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Assessment of the 8-year prognosis of fatal and nonfatal complications in patients with arterial hypertension combined with noncardiological pathology

Clinical and prognostic value of detecting postural orthostatic sinus tachycardia in young patients

State of nonspecific adaptive mechanisms of the body, assessed by heart rate variability, in patients with acute coronary syndrome depending on its type and outcome

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Contents

Editor's Welcome

Dear colleagues!

We are pleased to present you with the fiftyfirst issue of the International Heart and Vascular Diseases Journal, which includes a leading article, original research papers, and the results of an experimental study.

Leading Article section opens with a work by a team of authors presenting data from a retroprospective study with endpoint tracking in patients with arterial hypertension (AH) combined with noncardiological diseases. The 8-year study included 637 men and women with various stages of AH. In patients with two or more noncardiological diseases, allcause and cardiovascular mortality were found to be twice as frequent compared to patients with a single additional noncardiological disease.

Original Articles section presents four papers. The first study examined the feasibility of using screening testing to detect postural orthostatic sinus tachycardia (POST) in medical university students and assessed its clinical and prognostic value in a prospective study. POST was identified in 2.8% of medical students aged 20–26 years, predominantly in women. The sensitivity, specificity, and diagnostic accuracy of the screening test for POST were high. The second paper analysed the state of nonspecific adaptive mechanisms (NAM) of the body based on heart rate variability (HRV) parameters in patients with acute coronary syndrome (ACS), with subsequent comparison of the obtained data with disease outcomes. The openlabel prospective study included 151 patients with ACS. Cluster analysis allowed the identification of ACS patients with different degrees of NAM strain. More pronounced NAM strain was characteristic of patients with myocardial infarction and was associated with an unfavourable prognosis during 1 year followup; moreover, the association between patient status in the identified clusters and prognosis was stronger than with individual HRV parameters. In the third paper, colleagues from Belarus analysed significant risk factors for the development of AH in oil refining industry workers. A 10-year prospective study was conducted among 1,431 workers, in whom a high incidence of HT was found, especially under exposure to adverse occupational factors. The implementation of preventive measures demonstrated high efficacy in the high and mediumrisk groups for AH development among workers, as well as in the highrisk group for AH development among workers without hazardous working conditions. The fourth paper assessed the 10 year risk of cardiovascular complications using the SCORE 2-Diabetes scale in 224 patients aged 40–65 years with type 2 diabetes mellitus (T2DM) comorbid with other somatic diseases. Comorbidity of T2DM with a greater number of somatic diseases is associated with more pronounced disturbances of glycaemic status, lipid metabolism, and higher blood pressure levels, which is reflected in the overall risk of cardiovascular complications.

Experimental studies section includes one work aimed at studying the morphological substrate of atrial fibrillation in euthyroid pathology syndrome (EPS) in an experiment on outbred rats. It was established that different areas of atrial fibrosis against the background of EPS constitute the morphological substrate for the formation of reentry circuits during atrial fibrillation. Moreover, the fibrosis area in EPS was found to be twice as large as in euthyroidism.

We invite all authors to collaborate with our journal. We look forward to receiving your original articles, literature reviews, discussions, expert opinions on current issues, as well as treatment and prevention recommendations.

Mekhman N. Mamedov
Editor-in-Chief
President of the "Cardioprogress" Foundation

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Review of international medical news

American scientists assessed the impact of daily consumption of 1 avocado on the lipid profile of adults with abdominal obesity.

The study involved 786 adults with abdominal obesity living their usual lifestyle. Of these, 389 participants consumed one avocado daily for 26 weeks, while 397 participants maintained their usual diet without the additional inclusion of avocado.

Analysis showed that daily consumption of 1 avocado for 26 weeks led to a reduction in total low-density lipoprotein concentration compared to the usual diet without its addition. The mean difference between groups was 49.1 nmol/L.

The authors concluded that daily consumption of one avocado for 26 weeks contributes to lowering the concentration of atherogenic low-density lipoproteins in adults with abdominal obesity.

According to the American Journal of Clinical Nutrition

Scientists from New Delhi evaluated the effectiveness of an artificial intelligence (AI) algorithm based on smartwatch data for the early detection of heart failure (HF) progression.

Data from 124 patients with HF with reduced ejection fraction and NYHA functional class III were analyzed. Participants used smartwatches connected to an application that continuously monitored heart rate.

Analysis showed that the application's algorithm accurately predicted an increase in N-terminal pro-B-type natriuretic peptide levels as an indicator of worsening HF.

The authors concluded that the AI algorithm based on smartwatch data is able to detect worsening HF earlier than traditional weight monitoring.

According to the JACC: Heart Failure

Experts from the American College of Cardiology presented an updated algorithm for the management of patients with heart failure with preserved ejection fraction, with special emphasis on the treatment of comorbidities.

The document recommends simultaneous management of coronary artery disease, atrial fibrillation, arterial hypertension, chronic kidney disease, diabetes mellitus, and obesity, as these conditions largely determine the course of the disease and prognosis.

Furthermore, special attention is given to early and accurate diagnosis. For patients with dyspnea, edema, and other characteristic symptoms, a stepwise diagnostic algorithm is proposed, including the use of diagnostic scores, differential diagnosis, exclusion of conditions with similar manifestations, and consideration of sex differences.

According to the American College of Cardiology Journal

Scientists evaluated clinical outcomes after transcatheter aortic valve (AV) replacement depending on the anesthesia method.

The analysis included data from 3,586 patients who underwent transcatheter aortic valve replacement for the first time (1,793 in each group after matching). Moderate sedation, regional, epidural, local anesthesia, nerve block, or injectable anesthesia were used.

One year after the procedure, the risk of developing heart failure was 1.44 times higher in patients who received general anesthesia compared to patients who received less invasive anesthesia methods.

The authors concluded that less invasive anesthesia methods in transcatheter replacement are a safe alternative to general anesthesia.

According to the Journal of Clinical Anesthesia

Experts presented new research according to which people with a higher burden of modifiable risk factors, such as high blood pressure, high cholesterol, diabetes mellitus, smoking, and obesity, exhibit more extensive plaque formation in the major coronary arteries (CA).

Specialists analyzed 534 plaques in 131 patients who underwent optical coherence tomography. It was found that patients with a greater number of risk factors had more plaques in all three major CAs. Additionally, a higher number of modifiable risk factors was associated with a lower number of stable plaques and a more frequent presence of vulnerability features, such as lipid plaques with thin fibrous caps prone to rupture.

According to the authors, prospective studies involving larger cohorts, including patients previously treated for CA blockage, are needed to generalize the results obtained.

According to the JACC: Advances

Scientists from the University of Oxford developed a new method for assessing sarcopenic obesity based on cardiovascular magnetic resonance imaging data and studied its association with cardiovascular outcomes.

Data from 55,768 cardiovascular MRIs were analyzed. Using a deep learning algorithm, researchers assessed the mass of the pectoralis major muscle and combined this data with body weight to calculate a new index of sarcopenic obesity. The scientists then correlated it with cardiovascular outcomes, mortality, genetic features, and changes in gene expression.

Analysis showed that a higher sarcopenic obesity index was associated with a 31% increased risk of developing heart failure, a 51% increased risk of cardiovascular death, and a 37% increased risk of death from any cause. Furthermore, a high index was associated with adverse cardiac remodeling.

According to the Journal of the American College of Cardiology

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Assessment of the 8-Year prognosis of fatal and non-fatal complications in patients with arterial hypertension combined with non-cardiological pathology

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Objective—to evaluate the 8-year prognosis of fatal and non-fatal complications in patients with arterial hypertension (AH) combined with non-cardiological pathology.

Materials and methods. This retrospective-prospective clinical study included 637 patients who were routinely hospitalized at the National Medical Research Center

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for Therapy and Preventive Medicine of the Ministry of Health of the Russian Federation for diagnostic procedures and adjustment of drug therapy. Inclusion criteria: men and women aged 40-80 years with AH (according to the Russian Society of Cardiology guidelines, 2024) without other cardiovascular diseases. The presence of other somatic diseases and risk factors for chronic non-communicable diseases was permitted. After 8 years of follow-up, telephone interviews were conducted with patients and their close relatives to record complications, including fatal and non-fatal cases. The response rate was 91.4%.

Results. Initially, patients with AH were divided into two groups depending on the number of additional non-cardiological diseases: AH combined with one non-cardiological disease and AH combined with two or more non-cardiological diseases. In the first group, all-cause death was registered in 13.3%, while in the second group, fatal outcomes were twice as high, amounting to 24.8% of cases (p = 0.001). All-cause mortality rates differed significantly between men and women in both groups. Cardiovascular death in the second group was registered in 15.8% of cases, and in the first group in 9.7% of cases. During the follow-up period, myocardial infarction was detected in 2.6% of cases in the first group and in 4.9% of patients in the second group. In the first group, stroke was registered in 3.6% of patients, and in the second group in 4.4% of patients. The majority of deceased patients from cardiovascular complications in the first group initially had stage 2 hypertension and high cardiovascular risk, whereas in the second group, this status was registered in every second deceased patient. In the second group, about 46% of deceased patients initially had stage 3 hypertension and very high cardiovascular risk.

Conclusion. Thus, over the 8-year follow-up period, in the group of patients with AH combined with two or more non-cardiological diseases, all-cause mortality was twice as high, and cardiovascular mortality was 1.5 times higher compared to the group of patients with AH combined with one non-cardiological disease. It is evident that when developing preventive programs, it is necessary to take into account not only the stages of AH, modifiable risk factors, and target organ damage, but also the presence of additional non-cardiological diseases, which collectively increase the risk of complications and fatal outcomes.

Keywords: arterial hypertension, fatal and non-fatal outcomes, 8-year prognosis, non-cardiological diseases.

Conflict of interest: none declared.

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Introduction

Arterial hypertension (AH) remains one of the pressing problems of modern medicine. Globally, its direct contribution to adult mortality is very significant. According to agestandardised data from 2022, among the causes of cardiovascular mortality, AH (16.1 cases per 100,000 population) ranks third after coronary heart disease (CHD) (108.8 cases per 100,000) and stroke (39.4 cases per 100,000). According to experts, the disabilityadjusted life years (DALYs) indicator for AH is 292.7 per 100,000 population, which is three times higher than the corresponding figures for atrial fibrillation [1].

AH is the most common cardiovascular disease worldwide, and Russia is no exception [2]. In the national populationbased study ESSERF3, the prevalence of AH was 44.8% in men and 33.9% in women (average 38.8%). Over recent years, the dynamics of AH prevalence have been insignificant, indicating the medical and social significance of this disease [3].

Experts agree that the high risk of cardiovascular complications and mortality is determined by a combination of the grade of AH, target organ damage, the presence of risk factors (RFs), and associated clinical conditions [4]. The developed scales for determining cardiovascular risk (CVR) and its gradations are determined by the severity of these parameters. In real clinical practice, patients with AH often have various somatic comorbidities. It is evident that comorbidity of somatic diseases in individuals with AH can affect both quality of life and prognosis [5, 6]. An increase in the number of concomitant diseases may also contribute to the development of overall complications in AH patients.

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Aim—to evaluate the 8-year prognosis of fatal and nonfatal complications in patients with AH combined with noncardiological pathology.

Materials and methods

In a retrospectiveprospective clinical study, medical records of 805 men and women hospitalised at the National Medical Research Centre for Therapy and Preventive Medicine of the Ministry of Health of Russia on a planned basis for diagnostic procedures and adjustment of drug therapy in 2016 were analysed.

Inclusion criteria: men and women aged 4080 years with a clinical diagnosis of AH grade 13 (Russian Society of Cardiology (RSC), 2024) without other cardiovascular diseases (CVD).

Exclusion criteria: age <40 or >80 years, presence of other CVD (CHD, cardiac arrhythmias, chronic heart failure (CHF), left ventricular aneurysm, cardiomyopathies, pulmonary hypertension, cerebrovascular disease, lower extremity atherosclerosis), severe somatic diseases in the decompensation stage at the time of hospitalisation, as well as mental disorders. Patients participating in various clinical trials were also excluded.

The study included 637 patients with RFs for chronic noncommunicable diseases and other somatic pathologies. A patient interview was conducted to identify sociodemographic indicators, family history, and behavioural RFs. AH stages and CVR gradations were determined according to the 2024 clinical guidelines "Arterial Hypertension in Adults" of the RSC [4].

Somatic diseases were recorded based on medical documentation (discharge summaries and results of clinical, instrumental, and laboratory examinations). Patients underwent standard examinations (blood pressure measurement, heart rate, resting electrocardiography, echocardiography, complete blood count, urinalysis, lipid profile assessment, fasting glucose, creatinine, uric acid and electrolytes), as well as additional instrumental and laboratory tests when necessary.

After 8 years of followup, telephone interviews were conducted with patients and their close relatives to record the development of complications, including allcause death, cardiovascular death, myocardial infarction (MI), acute cerebrovascular accident (ACVA), and coronary revascularisation.

The study protocol and medical documentation forms were approved by the independent local ethics committee in 2026.

Statistical analysis

Statistical analysis was performed using R 4.2.3. Qualitative data are presented as proportions and percentages. Differences between two independent samples for continuous variables were assessed using the MannWhitney U test, and for categorical variables using Fisher's exact test. Differences with $p < 0.05$ were considered statistically significant.

