute coronary syndrome with segment depression ST	12 (17,4%)	-
Thrombolytic therapy	8 (11,4%)	1 (6,6%)
Family history	30 (2,8%)	7 (46,6%)
The experience of CHD, years	3,24±0,82	10±0,52
History of PICS	2 (2,8%)	1(6,6%)
History of coronary artery bypass grafting	2 (2,8%)	1(6,6%)

Presence of hypertension	32(45,7%)	14 (93,3%)
DM type 2	8 (11,4%)	1 (6,6%)
Overweight	39 (55,7%)	-
Obesity I degree	7 (10%)	I ст – 3 (20%)
Obesity II degree	9(12,8%)	4(26,6%)
Cholesterol	6,19±0,17	6,39±0,16
Tg	2,45±0,12	2,49±0,19
LDL Cholesterol	3,24±0,17	3,54±0,19
Hdl Cholesterol	0,99±0,12	0,96±0,11
AHF FC (Killip) II III IV	 17 (24,2%) 7 (10%) 1 (1,4%)	13 (86,6%)
ChAC FC (NYHA): II III	 6 (8,5%) 11 (15,4%)	 2 (13,3%) 5 (33,3%)
Smoking	43 (61,4%)	7 (46,6%)
Ventricular premature beats	1 (1,4%)	2 (13,3%)
AF	3 (4,2%),	-
WPW syndrome	2 (2,8%)	-
PT	1 (1,4%)	-

The average level of total cholesterol (TC) was 6.19±0.17 mmol/L, triglycerides (TG) – 2.45±0.12 mmol/L, low – density lipoprotein cholesterol (LDL) – 3.24±0.17 mmol/L, high-density lipoprotein cholesterol (HDL) - 0.99±0.12 mmol/l. Ischemic changes on the ECG were recorded in 63 cases of NVS (90%). According to the localization of ischemia, the following variants of NVS were identified: anterior wall ischemia was diagnosed in 29 (41.4%) patients, anterior-septal – in 20 (28.5%), posterior – in 9 (12.8%), high lateral – in 5 (7.1%). The following complications were found in the examined patients: Killip II – 17 (24.2%), Killip III – 7 (10%), Killip IV – 1 (1.4%), ventricular extrasystole (VE) was detected in 1 (1.4%) patient, atrial fibrillation (AF) – in 3 (4.2%), paroxysmal tachycardia (PT) – 1 (1.4%), WPW syndrome – 2 (2.8%). Chronic heart failure (CHF) of stage II A was registered in 6 (8.5%), and stage II B in 11 (15.4%) patients with NVS.

Morphofunctional parameters of the heart were evaluated in patients with NVS (n = 70). According to the results obtained echocardiographic data revealed

that end-diastolic size (CRA) of the left ventricle was 54.5±0,3 (mm), end-systolic size (DAC) of the LV – 36,8±0,4 (mm), ejection fraction (EF) of the LV – 59,2±0,5 (%), interventricular septum (is) and 10.4±0,11(mm), the back wall LZH – 10,48±0,09 (mm). 86% for Echocardiography revealed hypokinesia: one area of hypokinesia was 59 (84,2%), two or more – 11 (15,7%).

In the second group of 15 patients, 13 (86.6%) were diagnosed with progressive angina pectoris, and 2 (13.3%) with STEMI. Thrombolytic therapy in patients with STEMI was performed in 1 (6.6%) cases. 7 (46.6%) people had burdened heredity according to KVZ. 1 (6.6%) patients previously had PIX, CABG was performed in 1 (6.6%) patients. The analysis of concomitant diseases revealed that 14 (93.3%) patients had hypertension, 1 (6.6%) - type 2 diabetes. Most of the patients in the main group were smokers – 7 (46.6%). Obesity of I st-3(20%), II st – 4 (26.6%) patients. The average level of OHS was 6.39±0.16 mmol/L, TG-2.49±0.19 mmol/L, LDL-3.54±0.19 mmol/L, HDL – 0.96±0.11 mmol / l. Ischemic changes on the ECG were recorded in 13 cases of NVS (86.6%). According to the localization of ischemia, the following variants of NVS were identified: anterior wall ischemia was diagnosed in 6 (40%) patients, anterior-septal – in 3 (20%), posterior – in 4 (26.6%), high lateral – in 2 (13.3%). Killip II – 13 (86.6%), FE in 2 (13.3%) patients, stage II A CHF was observed in 2 (13.3%), and stage II B in 5 (33.3%) patients with NVS (Table-1).