Results

Depending on the number of additional noncardiological diseases, patients with AH were divided into two groups. Noncardiological pathologies included: bronchopulmonary diseases, type 2 diabetes mellitus (T2DM), chronic gastrointestinal diseases, urogenital diseases, and thyroid diseases.

The first group comprised patients with AH combined with one noncardiological disease, and the second group comprised patients with two or more noncardiological diseases. The number of patients in the second group was twice as large as in the first group (n = 423, 66.4% and n = 214, 33.6%, respectively). The gender composition between the groups was also comparable (Table 1). In both groups, stage 2 hypertension predominated; its frequency in the first group was significantly higher than in the second group. The frequency of stage 3 hypertension in the

Table 1. **Agesex characteristics and clinical status of patients with AH**

Parameter	Group of AH patients with one noncardiological disease, n = 214	Group of AH patients with two or more noncardiological diseases, n = 423	Significance, p
Mean age, years	59.9±11.5	62.87±10.39	0.002
Men	91 (42.5 %)	162 (38.3 %)	0.305
Women	123 (57.5 %)	261 (61.7 %)	0.305
Stage 1 hypertension	21 (9.8%)	23 (5.4%)	0.047
Stage 2 hypertension	164 (76.6 %)	277 (65.5 %)	0.0048
Stage 3 hypertension	29 (13.5 %)	123 (29.1 %)	<0.0001

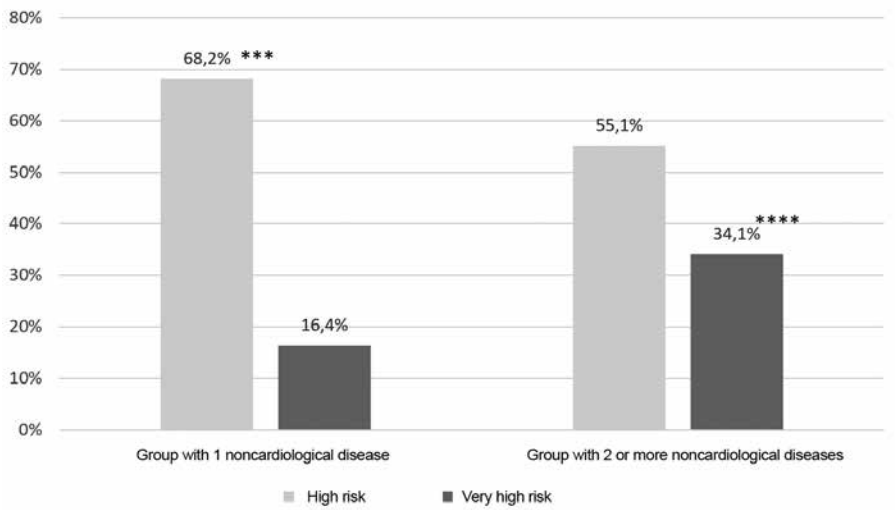

Fig. 1. Would be inserted here – description: Frequency of high and very high CVR in patients with AH combined with noncardiological diseases
Note. ***p < 0.001, ****p < 0.0001 for betweengroup differences.

second group was twice as high as in the first group. Consequently, in the cohort of stage 1 hypertension, up to 10% of cases were verified.

Analysis of different gradations of total CVR in groups with different numbers of additional somatic diseases demonstrated that in the second group, initially every second patient had high CVR, while in the first group high risk was registered in about 70% of cases (Fig. 1). Very high risk in the second group was identified in every third patient, while in the first group its frequency was half as low. The difference between groups was statistically significant (p < 0.0001). Overall, about 85% in the first group and 90% in the second group of individuals with AH during the examination in 2016 had high and very high CVR.

Analysis of the 8 year prognosis for the development of complications demonstrates that in the group of patients with AH combined with one noncardiological disease, allcause death was registered in 13.3%, while in the group with two or more noncardiological diseases, fatal outcomes were twice as frequent, accounting for 24.8% of cases (p < 0.001). This pattern was observed both in men and women (Table 2). Cardiovascular death was also 1.5 times more frequent in the second group compared to the first (15.8% and 9.7%, respectively).

During the followup period, MI developed in 2.6% of patients in the first group and in 4.9% in the second group. A similar trend was found for ACVA: in the first group, ACVA was registered in 3.6%, and in the

Table 2. **Fatal and nonfatal complications in individuals with AH combined with noncardiological pathology**

Endpoints	Group of AH patients with one noncardiological disease, n = 195 (83 men, 112 women)	Group of AH patients with two or more noncardiological diseases, n = 387 (152 men, 235 women)	Significance, p
Allcause death, total	26 (13.3%)	96 (24.8%)	0.0012
Men	10 (12%)	34 (22.4%)	0.0561
Women	16 (14.3%)	62 (26.4%)	0.0130
Cardiovascular death, total	19 (9.7%)	61 (15.8%)	0.0553
Men	8 (9.6%)	22 (14.5%)	0.3153
Women	11 (9.8%)	39 (16.6%)	0.1037
MI, total	5 (2.6%)	19 (4.9%)	0.269
Men	2 (2.4%)	7 (4.6%)	0.499
Women	3 (2.7%)	12 (5.1%)	0.403
ACVA, total	7 (3.6%)	17 (4.4%)	0.8257
Men	3 (3.6%)	6(3.9%)	1.000
Women	4 (3.6%)	11 (4.7%)	0.7817
Coronary revascularisation, total	9 (4.6%)	27 (7%)	0.362
Men	5 (6%)	15 (9.9%)	0.464
Woman	4 (3.6%)	12 (5.1%)	0.597

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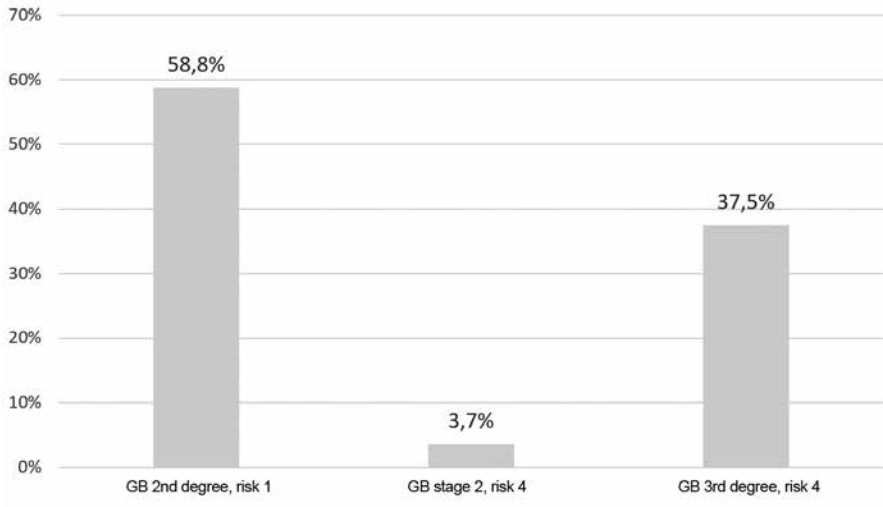

Fig. 2. Would be inserted here – description: Baseline CVR and AH stages among patients with fatal CVD outcomes (n = 80)

second group—in 4.4% of cases. It should be noted that the incidences of MI and ACVA between groups, as well as by gender, did not show statistically significant differences.

In the cohort, coronary revascularisation was performed in up to 10% of cases; in the second group its frequency was 1.5 times higher compared to the first group, but without statistical significance.

Within the study, the association between cardiovascular mortality and baseline CVR was analysed. Overall, in the examined cohort, among individuals with fatal cardiovascular outcomes, initially every second patient had stage 2 hypertension and high CVR. About 40% of patients who died from CVD had initially stage 3 hypertension and very high CVR, and only 3.7% of deceased patients initially had stage 2 hypertension and very high CVR (Fig. 2).

Table 3 presents data on baseline CVR in groups with different numbers of noncardiological pathologies among patients with fatal complications.

Most patients who died from cardiovascular events in the first group initially had stage 2 hypertension and high CVR; in the second group, a similar level of CVR and hypertension stage was found in every second deceased patient. In the second group, about 46% of patients who died from CVD initially had stage 3 hypertension and very high CVR, whereas in the first group only every tenth deceased patient initially had stage 3 hypertension and very high CVR. The differences between the groups were statistically significant (p = 0.0061). Stage 2 hypertension and very high CVR were identified in 10.5% of patients who died from CVD in the first group. A similar indicator in the second group was found in one deceased patient.

Discussion

The retroprospective study was aimed at evaluating the 8 year prognosis of middleaged patients with AH without other CVD. Overall, a varying frequency of noncardiological diseases was found in the AH cohort. The most common were: obesity, nonalcoholic fatty liver disease (NAFLD), chronic obstructive pulmonary disease (COPD), chronic gastroduodenitis, type 2 diabetes mellitus, and chronic kidney disease. Chronic diseases such as varicose veins of the lower extremities, hypothyroidism/nodular goitre, and eye diseases were verified in every sixthseventh patient with AH.

In this study, the tracking of endpoints was performed taking into account the presence of additional

Table 3. **Analysis of baseline clinical status in the group with cardiovascular mortality**

Hypertension stage	Cardiovascular mortality in group with one noncardiological disease, n = 19	Cardiovascular mortality in group with two or more noncardiological diseases, n = 61	Significance, p
Stage 2, risk 3	15 (79%)	32 (52.5%)	0.0608
Stage 2, risk 4	2 (10.5%)	1 (1.6%)	0.1388
Stage 3, risk 4	2 (10.5%)	28 (45.9%)	0.0061

noncardiological diseases. For this purpose, patients were conventionally divided into two groups regardless of the presence of a specific somatic disease.

In real clinical practice, AH is often combined with other somatic diseases. A study involving 67,385 patients with AH from primary care institutions in Canada found that at a mean age of 70 years, 80.6% had concomitant diseases [7].

In the literature, when analysing multimorbidity in patients with AH, cardiometabolic disorders are primarily considered [8, 9]. For example, an analysis of the comorbidity structure of chronic diseases among the German population aged 40 years and older (6,554 individuals, mean age 62.0 years) showed that 53.3% of participants had combined pathology in various combinations, with the group with hypertension and metabolic diseases accounting for 21.7% [10].

As a rule, some cardiometabolic disorders have been considered as additional RFs for the development of complications in AH [4].

In our study, NAFLD was one of the most common somatic diseases in patients with AH. Experts agree that AH and NAFLD are interrelated independently of other components of the metabolic syndrome, such as obesity and T2DM. Clinical data indicate that NAFLD is associated with incident AH, while elevated blood pressure is associated with the development of NAFLD and possible subsequent progression to liver fibrosis. Insulin resistance and activation of the reninangiotensinaldosterone system may provide potential pathophysiological links between these clinical conditions [11].

In the NHANES project involving 3,144 patients, it was shown that hypertension was positively associated with the risk of NAFLD (odds ratio = 1.677; 95% confidence interval (CI) 1.1592.423). Systolic blood pressure (≥130 mm Hg) and diastolic blood pressure ≥ 80 mm Hg were also significantly positively associated with NAFLD. Moreover, hypertension was independently associated with hepatic steatosis (β = 7.836; 95% CI 2.33413.338). Results from Mendelian randomisation analysis also confirmed a causal relationship between hypertension (relative risk = 7.203 [95% CI 2.29722.587]) and NAFLD [12].

Another important somatic disease combined with AH is COPD, which was found in every fifth patient in the examined cohort. According to data from the Russian National Registry of AH, cardiovascular (CHD, myocardial infarction, CHF, peripheral artery atherosclerosis) and cerebrovascular (stroke/transient ischaemic attack) diseases are more frequently diagnosed in patients with AH and COPD. The analysed sample included 32,571 patients with AH followed up in primary care institutions, with a mean age of 64 ± 7 years (64% women); COPD was diagnosed in 5.4% of patients with AH. The study showed that male sex and age are the strongest independent factors influencing the risk of CVD in these patients. COPD significantly increases the risk of developing CHF [13].

In the present study, the mean age in the group with two or more noncardiological diseases was 3 years higher, which obviously also contributed to the development of fatal complications. At the same time, the gender composition was comparable between the groups.

Nonfatal complications individually did not differ significantly between the groups (the combined frequency of MI and stroke in the first group was 6.2%, in the second – 9.3%), whereas in the group with two or more noncardiological diseases, a significantly higher frequency of allcause mortality and cardiovascular death was registered compared to the group with one noncardiological disease. In the second group, almost every second patient who died from cardiovascular complications initially had stage 3 hypertension and very high CVR. About 80% of patients who died from cardiovascular complications in the first group and every second deceased patient in the second group initially had stage 2 hypertension and high CVR. It is obvious that, along with patients with very high CVR, patients with stage 2 hypertension and high CVR should be under medical supervision.

Conclusion

Thus, over 8 years of followup, in the group of patients with AH combined with two or more noncardiological diseases, allcause death was twice as frequent, and cardiovascular death was 1.5 times more frequent compared to the group with AH combined with one noncardiological disease. Obviously, when developing preventive programmes, it is necessary to consider not only the grade of AH, modifiable RFs, and target organ damage, but also the presence of additional noncardiological diseases, which together increase the risk of complications and fatal outcomes.

Conflict of interest: none declared.