In elderly patients with NVS (n = 15), according to the results of the obtained EchoCG data, it was revealed that LV CDR was 56.5±0.6 (mm), LV CSR was 38.8±0.5 (mm), LV EF was 53.2±0.5 (%), LVL was 11.9±0.11(mm), and LV posterior wall was 12.48±0.09 (mm). In 89% of echocardiography revealed hypokinesis: one zone of hypokinesis had 9 people (60%), two or more-6 (40%) (Table 2).

Table 2.

Heart parameters in patients with NVS according to EchoCG data

Indicators	Patients with NVS at a young age	Patients with NVS in the elderly
End-diastolic size (CDR)	54,5±0,3 (мм)	56,5±0,6 (мм)
End-systolic size (CSR) ejection	36,8±0,4 (мм)	38,8±0,5 (мм)
EF	59,2±0,5 (%)	53,2±0,5 (%)
interventricular septum LVP	10,4±0,11(мм)	11,9±0,11(мм)
posterior wall of the left ventricle LVL	10,48±0,09(мм)	12,48±0,09 (мм)
1 zone of hypokinesis by echocardiography	59(84,2%)	9 (60%)
2 or more zones of hypokinesis by Echo KG	11(15,7%)	6 (40%)

One of the objectives of our study was to evaluate the genetic polymorphism of the IL-1β gene at position - 3953 S/T (rs1143634) and IL-10 at position -1082 G/A (rs1800896) in young and old men to determine predictors of the prognosis of NVS. In this regard, we studied the frequency of occurrence of S/T alleles at the locus 3953 of the IL-1β gene in 85 patients with NVS and 15 healthy donors of Uzbek ethnicity, with no clinical manifestations of the disease.

Table 3 shows that the T allele is 36.7% more common among patients with NVS than among healthy individuals. The C allele, in contrast to the T allele, is more common in the control group and is also 36.7%.

Table 3.

Frequency distribution of alleles 3953 S/T (rs1143634) of the IL-1β gene in patients with NVS and healthy individuals.

Allele	Frequency (%)		χ^2	P-value	OR	Lower gr. 95% CI	Upper gr.95% CI
	Basic gr. (n=85)	Control (n=15)					
C	44,3	80,0	15,37	0,000	0,18	0,09	0,45
T	55,7	20,0	15,37	0,000	5,23	2,18	12,53

Among patients with NS in relation to the control group, the homozygous variant of S/S in the position -3953 S/T of the IL-1β gene polymorphism was 47.4% less, the homozygous variant of T/T by 35.36% and the heterozygous variant of S/T by 11.9% more (Table 4).

Table 4

Frequency distribution of the polymorphic locus-3953ST (rs1143634) of the IL-1β gene in NVS patients and healthy individuals.

Genotype	Frequency (%)		$\chi 2$	P	OR	Lower gr. 95% CI	Upper gr. 95% CI
	Basic gr. (n=85)	Control (n=15)					
C/C	23,6	70	27,36	0,000	0,13	0,06	0,29
C/T	30,9	20	1,99	0,158	1,88	0,78	4,55
T/T	45,36	10	15,56	0,000	7,47	2,47	22,62

Thus, in the course of our study, it was found that among patients with NVS, the T allele of the IL-1β gene is 36.7% more common than in the control group. Patients with S / T and T/T alleles of the IL-1β (T3953C) rs1143634 gene are more prone to cytokine imbalance and atherosclerotic changes, which in turn worsens the clinical course of the underlying disease and therefore requires more careful monitoring and treatment of patients to improve the prognosis of NVS.

In this study, we performed a frequency distribution of alleles and genotypes of the locus -1082 G/A (rs1800896) of the IL-10 gene in patients with NVS to establish an “unfavorable” combination that leads to a high probability of developing the disease in the Uzbek population. The features of the frequency distribution of alleles and genotypes of the polymorphic variant 1082 G/A (rs1800896) of the IL-10 gene in patients with NVS and healthy individuals of Uzbek nationality were studied. Genotyping of the polymorphic locus of the IL-10 1082 G/A gene (rs1800896) was performed in 85 patients with unstable angina of Uzbek nationality.

Table 5

Frequency distribution of IL-10 (A1082G) rs1800896 gene alleles in NVS patients and healthy individuals

Allele	Frequency (%)		$\chi 2$	P-value	OR	Lower gr. 95% CI	Upper gr.95% CI
	Basic gr. (n=85)	Control (n=15)					
A	68	82,4	2,59	0,108	0,47	0,19	1,19
G	32	17,6	2,59	0,108	2,11	0,84	5,31

The study of polymorphism of the genotypes (table.3.5.1.) revealed that in the group of patients with NVS, the frequency of the homozygous G/G variant of the IL-10 (A1082G) rs1800896 gene significantly exceeds the indicators of the control group of individuals (32.0% vs. 17.6%, respectively, $\chi 2$=2.59; P=0.108; OR=2.11).