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Clinical and prognostic significance of detecting postural orthostatic sinus tachycardia in young patients

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Postural orthostatic sinus tachycardia (POST) is characterized by pronounced tachycardia upon transitioning from a supine to an upright position, without orthostatic hypotension, accompanied by various symptoms such as palpitations, dizziness, headache, fatigue, weakness, reduced exercise tolerance, blurred or "foggy" vision, anxiety, shortness of breath, and others. However, the detection rate and prognostic significance of POST in medical university students during a prospective study have not been fully investigated. Furthermore, data on the clinical value of using screening tests for its detection are lacking.

Aim. To determine the feasibility of using screening testing for detecting POST in medical university students and to evaluate its clinical and prognostic significance in a prospective study.

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Material and methods. Over the period from 2007 to 2012, 5,560 medical university students aged 20-26 years were examined. Various orthostatic symptoms at rest and/or during the transition from supine to upright position were observed in 534 (9.6%) patients. When these symptoms were identified, screening testing was performed, including measurement of heart rate and blood pressure (BP) in the supine position, followed by measurements in the orthostatic position, with subsequent verification using a tilt-table test. Cardiac and extracardiac causes of POST were excluded. Patients with POTS were advised to modify their lifestyle, and, if ineffective, to receive beta-blockers and/or a selective inhibitor of If-channels (ivabradine). The follow-up period after inclusion in the study was 12–14 years.

Results. POTS was identified in 2.8% of medical university students aged 20-26 years, predominantly in women (83%). The sensitivity, specificity, and accuracy of POST diagnosis based on screening testing results with subsequent verification using the tilt-table test were 79.35%, 90.05%, and 85.26%, respectively. Following lifestyle modification and/or treatment with beta-blockers or ivabradine, all patients with POTS showed significant clinical improvement both at the start of treatment and during subsequent follow-up: orthostatic symptoms resolved. On repeated examinations, including during tilt-table testing, POTS was no longer registered. During prospective follow-up, 36.13% of patients with POTS developed hypertension (HTN), 23.87% were found to have mitral valve prolapse (MVP), and 38.06% registered ventricular extrasystole. The development of HTN was highly correlated with a family history of arterial hypertension (odds ratio (OR) = 5.02) and increased BP in the orthostatic position (OR = 3.05), while MVP was correlated with retrograde atrial activation immediately following ventricular extrasystole (OR = 12.4).

Conclusion. POTS was identified in 2.8% of medical university students aged 20–6 years, predominantly in females. The sensitivity, specificity, and accuracy of POTS diagnosis based on screening test results were 79.35%, 90.05%, and 85.26%, respectively. The occurrence of POST with elevated BP during orthostatic testing are predictors for the development of HTN, MVP, and ventricular extrasystole.

Keywords: postural orthostatic sinus tachycardia, clinical and prognostic significance, screening testing, manifesting symptoms, principles of therapeutic treatment.

Conflict of interest: none declared.

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Introduction

Postural orthostatic sinus tachycardia (POST) is a relatively common disorder, and its diagnosis has increased significantly in recent years [1]. However, the causes and mechanisms of its development remain insufficiently understood [2]. POST has been described following viral infections (including coronavirus), surgical procedures, pregnancy, irritable bowel syndrome, and other diseases and/or conditions [1, 2]. In addition to the main clinical manifestations—pronounced tachycardia upon transitioning from a supine to an upright position without orthostatic hypotension—various symptoms may be present, such as palpitations, dizziness, headache, fatigue, weakness, reduced exercise tolerance, blurred or "foggy" vision, anxiety, shortness of breath, and others [1, 2]. In most patients with POST, nonpharmacological and pharmacological measures are chosen empirically, based on the presenting symptoms [3]. POST is most frequently observed in young adult women, who are typically either in education or at the beginning of their careers [1, 2, 4].

However, the frequency of detection and the prognostic value of POST in medical university students in a prospective study have not been fully investigated. Moreover, data on the clinical utility of screening testing for this syndrome are lacking.

Aim—to determine the feasibility of using screening testing to detect POST in medical university students and to evaluate its clinical and prognostic significance in a prospective study.

Material and methods

During the period from 2007 to 2012, a total of 5,560 medical university students aged 20–26 years (mean 22.7 ± 0.1 years) were examined. During a screening

questionnaire, which included collection of complaints, medical history, etc., it was found that 534 (9.6%) patients experienced palpitations, chest pain or discomfort, dizziness, blurred vision, dyspnoea, headache, fatigue, and "trembling" in the body or limbs at rest and/or upon transitioning from supine to upright position; these symptoms diminished or resolved completely in the supine position or at rest. After an indepth clinical, laboratory, and instrumental examination, which included 1 to 3 day Holter electrocardiogram (ECG) monitoring, and assessment of central and intracardiac haemodynamics using a Hitachi EUB 5500 echocardiograph according to standard methods [4], 356 (66.67%) of the 534 patients were enrolled in the study. Inclusion criteria: sinus rhythm, absence of structural heart disease, left ventricular ejection fraction ⩾ 55%, and informed consent from the patient to participate in the study and receive treatment. Exclusion criteria: presence of cardiac and extracardiac diseases such as hypertension (HT), mitral valve prolapse (MVP), cardiomyopathies, thyrotoxicosis, phaeochromocytoma, epilepsy, anaemia, frequent supraventricular and ventricular extrasystoles (⩾ 100 per day), or other factors such as anxiety disorders, hyperventilation, fever, pain of various localisation, acute and chronic infections, dehydration, venous insufficiency of the lower extremities, irritable bowel syndrome, chronic fatigue, neurological pathology, alcohol abuse, coffee consumption, intake of cardioactive drugs, etc. [3–5].

In all patients included in the study, when one or more of the above symptoms were detected, screening testing was performed. This involved measuring heart rate (HR) and blood pressure (BP) after 20–30 minutes of rest in the supine position, then in the upright position and/or with headup tilt for 10–20 minutes, followed by repeated recordings of these haemodynamic parameters in the supine position. HR was determined by pulse palpation and/or using a pulse oximeter, and BP was measured using a domestic automatic sphygmomanometer that recorded pulse rate and pressure parameters every 3–4 minutes after the first measurement. Screening testing was conducted 3–4 times a week, always in the morning immediately after waking up, in the evening, and several times during the day.

In all patients with positive screening questionnaire results, 1 to 3 day Holter ECG and BP monitoring ("Kardiotekhnika04AD3(M)", INCART Ltd., Cardiology Research Institute, Ministry of Health of Russia, St. Petersburg) were performed, and a tilttable test according to the Westminster protocol was carried out [4]. The tilt test was conducted between 8:00 and 11:00 a.m. in a quiet environment, on an empty stomach, at a comfortable room temperature of 20–23 °C and humidity of 30–50%. Intake of any medications and smoking were prohibited. In the first stage, the patient remained supine for 20 minutes; in the second stage, they were tilted to a 60° upright position for up to 40 minutes; and in the third stage, they returned to the supine position for another 20 minutes. POST was diagnosed both during screening testing and during the tilt test when an increase in HR of ⩾ 30 beats/min compared with baseline was noted, with the HR reaching 120 beats/min or more, accompanied by a decrease in systolic and diastolic BP of no more than 20 mmHg and 10 mmHg, respectively, or by an increase in BP [3–7]. Throughout all stages of the tilt test, ECG was continuously recorded, and heart rate variability (HRV) parameters were calculated with automatic exclusion of extrasystoles using an electrocardiograph "PolispektrVR" (Neirosoft Ltd., Ivanovo), along with systolic and diastolic BP. For HRV assessment, 5 minute ECG fragments were used, recorded during the last 5 minutes in the supine position before tilting, then during the last 5 minutes of orthostasis, and at the end of the subsequent return to the supine position (last 5 minutes). HRV analysis included quantitative and spectral parameters: SDNN—standard deviation of normal RR intervals (ms), VLF—very lowfrequency component (0–0.04 Hz, ms^2), reflecting neurohumoralmetabolic regulatory pathways; LF—lowfrequency component (0.04–0.15 Hz, ms^2), reflecting sympathetic activity; HF—highfrequency component (0.15–0.4 Hz, ms^2), reflecting parasympathetic activity; and the LF/HF ratio (in units) [5, 8, 9].

All patients were advised to modify their lifestyle, including aerobic physical exercise for 20–40 minutes a day, 3–5 times a week. In cases of POST with BP reduction during the tilt test, compression garments, countermanoeuvres, and increased water intake (e.g., up to 2–3 litres per day, especially after waking up) were recommended. If these measures were ineffective, or if BP increased upon standing, subtherapeutic doses of betablockers (metoprolol tartrate 6.25–12.5 mg, bisoprolol fumarate 1.25–2.5 mg) and/or the selective Ifchannel inhibitor ivabradine hydro-

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chloride 1.25–2.5 mg were used, in accordance with the guidelines in force at the time of the study [1–3, 4]. It should be noted that none of the nonpharmacological or pharmacological methods recommended for treating POST, including at the time of writing this article, have been confirmed by large randomised clinical trials [1–3, 5].

The followup period after enrolment was 12–14 years. Patients selfmonitored HR and BP in the supine and upright positions daily. All examinations, including assessment of patient status and ECG recording, were performed once a month; Holter ECG and BP monitoring were performed at least once every 3–6 months; and the tilt test was performed once a year (with the patient's informed consent).

The study was conducted in accordance with Good Clinical Practice standards and the principles of the Declaration of Helsinki.

Ethical approval. The study was approved by the Ethics Committees of the I.I. Mechnikov St. Petersburg State Medical Academy of Roszdrav (Protocol No. 12, dated 30 December 2010). (In 2012, the I.I. Mechnikov St. Petersburg State Medical Academy was merged with MAPO and renamed the I.I. Mechnikov NorthWestern State Medical University of the Ministry of Health of Russia).

Statistical analysis

For statistical processing of the obtained data, the normality of the distribution of quantitative variables was assessed using the Kolmogorov–Smirnov and Gaussian tests. Mean values and standard deviations (M ± SD), Student's ttest, and x^2-test were used. A pvalue < 0.05 was considered statistically significant. Linear pairwise and rank (Pearson) correlation were used, and the association between quantitative and qualitative binary variables was assessed using logistic regression with calculation of odds ratios (OR).

Results

Screening testing data showed that when HR was determined by pulse palpation and/or pulse oximeter, and BP measured with a domestic sphygmomanometer in the supine position, followed by assessment of these parameters in the upright position, POST was diagnosed in 152 (42.70%) of the 356 enrolled patients, with reproduction of orthostatic tachycardia symptoms at least 2–3 times per week over 3–6 months. Upon tilttable testing and Holter ECG and BP monitoring, POST was confirmed in 123 (80.92%) of the 152 patients with positive screening results, and was identified in 32 (15.69%) of the 204 patients with negative screening results; no patient developed presyncope or syncope. The sensitivity, specificity, and diagnostic accuracy of POST detection by screening testing were 79.35%, 90.05%, and 85.26%, respectively.

All patients were divided into two groups. The main (I) group consisted of 155 (43.54%) of the 356 patients with confirmed POST by tilt test and Holter monitoring, with a mean age of 22.4 ± 1.6 years. The remaining patients formed the control (II) group, with a mean age of 23.1 ± 1.9 years (p > 0.05). Women predominated in both groups. In group II, there were significantly more 6thyear students and those consuming more than 5 g/day of table salt, and significantly fewer 4th and 5thyear students and those with a family history of hypertension (HT) compared with group I (Table 1). No statistically significant differences were found for the other studied parameters.

It should be noted that 4th and 5th year students take 6 and 5 exams, and 4 and 5 differentiated credit

Table 1. **Characteristics of patients in Groups I and II at enrolment**

Parameter	Group I, n = 155	Group II, n = 201
Men	26 (16.77 %)	32 (15.92%)
Woman	129 (83.23%)	169 (84.08%)
4th year students	88 (56.77%)	67 (33.34%)*
5th year students	41 (26.45%)	11 (5.47%)*
6th year students	26 (16.77%)	123(61.19%)*
Body mass index ⩽ 18,5 kg/m^2	12 (7.74%)	16 (7.96%)
Body mass index ⩾ 25 kg/m^2	23 (14.84%)	35 (17.41%)
Family history of hypertension†	143 (92.26%)	64 (31.84%)*
Family history of cardiovascular diseases, including coronary heart disease†	73 (47.10%)	77 (38.30%)
Joint hypermobility	67 (43.23%)	89 (44.28%)
Salt intake > 5 g/day	16 (10.32%)	89 (44.28%)*
Smoking	56 (36.13%)	82 (40.80%)
Excessive psychoemotional stress	86 (55.48%)	94 (46.77%)
Physical inactivity	58 (37.42%)	66 (32.84%)
Palpitations and/or cardiac "irregularities"	127 (81.94%)	176 (87.56%)
Discomfort and/or stabbing pain in the left chest	68 (43.87%)	93 (46.27%)
Dizziness	59 (38.06%)	76 (37.81%)
Increased fatigue	83 (53.55%)	114 (56.72%)
"Trembling" in the body or lower extremities	18 (11.61%)	26 (12.94%)

Note. †—development of diseases at a young age in parents or in the family;
*—significant difference compared with Group I (p < 0.05).

tests (equivalent in importance to exams), respectively, while in the 6th year there is mainly only one—the final state exam. The average grade point during the training period in groups I and II was 3.4 ± 0.4 and 4.6 ± 0.5, respectively ($p < 0.05$).

Before the tilt test, patients in group II had a statistically significant increase in the power of all HRV parameters with a significant decrease in LF/HF compared with group I. At the end of the tilt test and after its completion, both groups showed a significant increase in VLF power and LF/HF ratio, and a decrease in LF and HF. In group I, in the upright position, a significant increase in HR and a rise in BP were observed compared with baseline; in all these patients, maximal BP during orthostasis did not exceed 139/89 mmHg. Importantly, in group I at the beginning of the tilt test, BP remained virtually unchanged or slightly decreased (by 5–10 mmHg), and then increased. No significant changes were observed in other parameters (Table 2).

Within 3–6 months of adherence to the recommended therapy, including lifestyle modification and pharmacological agents (betablockers or ivabradine), the clinical condition of patients in both groups significantly improved: symptoms such as palpitations, discomfort in the left chest, dizziness, increased fatigue, etc., resolved. To eliminate palpitations following excessive psychoemotional stress, patients used betablockers or ivabradine. Upon reexamination, including tilttable testing, POST was not diagnosed in any patient of group I.

After graduation, 127 (81.94%) of group I and 179 (89.05%) of group II remained working in the national healthcare system ($p > 0.05$); among them, 64 (50.39%) and 145 (81.01%) respectively were physicians in therapeutic specialties (family medicine, dermatology, cardiology, gastroenterology, neurology, etc.) ($p < 0.05$), while the rest were engaged in diagnostic activities, i.e., laboratory physicians, endoscopists, echocardiographers, ultrasound specialists, etc.

During prospective followup, HT was diagnosed in 56 (36.13%) of group I and in 11 (5.47%) of group II ($p < 0.05$) (Fig. 1); MVP was found in 37 (23.87%) and 6 (2.99%) respectively ($p < 0.05$) (Fig. 2). Ventricular extrasystoles of class II–V according to M. Ryan (1975) [10] were recorded in 59 (38.06%) of group I and in 5 (2.49%) of group II ($p < 0.05$), including those with retrograde atrial activation after premature ventricular complexes. Irritable bowel syndrome was observed in 6 (3.87%) and 7 (3.48%) patients, respectively ($p > 0.05$). The development of HT was highly correlated (OR > 1) with a family history of HT (OR = 5.02) and with increased BP during orthostasis compared with supine baseline (OR = 3.05), while MVP was associated with retrograde atrial activation after premature ventricular complexes (OR = 12.4).

Discussion

Precise epidemiological data on the prevalence of POST are lacking; however, some reports suggest that this syndrome affects 0.1–0.5% of the general population, and in young women it may be found in up to 3% of cases [1–3]. POST is identified across different age groups but is most common in young women, with a femaletomale ratio of approximately 4:1 [1–3].

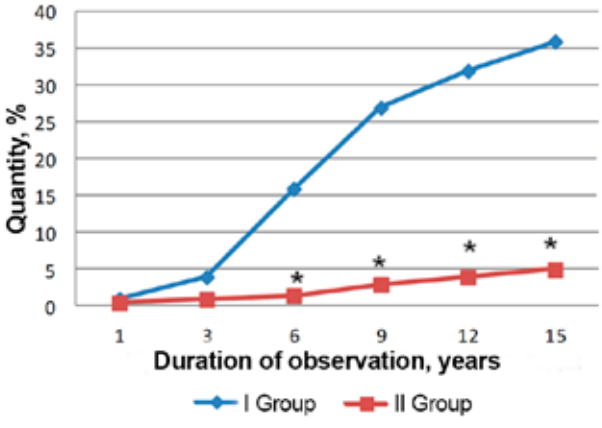

Fig. 1. Kaplan–Meier curves for the development of hypertension (HT) in patients of Groups I and II.
Note. *—significant difference compared with Group I($p < 0.05$).

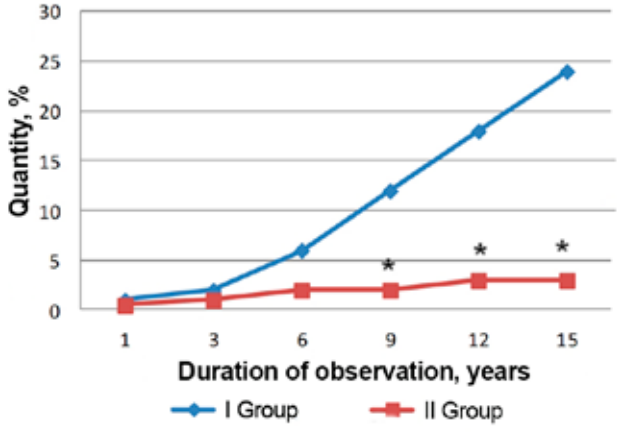

Fig. 2. Kaplan–Meier curves for the development of mitral valve prolapse (MVP) in patients of Groups I and II.
Note. *—significant difference compared with Group I ($p < 0.05$).

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Table 2. **Comparative characteristics of HR, BP and HRV parameters during the tilttable test in Groups I and II**

Parameter \ Groups	Group I, n = 155			Group II, n = 201		
	А	Б	В	А	Б	В
HR, beats/min	65±5	129±12†	68±6	69±5	73±7*	71±4
Systolic BP, mm Hg	109±6	125±5†	109±6	110±7	112±9	111±5
Diastolic BP, mm Hg	71±5	84±4†	69±4	72±5	74±4	71±5
SDNN, ms	27±7	29±6	28±6	42±6	49±7	41±6
VLF, ms^2	724±117	1975±147†	833±124†	1424±127*	2034±149*†	1556±159*
LF, ms^2	365±64	293±68†	389±69†	456±55*	369±52*†	463±58*
HF, msc^2	115±46	67±39†	127±48†	428±51*	286±46*†	412±54*
LF/HF, units	3.14±0.59	4.37±0.67†	3.06±0.61†	1.06±0.34*	1.37±0,46*†	1.12±0.43*

Note. А—parameters in the supine position before the tilttable test; В—at the end of the tilttable test; С—after the tilttable test while the patient was in the horizontal position.
*—significant difference compared with Group I; †—significant difference compared with baseline data ($p < 0.05$).

Similar data were obtained in the present study.

The clinical and pathogenic mechanisms of POST development are not well understood. This syndrome has been reported in patients with various conditions, including rheumatoid arthritis, hyperthyroidism, fibromyalgia, diabetes mellitus, amyloidosis, sarcoidosis, systemic lupus erythematosus, oncological diseases, epilepsy, and others [1–3]. The main proposed mechanisms include neuropathic, hyperadrenergic, and hypovolaemic [1–3]; however, the appearance of symptoms such as dizziness, headache, palpitations, sweating, etc., upon standing does not necessarily indicate a specific underlying mechanism [1, 2]. Likely, all mechanisms are interrelated, and the development of POST is determined by the predominant interplay among them [1–3, 10, 11].

In the present study, based on clinical, laboratory, and instrumental examination, the most probable diseases and conditions that could be a cause of POST were excluded.

According to screening testing, POST was diagnosed in 42.7% of all enrolled patients, with reproduction of orthostatic tachycardia symptoms at least 2–3 times a week over 3–6 months, which complied with the guidelines in force at the time of the study (2006) [4]. It should be noted that the same criteria are used in the latest international guidelines [2, 3]. The sensitivity, specificity, and diagnostic accuracy of POST detection by screening testing were 79.35%, 90.05%, and 85.26%, respectively.

Low power of all HRV parameters with a significant increase in the LF/HF ratio in patients with POST indicates a rigid rhythm with sympathetic predominance [5, 6]. Lower VLF power compared with patients without POST suggests a high risk of developing orthostatic tachycardia, possibly due to increased venous volume in the major veins of the lower extremities with normal venous valve function [3, 6]. The significant decrease in LF and HF power and the increase in LF/HF ratio during tilt testing reflect enhanced sympathoadrenal components of autonomic regulation, while the significant increase in VLF power indirectly indicates baroreceptor activation [3, 6], accompanied by vasoconstriction, increased HR, and elevated BP—with these changes being more pronounced in POST patients. Therefore, in the patients included in this study, the hyperadrenergic mechanism is likely the main driver of POST induction.

In recent years, an increase in systolic BP of ⩾ 20 mmHg upon standing has been termed "excessive orthostatic pressor response to standing," whereas the term "orthostatic hypertension" is used when systolic BP in the upright position reaches ⩾ 140 mmHg compared with supine baseline [7]. Diagnostic criteria for defining pathological "orthostatic arterial hypertension" in POST patients have not been established [1–3]. Notably, the term "pathological orthostatic arterial hypertension" is absent from clinical guidelines for the diagnosis and treatment of hypertension in adults [8]. On the other hand, according to the ARIC (Atherosclerosis Risk in Communities) study, identifying "orthostatic hypertension" in patients without cardiovascular pathology—defined as an increase in systolic BP ⩾ 20 mmHg and/or diastolic BP ⩾ 10 mmHg upon standing, or an upright systolic BP ⩾ 140 mmHg—is associated with a high risk of developing various cardiovascular diseases [9].

According to the results of the present study, all patients with POST exhibited an increase in diastolic BP of > 10 mmHg upon standing. These patients will be the subject of further followup.

In patients with joint hypermobility, POST with a hypotensive BP response to standing is frequently observed, but usually without orthostatic hypotension. However, in the present study, joint hypermobility syndrome was recorded with similar frequency (slightly over 40%) both in patients with POST and in those without tachycardia upon standing. The absence of BP reduction and orthostatic hypotension in hypermobile patients, despite having similar clinical symptoms to those with POST, may possibly be due to excessive dietary salt intake.

Within six months after starting the recommended therapy, including lifestyle modification and the use of betablockers and/or ivabradine, and during subsequent followup, the clinical condition of all POST patients significantly improved. Symptoms such as palpitations, left chest discomfort, dizziness, increased fatigue, etc., resolved, indirectly supporting a possible hyperadrenergic mechanism of orthostatic tachycardia. Later, during prospective followup, when periodic palpitations or cardiac irregularities occurred, e.g., after excessive psychoemotional stress, patients used betablockers and/or ivabradine to alleviate these symptoms. At repeated examinations, including tilttable testing, POST was not detected in any patient.

POST may have indirectly influenced the choice of specialty after medical school graduation. Among those who remained in the national healthcare system, about 50% and 80% of those with and without POST, respectively, were physicians in therapeutic disciplines. The impact of POST on specialty choice will be a subject of further investigation.

It is currently known that the contribution of hereditary predisposition to the development of HT, especially when hypertension is detected in parents or close relatives at a young age (< 55 years), ranges from 50 to 60% (possibly more). This is likely due to excessive sympathicotonic influence, manifested in the present study by increased HR and BP during orthostasis in POST patients, as well as by the effects of peptides produced in the medulla oblongata (vasoactive intestinal peptide, somatostatin, enkephalins, neurotensin, substance P, etc.) [10, 11]. Because depressor mechanisms that cause arteriolar dilation remain intact, HT manifests at a later stage [10, 11].

The source of ventricular ectopy in the region of the mitral and/or tricuspid annulus may be the papillary muscles or the left ventricular outflow tract. In patients without structural heart disease, there is a high risk of developing arrhythmogenic nonmyxomatous MVP, which appears to be due to thinning and/or elongation of chordae, and to a lesser extent, superficial fibrosis of the mitral valve leaflets [12–15]. Retrograde atrial activation after premature ventricular ectopy may induce MVP formation due to dyssynchrony (dysfunction) between papillary muscles and ventricular myocardium [12, 13, 16].

Thus, the development of POST with a concomitant increase in BP during orthostasis compared with supine baseline, in the absence of cardiac and extracardiac causes, can be considered a predictor of future cardiovascular diseases, such as HT, MVP, and ventricular arrhythmias.

Conclusion

POST was identified in 2.8% of medical university students aged 20–26 years, predominantly in women (83%), with a femaletomale ratio of 5:1. For initial diagnosis of POST, all patients presenting with orthostatic symptoms should undergo screening testing, including measurement of HR and BP in the supine position, followed by upright position and/or headup tilt. Based on screening test results, the sensitivity, specificity, and accuracy of POST detection were 79.35%, 90.05%, and 85.26%, respectively. A significant increase in HR and BP parameters during orthostasis was observed predominantly in POST patients, indirectly suggesting a possible hyperadrenergic mechanism of orthostatic tachycardia. In these patients, the main approach to managing orthostatic symptoms, in addition to lifestyle modification, is the use of betablockers and/or ivabradine. During prospective followup, HT was diagnosed in 36.13% of patients with POST, MVP in 23.87%, and ventricular extrasystoles in 38.06%. The development of HT was highly correlated (OR > 1) with a family history of HT (OR = 5.02), with increased BP in the upright position (OR = 3.05), while MVP was associated with retrograde atrial activation after premature ventricular complexes (OR = 12.4).

Conflict of interest: none declared.

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State of nonspecific adaptive mechanisms of the body, assessed by heart rate variability, in patients with acute coronary syndrome depending on its type and outcome

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The problem of acute coronary syndrome (ACS) remains relevant. Despite obvious progress in treatment, the medium and longterm prognosis remains unfavorable. Patients with ACS belong to the veryhighrisk category for complications, which necessitates the search for additional markers of adverse longterm outcomes.

Aim—to study the state of nonspecific adaptive mechanisms (NAM) of the body using heart rate variability (HRV)

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parameters in patients with ACS and to compare these data with disease outcomes.