The frequency of the heterozygous variant of the IL-10 gene (with 1082 T) rs1800896 in this group of patients did not differ from the control group. The analysis of the characteristics of the frequency distribution of alleles and genotypes of gene polymorphism of IL-10 (C1082T) rs1800896, showed the presence of statistically significant differences of allele T and genotype T/T vs. C/C in patients with NAF compared to the control group of healthy individuals (tab. 6).

Table 6.

Distribution of the polymorphic locus -1082 S / T (rs1800896) of the IL-10 gene in CHD patients and healthy individuals

Genotype	Frequency (%)		$\chi 2$	P	OR	Lower gr. 95% CI	Upper gr. 95% CI
	Basic gr. (n=85)	Control (n=15)					
G/G	54,6	72,5	3,76	0,052	0,46	0,21	1,02
G/A	28,8	20	1,15	0,284	1,62	0,67	3,95
A/A	16,6	7,5	1,92	0,166	2,44	0,67	8,88

It was found that among patients with NVS, the T allele of the IL-10 (G1082A) rs1800896 gene was 13.5% more common than in the control group.

In patients with GG polymorphism, HBC was detected in 37%, in individuals with AG polymorphism-in 14% of cases, in patients with AA polymorphism was verified in 15% of cases. In general, the presence of the G allele of the IL-10 gene (1082G/A; rs1800896) determines a higher risk of NVS in young people than the presence of the A allele in the genotype of the patient (21% and 14%, respectively) of the elderly.

Discussion.

According to our research results, it was found that the group at increased risk of early development of NVS is primarily young men, smokers who are overweight or obese, suffering from hypertension, having dyslipidemia, as well as people with a hereditary predisposition to early development of CVD. According to a number of studies, hypercholesterolemia and other lipid metabolism disorders are highly likely to increase the risk of developing NVS and acute MI [1,18]. A 10% decrease in the plasma concentration of total cholesterol reduces the increase in the incidence of NVS by 25% after 5 years. It is known that overweight and obesity are the main predictors of early development of NVS [11-15], and 40% of all cases of CVD are associated with smoking risk factors [16]. It has been reported that the prevalence of smoking in young people under the age of 45 with CHD ranged from 60% to 90%, compared with 24% to 56% in patients over 45 years of age [8]. Smoking increases the oxidation of LDL cholesterol, decreases the level of HDL cholesterol [17; 18], and increases spontaneous platelet aggregation [7; 9], neutrophil function is impaired [14]. It is smoking that provokes FR of coronary plaque erosion, which is a particularly common mechanism of ACS [11]. Increased blood pressure contributes to the early formation and progression of CVD, including increasing the risk of developing NVS [14, 17]. According to a study conducted by N. T. Vatutin and E. V. Sklyannaya (2017), the prevalence of

hypertension among young people is 14.2%, while men have a significantly higher prevalence of hypertension (22.2%) than women (4.5%), $p<0.05$ [13]. DM is the cause of increased morbidity and mortality from CVD, and this occurs at an earlier age and at a higher rate than in the non-diabetic group [18]. In patients with type 2 diabetes, the progression of the atherosclerotic process is particularly rapid, and myocardial damage as a result of MI is more extensive than in patients without diabetes, which is associated with a high frequency of complications of MI [11, 12]. The most important risk factor for the development and progression of atherosclerosis, along with smoking, hypertension, dyslipidemia, and obesity, is a genetic predisposition. Geneological studies demonstrate not only the influence of hereditary mechanisms on the early development of atherosclerosis as such, but also on its predominant localization [9].

Conclusion.

There is a fact that NVS in young people is still quite a rare event, in recent years there has been a steady increase in the frequency of its occurrence. Young men, smokers, and people with a hereditary predisposition to the early development of CVD are primarily at increased risk of early development of NVS. The causes of NVS are diverse and represent different variants of acute mismatch of myocardial oxygen demand and its delivery through the coronary arteries. In young patients with NVS, blood flow in the coronary artery can be disrupted due to atherothrombosis, spasm, artery obstruction due to hemorrhage in the atherosclerotic plaque, and many other non-atherogenic causes. Despite the different causes and the peculiar course of NVS, the process of developing myocardial ischemia is always individual, the features of its course are determined by a variety of frs. When providing medical care in a timely manner in full, the prognosis in patients with NVS at a young age is significantly better than in older patients. A better understanding of the main causes and mechanisms of the development of NVS in men at a young age is a serious task of modern cardiology. The ability to predict the risk of developing CVD in young men on the basis of

traditional RFS, half of which are modifiable, opens up new prospects in the formation of a strategic approach to the management of young people with high risk.

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