Materials and methods. This open prospective study included 151 patients with ACS (122 men, 29 women), median age 62.0 [55.0; 69.0] years, divided into 3 groups: Group 1—ACS with persistent STsegment elevation; Group 2—ACS without STsegment elevation who underwent percutaneous coronary intervention; Group 3—ACS without STsegment elevation managed conservatively. The state of NAM was assessed by HRV parameters on admission. Longterm outcomes were evaluated by telephone interview 1 year after hospitalization. The primary endpoint was hospitalization for any form of ACS and/or allcause death within 1 year.

Results. In patients with ACS without STsegment elevation who received only conservative treatment and in patients with unstable angina, heart rate was lower compared to patients with ACS without STsegment elevation who underwent percutaneous coronary intervention. No statistically significant relationship was found between HRV parameters and ACS outcome. Cluster analysis identified 4 clusters with different regulatory features: Cluster 1 was characterized by maximal reduction in HRV; Cluster 2—pronounced centralization of heart rate regulation; Cluster 3—predominance of autonomic loop regulation over central; Cluster 4—predominance of vasomotor center activity. In Clusters 1 and 2, with the greatest strain on NAM, a higher number of hospitalizations for ACS and deaths were observed during the 1 year followup.

Conclusion. Cluster analysis allows identification of ACS patients with different degrees of NAM strain. Greater NAM strain is characteristic of patients with myocardial infarction and is associated with an unfavorable prognosis during 1 year followup, while the association of patient status in the identified clusters with prognosis is stronger than that of individual HRV parameters.

Keywords: heart rate variability, state of nonspecific adaptive mechanisms of the body, acute coronary syndrome, cluster analysis, prognosis.

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Introduction

Acute forms of coronary heart disease contribute significantly to mortality from circulatory system diseases, which remain the leading cause of disability and death in industrialised countries [1]. The accuracy of current prognostic tools for longterm outcomes is limited; therefore, the search for new predictive methods remains relevant [2, 3].

Adaptation is a universal property of living matter that accompanies any pathological process. The state of nonspecific adaptive mechanisms (NAM) dynamically changes during the course of the disease, manifesting as alterations in heart rate variability (HRV) parameters. The universal nature of these processes allows them to be used as markers of disease progression and outcome, in addition to traditional clinical, laboratory, and instrumental characteristics. Cardiointervalography (CIG) is an accessible, noninvasive method for assessing the state of NAM via HRV parameters, widely used in clinical practice [4–6].

The physiological interpretation and prognostic significance of HRV parameters in acute coronary syndrome (ACS) have long been recognised and are undisputed [6–8]. However, in the vast majority of studies, this interpretation is limited to the balance between sympathetic and parasympathetic activity of the autonomic nervous system; the parameters are considered individually and are characterised by limited sensitivity and specificity [6, 7].

Cluster analysis, as a mathematical method that allows formal classification of heterogeneous groups, is widely and successfully used in biomedical research [5]. In our previous work, we demonstrated the heterogeneity of the group of patients with nonSTsegment elevation ACS (NSTEACS), which can be assessed using cluster analysis. The indicators of patients in the identified homogeneous groups correlate better with prognosis than individual HRV parameters in groups formed by formal clinical criteria [9, 10].

Aim—to assess the state of NAM in patients with ACS based on HRV parameters and to correlate these data with the longterm outcome of ACS.

Material and methods

This openlabel prospective study was conducted at the emergency cardiology departments of City Clinical Hospital No. 11, Rostov Region, during 2017–2019, and at the Regional Clinical Hospital, Rostov Region, in 2024, in compliance with Good Clinical Practice standards and the principles of the Declaration of Helsinki. All patients provided written informed consent.

Inclusion criteria: both sexes, age 40–80 years; diagnosis of ACS on admission; predominantly sinus rhythm; signed voluntary informed consent. Exclusion criteria: any form of acute heart failure and decompensated chronic heart failure; rhythm and conduction disturbances; respiratory failure; presence of oncological or any other severe acute or chronic diseases that could distort the study results.

A total of 151 patients with ACS were examined (122 men, 29 women), median age 62.0 [55.0; 69.0] years. The control group comprised 30 practically healthy individuals, matched for sex and age. Examination and treatment of patients were carried out according to the clinical guidelines in force at the time of the study [11, 12]. Group 1 included 29 patients with persistent STsegment elevation who underwent primary percutaneous coronary intervention (PCI). Group 2 included 30 patients with NSTEACS who underwent primary PCI, and Group 3 consisted of 92 patients with NSTEACS managed conservatively. Cardiointervalography (CIG) was performed on the first day in the morning, after 15 minutes of adaptation in the supine position, using the hardwaresoftware complex "Varicard 2.51" (Ramena Ltd., Russia) and Iskim software version 6.0, based on 5minute ECG recordings. The following parameters were analysed: heart rate (HR), standard deviation of normal RR intervals (SDNN), stress index (SI), spectral power of the oscillatory process of the envelope curve of the RR interval series (in highfrequency (HF), lowfrequency (LF), and very lowfrequency (VLF) bands), and total spectral power (TP).

The activity of NAM was characterised by the balance between autonomic and central regulatory circuits. Predominance of the autonomic circuit was considered as decreased NAM activity, while predominance of the central circuit was regarded as increased NAM activity. HR was considered an integral, general indicator of regulatory influences on heart rhythm, with its increase reflecting NAM stress. SDNN was evaluated as a characteristic of autonomic regulation activity, assuming that the main contribution to its value comes from respiratory arrhythmia; its increase reflects predominance of the autonomic circuit, and its decrease—predominance of the central circuit. SI, calculated by geometric methods, characterises the state of NAM in the opposite way to SDNN: its increase indicates predominance of the central circuit, and its decrease—predominance of the autonomic circuit. Spectral parameters were interpreted as the influence on heart rhythm of periodic activity of the respiratory (HF), vasomotor (LF), and higher hypothalamic integrative autonomic (VLF) centres. Predominance of HF was assessed as greater autonomic activity and lower NAM stress; LF and VLF predominance indicated greater central regulation and, consequently, higher NAM stress. The greater the prevalence of wave influences in the VLF range, the higher the activity of the central regulatory circuit. TP, calculated as the sum of HF, LF, and VLF, was considered a characteristic of the combined influence of periodic modulating processes on heart rhythm, analogous to SDNN but excluding nonperiodic processes. Longterm prognosis was assessed via telephone interviews and medical records (outpatient cards, electronic records). Endpoints: hospitalisation for any form of ACS and allcause death within 1 year.

Statistical analysis

Statistical data processing was performed using Statistica 6.0 (StatSoft Inc., USA). Normality of distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Since the studied parameters showed a nonnormal distribution, data are presented as Me [Q25; Q75], where Me is the median, and Q25 and Q75 are the lower and upper quartiles, respectively. Statistical significance of differences was determined using the Mann–Whitney, Kruskal–Wallis, Pearson X^2, and Fisher's exact tests. Differences were considered statistically significant at $p < 0.05$. To identify homogeneous subgroups, exploratory analysis was performed using hierarchical classification with nearestneighbour clustering and Euclidean distance as the measure. Final clusters were formed using the kmeans method.

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Table 1. **HRV parameters in the control group and patients with ACS (Me [Q25;Q75])**

Parameter	Control group, n = 30	Patients with ACS, n = 151	Significance level, p
HR, bpm	68.0 [64.0;71.0]	68 [58.0;77.0]	0.886820
SDNN, ms	40.0 [34.0;44.0]	24.0 [17.0;37.0]	0.000001
SI, y.e.	162.0 [122.0;189.0]	367.0 [153.0;896.0]	0.000013
HF, %	24.3 [19.3;29.7]	23.7 [14.9;38.3]	0.907843
LF, %	33.8 [26.5;39.1]	34.6 [24.5;43.7]	0.588434
VLF, %	41.8 [33.3;48.5]	35.2 [23.2;54.7]	0.183345
TP, ms2	940.0 [673.0;1284.0]	454.0 [193.0;1046.0]	0.001485

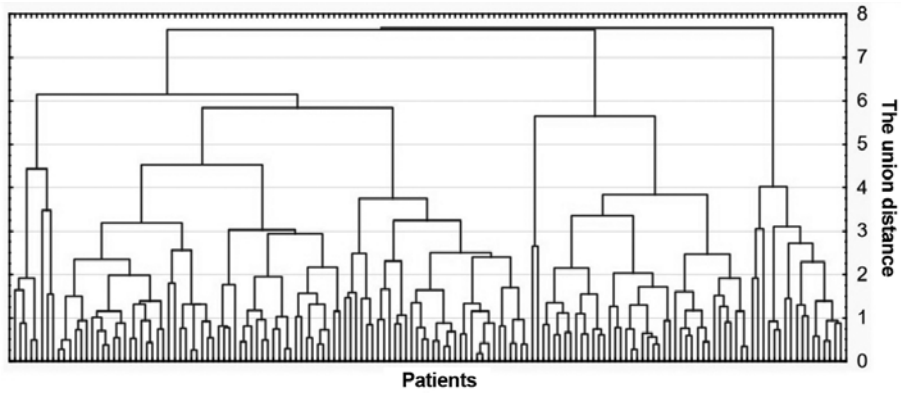

Fig. 1. Distribution of patients in exploratory cluster analysis

Ethical approval. The study protocol was approved by the Ethics Committee upon approval of the dissertation research topic.

Results

In patients with ACS, SDNN and TP were significantly reduced, and SI was elevated, indicating NAM stress (Table 1). The ratio of wave components (HF, LF, VLF) remained within normal limits. Notably, there was considerable dispersion of parameters, reflecting the heterogeneity of HRV indicators in ACS patients.

After exploratory analysis of the studied HRV parameters (Fig. 1) using kmeans clustering, four clusters were formed, providing adequate comparison group sizes.

In Cluster 1, SI was elevated, SDNN and TP were reduced—the most pronounced among all clusters (Table 2). Among spectral parameters, vasomotor

Table 2. **HRV parameters by cluster (Me [Q25;Q75])**

Parameter	Cluster 1, n = 34	Cluster 2, n = 43	Cluster 3, n = 38	Cluster 4, n = 36
HR[1], bpm	75.0 [70.0; 83.0]	77.0 [69.0; 86.0]	59.5 [55.0; 64.0]	61.0 [56.5; 67.0]
SDNN[2], ms	16.5 [13.0; 22.0]	21.0 [15.0; 28.0]	27.0 [22.0; 37.0]	41.5 [35.7; 57.0]
SI[3], y.e.	1002.5 [541.0; 1489.0]	594.0 [325.0; 1597.0]	295.0 [155.0; 506.0]	131.5 [63.0; 175.5]
HF[4], %	24.9 [15.8; 32.2]	15.1 [7.4; 21.5]	44.6 [39.7; 53.0]	18.9 [14.6; 26.1]
LF[5], %	46.5 [39.5; 52.9]	23.4 [16.6; 28.0]	28.5 [24.9;35.1]	43.7 [39.1; 50.0]
VLF[6],%	28.0 [22.0; 37.1]	60.1 [54.7; 65.8]	24.1 [19.3; 30.9]	35.8 [23.1; 45.5]
TP[7], ms^2	192.0 [109.0; 393.0]	321.0 [122.0; 633.0]	474.0 [322.0; 811.0]	1442.0 [953.5; 2139.0]

Note. Statistically significant differences ($p < 0.05$) between comparison groups:
[1]—Clusters 1 and 2 vs. Clusters 3 and 4 ($p < 0.000001$).
[2]—Control vs. Cluster 1 ($p < 0.000001$), Cluster 2 ($p < 0.000001$), Cluster 3 ($p = 0.006842$); Cluster 1 vs. Cluster 3 ($p = 0.000227$), Cluster 4 ($p < 0.000001$); Cluster 2 vs. Cluster 4 ($p < 0.000001$).
[3]—Control vs. Clusters 1 and 2 ($p < 0.000001$); Cluster 1 vs. Cluster 3 ($p = 0.000101$), Cluster 4 ($p < 0.000001$); Cluster 2 vs. Cluster 4 ($p < 0.000001$); Cluster 3 vs. Cluster 4 ($p = 0.001382$).
[4]—Control vs. Cluster 4 ($p = 0.000004$); Cluster 1 vs. Cluster 2 ($p = 0.008165$), Cluster 3 ($p = 0.000002$); Cluster 3 vs. Clusters 2 and 4 ($p < 0.000001$).
[5]—Control vs. Cluster 1 ($p = 0.000843$), Cluster 2 ($p = 0.002333$), Cluster 4 ($p = 0.004088$); Cluster 1 vs. Cluster 2 ($p < 0.000001$), Cluster 3 ($p = 0.000006$); Cluster 2 vs. Cluster 4 ($p < 0.000001$); Cluster 3 vs. Cluster 4 ($p = 0.000001$).
[6]—Control vs. Cluster 2 ($p = 0.000060$), Cluster 3 ($p = 0.000355$); Cluster 1 vs. Cluster 2 ($p < 0.000001$); Cluster 2 vs. Clusters 3 and 4 ($p < 0.000001$).
[7]—Control vs. Cluster 1 ($p < 0.000001$), Cluster 2 ($p = 0.000225$); Cluster 1 vs. Cluster 3 ($p = 0.006402$), Cluster 4 ($p < 0.000001$); Cluster 2 vs. Cluster 4 ($p < 0.000001$); Cluster 3 vs. Cluster 4 ($p = 0.006402$).

Table 3. **Distribution of clusters by type of ACS**

Cluster	Group 1, n = 29 STEMI	Group 2, n = 30 NSTEACS with PCI	3 группа, n = 92 NSTEACS without PCI
Cluster 1[1]	7 (24.1%)	8 (26.7%)	19 (20.7%)
Cluster 2[1]	13 (44.8%)	11 (36.7%)	19 (20.7%)
Cluster 3[1]	4 (13.8%)	4 (13.3%)	30 (32.6%)
Cluster 4[1]	5 (17.2%)	7 (23.3%)	24 (26.1%)
1+2 Clusters[2]	20 (69.0%)	19 (63.3%)	38 (41.3%)
3+4 Clusters[2]	9 (31.0%)	11 (36.7%)	54 (58.7%)

Note. Statistically significant differences ($p < 0.05$) between comparison groups:
[1]—$x^2 = 11.7249$, $p = 0.068394$;
[2]—$x^2 = 9.03232$, $p = 0.010931$; Group 1 vs. Group 3: $x^2 = 6.76$, $p = 0.0093$; Group 2 vs. Group 3: $x^2 = 4.41$, $p = 0.0357$.

Table 4. **Distribution of clusters by final clinical diagnosis**

Cluster	Qwave MI, n = 34	NonQwave MI, n = 47	Unstable angina, n = 70
Cluster 1[1]	8 (23.5%)	14 (41.2%)	12 (35.3%)
Cluster 2[1]	15 (34.9%)	11 (25.6%)	17 (39.5%)
Cluster 3[1]	6 (15.8%)	10 (26.3%)	22 (57.9%)
Cluster 4[1]	5 (13.9%)	12 (33.3%)	19 (52.8%)
1+2 Clusters[2]	21 (63.6%)	18 (58.1%)	17 (29.8%)
3+4 Clusters[2]	23 (29.9%)	25 (32.5%)	29 (37.7%)

Note. Statistically significant differences ($p < 0.05$) between comparison groups:
[1]—$x^2 = 2.43$, $p = 0.487894$;
[2]—$x^2 = 6.43$, $p = 0.040218$.

centre activity (LF) predominated. In Cluster 2, reductions in SDNN and TP were less pronounced than in Cluster 1, with elevated SI and predominance of verylowfrequency periodic influences over high and lowfrequency ones (centralisation of regulation) [4]. In Clusters 1 and 2, HR was higher than in Clusters 3 and 4, but did not differ from the control group. This pattern reflects marked NAM stress in patients of Clusters 1 and 2 [4]. In Cluster 3, SDNN reduction was less than in Clusters 1 and 2, with HF predominance in the spectral parameters due to decreased LF and VLF. In Cluster 4, HF was reduced and LF elevated, indicating more pronounced NAM stress than in Cluster 3, but less than in Clusters 1 and 2. These HRV changes suggest lower NAM stress in patients of Clusters 3 and 4 compared with Clusters 1 and 2.

When comparing HRV parameters according to the type of ACS, a statistically significant difference was found for HR: Group 1—78 [69.0; 85.0], Group 2—73.0 [64.0; 85.0], Group 3—66 [58.0; 75.0] per minute, $p < 0.0001$. Significant differences between Groups 1 and 3 ($p = 0.000024$) and between Groups 2 and 3 ($p = 0.002222$) indicate lower NAM stress in Group 3. Patients in Group 1 more frequently exhibited pronounced NAM stress than those in Group 3, with a statistically significant difference when clusters were combined (Table 3).

In Group 1, 28 patients (93.1%) developed Qwave myocardial infarction (MI), and one patient (6.9%) had nonQwave MI. In Group 2: one patient (3.3%) had Qwave MI, 16 (53.3%) had nonQwave MI, and 13 (43.3%) had unstable angina (UA). In Group 3: 6 patients (6.5%) were diagnosed with Qwave MI, 29 (31.5%) with nonQwave MI, and 57 (62.0%) with UA.

When comparing HRV parameters according to the final clinical diagnosis, a statistically significant difference was found for HR. For Qwave MI—77.0 [66.0; 85.0], nonQwave MI—69.0 [60.0; 80.0], UA—64.0 [57.0; 72.0] per minute, $p = 0.0013$; significant difference between Qwave MI and UA, $p = 0.000975$. Thus, MI was associated with pronounced NAM stress (Table 4).

One year after discharge, contact was lost with 5 patients, 4 died, and 49 were rehospitalised for ACS. Due to the small number of endpoints, they were combined into a composite endpoint (CEP)—allcause death or hospitalisation for ACS. At 1 year, CEP was registered in 7 patients (25.9%) of Group 1, 13 (43.3%) of Group 2, and 34 (37.1%) of Group 3. No statistically significant differences were found between groups.

Among patients with Qwave MI, CEP occurred in 9 (29.0%), in nonQwave MI—in 22 (47.8%), and in UA—in 22 (31.9%). No significant differences were obtained.

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Table 5. **Distribution of clusters and longterm outcome of ACS**

Cluster	No CEP, n = 93	CEP present, n = 53
Cluster 1[1]	18 (19.4 %)	14 (26.4 %)
Cluster 2[1]	20 (21.5 %)	20 (37.7 %)
Cluster 3[1]	28 (30.1 %)	10 (18.9 %)
Cluster 4[1]	27 (29.0 %)	9 (17.0 %)
1+2 Clusters[2]	38 (40.9 %)	34 (64.2 %)
3+4 Clusters[2]	55 (56.1 %)	19 (35.8 %)

Note. Statistically significant differences ($p < 0.05$) between comparison groups:
[1]—$x^2 = 7.64$, $p = 0.054045$;
[2]—$x^2 = 7.33$, $p = 0.006793$.

When comparing HRV parameters according to longterm outcome, no statistically significant differences were found.

The association between longterm outcome and the NAM state variant identified by cluster analysis is presented in Table 5. Pronounced NAM stress in Clusters 1 and 2, as opposed to Clusters 3 and 4, was associated with a negative prognosis—hospitalisation for ACS or death.

Discussion

Patients with ACS constitute a heterogeneous group in terms of clinical presentation, management strategy, and outcomes. Coronary revascularisation is the key intervention determining prognosis in ACS; however, objective difficulties—such as low population density in some regions, long transport times, limited availability of endovascular surgery, and late patient presentation—often lead to a conservative approach. In 2023, PCI was performed in 75.7% of patients with STsegment elevation ACS and in only 39.1% of patients with NSTEACS, highlighting the ongoing relevance of conservative management and the need for accurate assessment of course and prognosis in these patients [1].

HRV parameters have long been studied for prognostic assessment in MI. Recent metaanalyses and systematic reviews emphasise the limited predictive accuracy of individual HRV indices, difficulties in comparing parameters across studies, and wide variability in values during the first 24 hours of ACS [6, 7]. In 2025, Yang X. et al. developed a risk stratification system incorporating HRV parameters alongside clinical and laboratory data, which demonstrated good predictive ability for major cardiovascular events such as death, unplanned revascularisation, recurrent MI, or hospitalisation for UA [9]. In the study by Pukkila T. et al., the prognostic value of HRV parameters decreased after adjustment for the GRACE score and left ventricular ejection fraction, while Wang N. et al. found no predictive value for HRV parameters [13, 14].

We attempted to address this problem by identifying groups of patients with a specific, stable combination of HRV parameters on the first day of hospitalisation using cluster analysis. These combinations have a physiological interpretation through the concept of NAM. The obtained variants of NAM states show a clear relationship with disease outcomes, including longterm prognosis. This pattern holds across different types of ACS and approaches to reperfusion therapy. Among all HRV parameters, only HR differed significantly between the compared groups, reflecting the sum of regulatory influences and thus being more sensitive but less specific. Importantly, the NAM states in ACS are not limited to simple sympathetic or parasympathetic predominance, nor can they be described by deviations of any single HRV parameter. The association between NAM state and prognosis emerges when detailed variants of NAM state are identified using multiple HRV parameters.

Conclusion

Among all HRV parameters, significant differences between different ACS variants were found only for HR. Cluster analysis of HRV parameters, as a formal mathematical method, performed on the first day of hospitalisation in patients with ACS, irrespective of its type or revascularisation approach, allows the identification of subgroups with clearly defined characteristics of the state of nonspecific adaptive mechanisms. These states unambiguously characterise the degree of NAM stress. The most pronounced NAM stress, as identified by cluster analysis, was demonstrated in patients with MI who developed the composite endpoint, providing an additional tool for assessing longterm prognosis in ACS.

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Development of arterial hypertension in oil refining industry workers: prevention issues

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The prevalence of arterial hypertension (AH) at the oil refining complex, even considering the selection of individuals for work with occupational hazards, is quite high and comparable to the prevalence of this disease in the general population. In this regard, studying the influence of adverse occupational and other significant factors on the development of AH among industrial enterprise workers is a pressing issue in modern medicine.

Aim—to identify significant risk factors for the development of AH among oil refining industry workers and to evaluate the effectiveness of preventive measures.

Materials and methods. A 10-year prospective study (2004/2005–2014/2015) was conducted involving 1,431 employees of JSC "Naftan". Among 986 individuals with normal baseline blood pressure (BP), 664 worked under conditions of exposure to unfavorable occupational factors (UOF). Standard questionnaires, anthropometry, determination of the taste sensitivity threshold to table salt, electrocardiography, and biochemical blood analysis (lipid profile, glucose, creatinine) were used.

Results. According to the follow-up results, the incidence of AH was 31.5% among individuals without UOF and 40.1% among those exposed to UOF ($p<0.05$). The most significant association was found with psychophysiological factors determined by labor intensity. A multifactorial predictive model was constructed ($\chi^2=227.3$; $df=15$; $p<0.001$) with a sensitivity of 80.2% and specificity of 86.5%. The model included: age, sex, presence of unfavorable occupational factors, sum of SV_1+RV_{5-6} amplitudes ≥24 mm, alcohol abuse, salt taste sensitivity threshold ≥0.25%, diastolic BP ≥80 mmHg, low physical activity, body mass index ≥25 kg/m², glucose >6.4 mmol/L,

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triglycerides ≥2.0 mmol/L, total cholesterol ≥5.2 mmol/L, suboptimal glomerular filtration rate (<88 or ≥100 mL/min), smoking, and high-density lipoprotein cholesterol ≤1.25 mmol/L. Preventive measures implemented at a health resort showed effectiveness primarily in the high- and moderate-risk groups among workers exposed to UOF.

Conclusion. Thus, a high incidence of AH was identified among oil refining industry workers, primarily under exposure to UOF. The developed multifactorial model allows for the identification of risk groups for targeted prevention. The implementation of preventive measures demonstrated high effectiveness in the high- and moderate-risk groups for AH development among workers exposed to UOF, as well as in the high-risk group for AH development among workers without hazardous working conditions.

Keywords: arterial hypertension, oil refining industry, occupational risk factors, multifactorial model, prevention, spa treatment.

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Introduction

Arterial hypertension (AH) is the most common cardiovascular disease (CVD) and largely determines disability and premature mortality in many countries worldwide. According to epidemiological studies, the prevalence of AH in the Belarusian population is 39.4%, awareness of AH among the population is 75%, 53.3% receive medical treatment for AH, 35.9% take medications regularly (daily), and 9.3% effectively control blood pressure (BP) (achieve target levels). The most significant risk factors (RFs) include: overweight, family history of premature CVD, alcohol abuse, current and past smoking, low physical activity, lack of higher education, hypercholesterolemia, and hypertriglyceridemia [1]. Similar data on the high prevalence of AH and its RFs have been obtained in the Russian Federation [2].

In economically developed countries, including the Russian Federation and the Republic of Belarus, insufficient attention is paid to the influence of working conditions on the health of workers in modern large-scale industrial enterprises [3]. These include leading oil refining facilities characterized by exposure to chemical, physical, and psycho-emotional factors [4].

Thus, the relevance of this work is determined by obtaining new clinical and epidemiological data on the impact of adverse occupational factors (AOF) on the development of CVD among oil refining industry workers, taking into account current socio-economic conditions, as well as the need to develop measures to minimize occupational risk.

Aim—to identify significant RFs for the development of AH and to evaluate the possibilities of preventive interventions at the health resort of JSC "Naftan" for the prevention of new cases of this disease among oil refining industry workers.

Materials and methods

A 10-year prospective clinical and epidemiological study was conducted at JSC "Naftan" in 2004/2005–2014/2015, including 1,431 individuals (examination coverage was 99.8%).

According to the first screening (2004–2005), 986 individuals with normal blood pressure (BP) were selected for studying the development of AH. Of these, 322 individuals (118 men and 204 women) worked without AOF, and 664 individuals (415 men and 249 women) were exposed to AOF. The mean age of workers without adverse working conditions was 38.0±0.5 years, and that of workers exposed to AOF was 36.2±0.4 years.

The examination results were recorded in a specially designed preventive examination card, which included: socio-demographic data (sex, age, education, profession); a standard questionnaire according to World Health Organization questionnaires to detect angina pectoris, history of myocardial infarction, and chronic heart failure; questionnaires on heredity, physical activity, smoking, and alcohol consumption; anthropometry; data on the determination of the taste sensitivity threshold to table salt (TSTTS); and results of instrumental and laboratory examination methods.

BP was measured with a sphygmomanometer in accordance with the WHO/ISH 1999 guidelines. AH was diagnosed when systolic BP (SBP) was above 140 mm Hg and/or diastolic BP (DBP) above 90 mm Hg, as well as in the case of taking antihypertensive drugs [5].

Family history of premature cardiovascular disease (FHP-CVD) was determined if the mother had a cardiovascular event (premature death, myocardial infarction, or stroke) before age 65 and/or the father before age 55 [6].

Alcohol abuse was considered when consuming more than 168 g of ethanol per week for men and more than 112 g for women [6].

Smokers were defined as persons who smoked at least one cigarette daily, or had stopped regular smoking less than 12 months before the examination. Past smokers were those who had previously smoked regularly and quit more than 12 months before the examination. Never smokers were those who had never used tobacco products, or had smoked regularly for less than one year [6].

Low physical activity (LPA) was defined when the subject sits at work for 5 hours or more, and active leisure time in winter and summer, including time spent walking to and from work, is less than 10 hours per week [6].

Height was measured using a medical stadiometer with an accuracy of 0.5 cm. Weight was measured on medical scales with an accuracy of 0.1 kg. Body mass index (BMI) was calculated using the formula [6]:

$$\text{BMI} = \text{body weight (kg)} / \text{height}^2 \text{ (m}^2\text{)}$$

Salt intake was assessed by an indirect indicator — TSTTS, which was calculated using a modified method of R. I. Henkin by applying drops of sodium chloride (NaCl) solutions of increasing concentration (0.03125% — 2%) onto the anterior third of the tongue. The TSTTS value was taken as the lowest NaCl concentration at which the subject first perceived a salty taste [7].

Electrocardiography was performed at rest in 12 standard leads: I, II, III, aVR, aVL, aVF, V_1–V_6. Heart rate (HR) was determined in leads V_5–V_6 in the supine position after 10 minutes of rest. The sum of SV_1+RV_{5-6} amplitudes was determined from the ECG data.

Total cholesterol (TC) and triglycerides (TG) concentrations were measured by enzymatic methods. High-density lipoprotein cholesterol (HDL-C) was analyzed in the supernatant after chemical precipitation of apo-B-containing lipoproteins [8]. Low-density lipoprotein cholesterol (LDL-C) was calculated [9]:

$$\text{LDL-C} = \text{TC} - (\text{HDL-C} + \text{TG}/2.2) \text{ (mmol/L)}$$

Biochemical plasma glucose was determined by the enzymatic colorimetric method. Diabetes mellitus (DM) and impaired glucose tolerance were diagnosed based on the data of the working group of the European Society of Cardiology in collaboration with the European Association for the Study of Diabetes [10].

Creatinine was determined by the kinetic method, followed by calculation of glomerular filtration rate (GFR) using the Cockcroft–Gault formula [11]:

$$\text{GFR (mL/min)} = [(140 - \text{age in years}) \times \text{body weight (kg)}] / (0.814 \times \text{serum creatinine (μmol/L)});$$

for women, this value is multiplied by 0.85.

The possibilities of preventive interventions at the "Naftan" health resort for the prevention of new AH cases were studied by monitoring significant RFs among workers according to an individual preventive intervention program, which was subsequently (over 10 years) adjusted if necessary and implemented at the workplace. The following groups were formed: Group I (n = 62) — with preventive measures, without hazardous working conditions; Group II (n = 191) — with preventive measures, working with AOF; Group III (n = 198) — without preventive measures, without hazardous working conditions; Group IV (n = 420) — without preventive measures, working with AOF.

Statistical analysis

Statistical data analysis was performed using SAS (Statistical Analysis System) 6.12 [12] and IBM SPSS Statistics 19.0 [13] at the Biostatistics Laboratory of the Federal State Budgetary Institution "State Research Center for Preventive Medicine" of the Ministry of Health of the Russian Federation.

Based on risk factor data $X = (x_1, x_2, \ldots, x_i)$ and regression coefficients β calculated for each variable, the 10-year risk of AH development was estimated using the formula:

$$P = 100 / (1 + e^{-(-8.790 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_{15} x_{15})}),$$

where P is the probability of AH development (%); e is the mathematical constant equal to 2.71828; x_i is the value of the risk factor for the subject; β_i is the regression coefficient of significance for each risk factor.

Results

According to the 10-year prospective study, a rather high incidence of AH was found among JSC "Naftan" workers, amounting to 31.5% in those without hazardous working conditions and 40.1% in those exposed to AOF (Wald χ^2 = 5.7; df = 1; p<0.05).

A significant positive association was also found between the incidence of new AH cases and the presence of AOF (Wald χ^2 = 5.7; df = 1; p<0.05). The most significant association was established with psychophysiological factors characterizing labor intensity (Wald χ^2 = 7.3; df = 1; p<0.01).

In addition, a significant association was found between the incidence of new AH cases and age (Wald x^2 = 86.2; df = 3; p<0.001) and sex (Wald χ^2 = 5.8; df = 3; p<0.05). When studying this relationship with consideration of AOF, an association was found with age (Wald χ^2 = 91.3; df = 3; p<0.001) and work with AOF (Wald χ^2 = 5.7; df = 3; p<0.05), whereas no association with sex was found (Wald χ^2 = 2.3; df = 3; p>0.05).

The mean SBP level was 119.9±0.4 mm Hg among workers without hazardous conditions and 121.9±0.3 mm Hg among those exposed to AOF (F = 14.9; df=1; p<0.001). An association was found between the incidence of new AH cases (adjusted for age, sex, and presence of AOF) and SBP levels (Wald χ^2 = 43.6; df = 4; p<0.001) and DBP levels (Wald χ^2 = 32.3; df = 4; p<0.001). A significant positive association (adjusted for age, sex, and presence of AOF) was revealed between the development of new AH cases and SBP ⩾ 120 mm Hg (Wald χ^2 = 15.3; df = 4; p<0.001) and DBP ⩾ 80 mm Hg (Wald χ^2 = 30.5; df = 4; p<0.001).

The incidence of new AH cases (adjusted for age, sex, and presence of AOF) had a significant association with FHP-CVD (df = 1; Wald χ^2 = 76.5; p<0.001).

A significant positive association was found between the incidence of new AH cases and lack of higher education (Wald χ^2 = 10.7; df = 4; p<0.001) after adjustment for age, sex, and presence of AOF.

Furthermore, an association was established between the development of AH and current and past smoking (Wald χ^2 = 14.7; df = 1; p<0.001), alcohol abuse (Wald χ^2 = 31.7; df = 1; p<0.001), and LPA (Wald χ^2 = 18.7; df = 1; p<0.001) after adjustment for age and presence of AOF.

BMI, after adjustment for age, sex, and presence of AOF, was associated with the development of AH (Wald χ^2 = 10.4; df = 4; p<0.001). A significant positive association was found between BMI ⩾25 kg/m² and new AH cases (Wald χ^2 = 11.6; df = 1; p<0.01) after adjustment for age, sex, and presence of AOF.

An association was also found between the incidence of new AH cases (adjusted for age, sex, and presence of AOF) and TSTTS level (Wald χ^2 = 10.4; df = 4; p<0.001). A significant positive association was found between TSTTS ⩾0.25% and above and the incidence of new AH cases (adjusted for age, sex, and presence of AOF) (Wald χ^2 = 12.7; df = 1; p<0.01).

No association was found between the development of AH, adjusted for age, sex, and presence of AOF, and HR level or its pentile distribution.

An association was found between the incidence of new AH cases (adjusted for age, sex, and presence of AOF) and the sum of SV_{1-2}+RV_{5-6} amplitudes (Wald χ^2 = 32.8; df = 4; p<0.001). A significant positive association was found between SV_{1-2}+RV_{5-6} ⩾24 mm and AH incidence (Wald χ^2 = 33.0; df = 1; p<0.001).

At the same time, a trend toward a higher incidence of new AH cases was observed with increasing TC levels (Wald χ^2 = 3.4; df = 4; p<0.1), as well as with decreasing HDL-C levels (Wald χ^2 = 3.1; df = 4; p<0.1), regardless of sex, age, and presence of AOF. An association was found between the incidence of new AH cases and TG levels (Wald χ^2 = 9.9; df = 4; p<0.01). Adjusted for age, sex, and presence of AOF, a significant positive association was established between the development of new AH cases and levels of: TC ⩾5.20 mmol/L (Wald χ^2 = 10.8; df = 1; p<0.01), TG ⩾ 2.0 mmol/L (Wald χ^2 = 6.8; df = 1; p<0.01), LDL-C ⩾ 2.8 mmol/L (Wald χ^2 = 4.9; df = 1; p<0.05), and HDL-C ⩽ 1.25 mmol/L (Wald χ^2 = 4.8; df = 1; p<0.05).

The development of new AH cases was also associated with GFR level (Wald χ^2 = 32.8; df = 4; p<0.001) adjusted for age, sex, and presence of AOF. A significant positive association was found between suboptimal GFR (<88.0 mL/min/1.73 m² or ⩾100 mL/min/1.73 m²) (adjusted for age, sex, and presence of AOF) and the incidence of new AH cases (Wald χ^2 = 15.7; df = 1; p<0.01).

Glucose level was significantly associated with new AH cases (Wald χ^2 = 32.8; df = 4; p<0.001) adjusted for age, sex, and presence of AOF. A significant positive

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Table 1. **Multifactorial model of RR for AH development in oil refining industry workers**

RF	OR (95 % DI)	p
Age, years	1.082 (1.062–1.103)	<0.001
Sex (0—male; 1—female)*	1.888 (1,179–3.023)	<0.01
Adverse occupational factors*	1.971 (1.003–2.890)	<0.05
Sum of SV_1+RV_{5-6} amplitudes ≥24 mm*	2.759 (1.781–4.275)	<0.001
Alcohol abuse*	3.515 (2.053–6.019)	<0.001
TSTTS≥0,25%*	5.184 (2.165–12.413)	<0.001
DBP≥80 mm Hg*	2.089 (1.369–3.189)	<0.001
LPA*	2.051 (1.275–3.301)	<0.01
BMI≥25 kg/m²*	1.552 (1.112–2.168)	<0.01
Glucose>6,4 mmol/L *	1.690 (1.072–2.665)	<0.05
TG≥2,0 mmol/L *	2.144 (1.056–4.353)	<0.05
TC≥5,20 mmol/L *	1.473 (1.026–2.115)	<0.05
Suboptimal GFR <88.0 mL/min/1.73m² and ≥100 mL/min/1.73m²*	1.551 (0.956–2.516)	<0.1
Current smoking*	1.383 (0.957–1.997)	<0.1
Low HDL-C ≤1.25 mmol/L*	1.510 (0.946–2.411)	<0.1

Note. *—nominal dichotomous variable: 0—no, 1—yes.

association was found between glucose >6.4 mmol/L (adjusted for age, sex, and presence of AOF) and the development of AH (Wald χ^2 = 6.8; df = 1; p<0.01).

The following factors were not selected into the final multifactorial model of significant RFs (adjusted for age, sex, and presence of AOF): SBP ≥120 mm Hg (p>0.05), HR (p>0.05), FHP-CVD (p>0.05), lack of higher education (p>0.05), LDL-C ≥2.8 mmol/L (p>0.05).

Using multifactorial regression analysis, a final model of relative risk (RR) for the development of AH (independent of age, sex, and presence of AOF) was constructed based on statistically significant risk factors in individuals with AH (Wald χ^2 = 227.3; df = 15; p<0.001). The sensitivity of the model was 80.2%, specificity 86.5%. The RR values for the development of AH for each statistically significant risk factor are presented in Table 1.

The multifactorial model allows the identification of risk groups and determination of how many times the RR of AH development is higher compared to the low-risk group. A probability of AH development equal to 36% or more indicates high risk, 16% to 36%—moderate risk, less than 16%—low risk.

According to the multifactorial model, risk groups for AH development were identified: low risk—108 individuals without AOF and 148 with AOF; moderate risk—72 individuals without AOF and 71 with AOF; high risk—80 individuals without AOF and 268 with AOF.

The effectiveness of preventive interventions was assessed by prevented new AH cases (Table 2).

In the low-risk group for AH development, no significant differences in the incidence of new AH cases were found between those with preventive measures and those without, both in the group with AOF (χ^2 = 1.0; df = 1; p>0.05) and in the group without AOF (χ^2 = 1.2; df = 1; p>0.05).

In the moderate-risk group, with preventive measures versus without, significant differences in the incidence of new AH cases were found only in the group of workers exposed to AOF; in those without AOF, the differences were not significant (χ^2 = 0.1; df = 1; p>0.05).

In the high-risk group, with preventive measures versus without, significant differences in the incidence of new AH cases were found both in the group with AOF (χ^2 = 10.1; df = 1; p<0.01) and in the group without AOF (χ^2 = 4.6; df = 1; p<0.05).

Thus, the effectiveness of preventive measures was proven in the high- and moderate-risk groups for AH development among workers with AOF, and only in the high-risk group among workers without hazardous working conditions.

Table 2. **Incidence of new AH cases depending on risk groups for its development, considering the presence of preventive measures**

Factor		Preventive measures present		Preventive measures absent		p
		n	AH (%)	n	AH (%)	
Low risk	No AOF	27	7.4	81	14.8	> 0.05
	AOF present	49	4.1	99	9.1	> 0.05
Moderate risk	No AOF	18	22.2	54	25.9	> 0.05
	AOF present	53	17.0	139	33.8	< 0.05
High risk	No AOF	17	29.4	63	71.4	< 0.05
	AOF present	87	57.5*	181	70.7	< 0.05

Note. *—p <0.05 compared with the reference subgroup;
§—reference subgroup

Discussion

This study showed that the health status of oil refining enterprise workers is determined not only by the direct impact of AOF, but also by the development of cardiovascular pathology against their background, the most common representative of which is AH [14].

The prevalence of AH at the oil refining complex, considering the selection of individuals for work with occupational hazards, is quite high and comparable to the prevalence of this disease in Vitebsk, the Republic of Belarus, and the Russian Federation [1, 15, 16].

The increase in prevalence and incidence of AH is significantly more pronounced among workers exposed to adverse occupational factors, especially those related to labor intensity, which requires improvement of measures not only regulating work activities, but also active implementation of preventive measures among workers.

This study for the first time proved the role of psychophysiological factors determined by labor intensity in the development of AH in the oil refining industry, which distinguishes these findings from those previously reported [14, 17, 18].

Identification, alongside occupational factors, of the most significant traditional RFs and their threshold levels for AH development allowed the development of a multifactorial model for AH development and the formation of risk groups, which is of considerable importance for preventive measures.

The proposed model of AH development based on a ten-year prospective study differs significantly from five-year models from the Vitebsk and Framingham studies, and allowed to establish the influence of TSTTS, lipid parameters, glucose, and GFR, characterizing metabolic processes in the long term [19, 20]. At the same time, it should be noted that the threshold DBP level is consistent with elevated BP in the American College of Cardiology and American Heart Association guidelines [21].

It should also be noted that for the first time, data on the effectiveness of preventive measures conducted at a company-owned health resort among oil refining enterprise workers over a ten-year follow-up were obtained.

Conclusion

Thus, the study results indicate a high incidence of AH among oil refining industry workers, especially among those exposed to adverse occupational factors. The developed multifactorial model based on significant RFs allows, with a sensitivity of 80.2% and specificity of 86.5%, to predict the development of AH and to identify corresponding risk groups for preventive measures. The implementation of preventive measures demonstrated high effectiveness in the high- and moderate-risk groups for AH development among workers exposed to AOF, as well as in the high-risk group for AH development among workers without hazardous working conditions.

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Assessment of cardiovascular complication risk using the Score2-Diabetes scale in patients with type 2 diabetes mellitus in comorbidity with other somatic diseases

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Aim—to assess the 10-year risk of cardiovascular complications using the Score2-Diabetes scale in patients with type 2 diabetes mellitus (T2DM) in comorbidity with other somatic diseases.

Materials and methods. This crosssectional (clinical) study included 224 patients aged 40–65 years with T2DM according to WHO criteria (1999–2013). Inclusion criteria: presence of risk factors for chronic noncommunicable diseases and somatic diseases. Exclusion criteria: cardiovascular diseases, pulmonary, renal or hepatic insufficiency, and oncological diseases. Patients underwent medical examination, questionnaire survey, instrumental and biochemical tests. Cardiovascular risk was assessed using the SCORE2-Diabetes scale based on the following parameters: age, sex, smoking, systolic blood pressure (SBP), total cholesterol, highdensity lipoprotein cholesterol, age at T2DM diagnosis, glycated haemoglobin level, and glomerular filtration rate. Patients were divided into two groups: the first group included individuals with 1–2 additional somatic diseases, and the second group included those with three or more somatic diseases.

Results. The mean cardiovascular risk (CVR) according to the SCORE2-Diabetes scale in the first group was 23.16±8.62%, and in the second group—29.94±13.31% (p<0.001). Gender analysis of CVR showed that in the first group, CVR was comparable between men and women (23.1±9.29% and 23.44±8.14%, respectively). In the second group, CVR among women was 31.43±12.52%, among men—27.72±14.28%. Analysis of CVR categories showed that in the first group, about 60% of patients had very high CVR. High CVR was found in every third patient in this group. In the second group, ¾ of patients had very high CVR, and every fifth patient had high CVR. Moderate CVR was observed in up to 4% of cases in both groups; low risk was not detected. Correlation analysis revealed a significant positive association between the triglyceride-glucose (TyG) index and CVR (Sρ=0.21, p=0.023 for the first group and Sρ=0.2541772, p=0.007 for the second group). A similar positive correlation was found for highsensitivity Creactive protein (hsCRP) levels (Sρ=0.50, p<0.001 for the first group and Sρ=0.43, p<0.001 for the second group).

Conclusion. Comorbidity of T2DM with a larger number of somatic diseases is associated with more pronounced glycaemic impairment, lipid metabolism disorders, and higher blood pressure levels, which is reflected in the overall risk of cardiovascular complications. High CVR correlates with the TyG index. Thus, the Score2-Diabetes scale can be recommended for clinical practice when developing personalized prevention programmes for cardiovascular events, taking into account the presence of additional somatic diseases.

Keywords: type 2 diabetes mellitus, cardiovascular complication risk, SCORE2-Diabetes scale, risk factors.

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Introduction

Cardiovascular diseases (CVD) hold a leading position in the development of complications and mortality in the EuroAsian region. Type 2 diabetes mellitus (T2DM), given the increasing prevalence and younger age at onset, contributes significantly to the structure of cardiovascular morbidity. In highincome countries, patients with T2DM have on average a twofold higher risk of cardiovascular events (CVE) compared with individuals without diabetes of the same age and sex [1].

At the end of the 20th century, the prevailing view was that T2DM is a CVD equivalent; consequently, patients with diabetes were managed using secondary prevention strategies. However, this approach has been challenged because not all patients with T2DM have the same CVD risk. Therefore, other potentially important factors, such as disease duration, presence of albuminuria, and comorbidities, should be considered. In recent years, the use of available noninvasive methods, including cardiovascular risk (CVR) assessment scales, has been recommended for developing primary prevention strategies [2].

Previous attempts have been made to create CVR scales for patients with T2DM [3]. The available diabetesspecific models have several limitations, particularly due to population differences and characteristics. These scales are typically based on a small

set of observational and prospective studies and have not undergone systematic statistical adaptation that accounts for variations in CVD incidence across different populations and countries [4, 5]. For example, the PRECISEDM system was developed using seven variables associated with an increased risk of coronary heart disease (total score from 0 to 9). This scale has been shown to predict not only the presence of coronary heart disease but also the risk of major adverse cardiovascular events in asymptomatic patients with T2DM [6]. However, this scale was based on data from a limited number of patients (n = 933).

The capabilities of the European SCORE2 scale, adapted for T2DM, are actively discussed in the literature. It is known that SCORE2 allows the prediction of fatal and nonfatal cardiovascular events (myocardial infarction, stroke) over 10 years and is calculated based on CVD risk factors: age, smoking status, systolic blood pressure (SBP), and nonhighdensity lipoprotein cholesterol (total cholesterol minus HDL cholesterol) [7].

European experts, by extending the recalibrated European 10-year risk models SCORE2 [8], developed an adapted scale for individuals with T2DM. The study included 229,460 patients with T2DM without prior CVD, of whom 43,706 CVE were recorded during followup. The analysis took into account common risk factors, including age, smoking, blood pressure (BP), total cholesterol (TC), HDL cholesterol, and diabetesrelated factors (disease duration, glycated haemoglobin level, and glomerular filtration rate (GFR)). The performance of Score2-Diabetes was validated using four cohorts from different European regions (low, moderate, high, and very high CVD risk) [912].

It is well known that in realworld clinical practice, patients with T2DM at the time of diagnosis often have a number of additional somatic diseases that may have a pathogenetic or causal relationship. Comorbidity of somatic diseases can worsen the course of the underlying disease and also affect the quality and duration of life in patients with T2DM [8, 13].

Aim—to assess the risk of cardiovascular complications (CVC) using the SCORE2-Diabetes scale in patients with T2DM comorbid with other somatic diseases over the next 10 years.

Material and methods

A crosssectional clinical study included 224 patients aged 40–65 years with T2DM (WHO criteria, 19992013). Inclusion criteria: T2DM with risk factors for chronic noncommunicable diseases and additional somatic diseases. Exclusion criteria: age under 40 or over 65 years, decompensated T2DM, type 1 diabetes, verified atherosclerotic CVD, congenital and acquired heart defects, active infectious disease, pulmonary, renal and hepatic failure with impaired renal function at estimated GFR (eGFR) <25 ml/min/1.73 m^2 and severe hepatic insufficiency (ChildPugh class C), oncological diseases, pregnancy, mental disorders, and antidepressant use.

All patients underwent a standard medical examination and questionnaire survey, including information on sociodemographic indicators, behavioral risk factors, past illnesses, presence of chronic diseases, and family history. When collecting this information, data from medical records (discharge summaries and results of clinical, instrumental, and laboratory examinations) were taken into account.

Instrumental examinations included measurement and calculation of anthropometric parameters, BP measurement, heart rate, and resting electrocardiography (ECG).

BP was measured using the standard auscultatory method. The examination was performed with a noninvasive sphygmomanometer on the right arm in a sitting position after 5 minutes of rest in a calm environment. BP readings were recorded twice with a 23 minute interval, and the mean value was calculated from the two measurements. Heart rate was counted over one minute.

Hypertension was diagnosed according to the criteria of the Russian Society of Cardiology (2024).

Standard resting 12lead ECG was recorded using a Schiller AT10 plus electrocardiograph. Rhythm and conduction disturbances, ectopic activity, and left ventricular hypertrophy according to SokolowLyon criteria were assessed.

Echocardiography was performed via the transthoracic approach in M and Bmodes. The following parameters were assessed: left atrial size, interventricular septum and left ventricular posterior wall thickness in diastole, enddiastolic dimension, endsystolic dimension, and left ventricular enddiastolic and endsystolic volumes, ejection fraction, and left ventricular myocardial mass were calculated.

Laboratory tests. Blood sampling from the cubital vein was performed on admission and in the morning on an empty stomach after a 12hour fast. The follow-

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ing biochemical parameters were analyzed: fasting glucose, glycated haemoglobin (HbA1c), lipid profile parameters including total cholesterol (TC), lowdensity lipoprotein cholesterol (LDLC), triglycerides (TG), HDLC, and creatinine.

The triglycerideglucose (TyG) index was calculated using the formula: ln [TG (mg/dL) × fasting glucose (mg/dL) / 2]. Conversion: TG in mmol/L × 88.5 = mg/dL; venous plasma glucose in mmol/L × 18 = mg/dL.

eGFR (ml/min/1.73 m²) was calculated using the CKDEPI formula, and creatinine clearance (ml/min) was calculated using the CockcroftGault formula.

CVD risk was assessed using the European SCORE2-Diabetes scale based on the following parameters: age, sex, smoking, SBP, total cholesterol, HDLC, age at T2DM diagnosis, HbA1c, and eGFR. Risk was determined considering geographic regions with low, moderate, high, and very high risk. Russia, like most former USSR countries, belongs to the very highrisk region. The risk of cardiovascular complications was categorized into four grades: <2%—low risk, 2–<10%—moderate risk, 10%–<20%—high risk, and ≥20%—very high risk.

Ethical approval. The study protocol, medical documentation forms, and patient informed consent were approved by the independent ethics committee.

Statistical analysis

Statistical analysis was performed using the open-source R 4.2.3 environment. Qualitative variables were described as absolute frequencies and percentages; quantitative variables as mean and standard deviation (M±SD). When comparing two independent groups, Fisher's exact test was used for discrete variables and Welch's ttest for continuous variables. Correlations were calculated using Spearman's rank correlation coefficient. Differences were considered statistically significant at $p < 0.05$.

Results

According to the study protocol, patients with T2DM were divided into two groups depending on the number of additional somatic diseases. The first group included 114 patients with T2DM combined with 12 somatic diseases, while the second group comprised 110 patients with T2DM and three or more somatic diseases.

Table 1 presents demographic indicators, behavioral and biological risk factors, glycaemic status, and renal filtration parameters used to calculate CVR.

The groups were comparable in terms of age and sex distribution.

Table 1. **Parameters for calculating the risk of cardiovascular complications using the SCORE2-Diabetes scale**

Parameter	(Group 1) T2DM with 12 somatic diseases	(Group 2) T2DM with 3 or more somatic diseases
Age, years	53.02 ± 6.54	54.91 ± 9.17
Sex: male/female	53/61	44/66
Current smoker	20 (17.5%)	24 (22.4%)
SBP, mm Hg	135.4 ± 11.34	139.41±12.68
Total cholesterol, mmol/L	5.19 ± 1.13	5.45 ± 0.89
HDLC, mmol/L	1.06 ± 0.15	1.03 ± 0.1
Age at T2DM diagnosis, years	47.58 ± 6.25	48.08±8.18
HbA1c, %	8.22 ± 1.22	8.61 ± 1.59
eGFR, ml/min/1.73 m²	81.89 ± 17.67	78.35 ± 16.69

One in five patients, predominantly men, were current smokers, with no difference in smoking frequency between groups. A significant difference was noted in mean age at T2DM diagnosis ($p < 0.005$). HbA1c levels in the second group were significantly higher than in the first ($p < 0.037$). Several risk factors also differed between groups, including SBP ($p < 0.01$) and total cholesterol ($p < 0.05$). For HDLC and eGFR, differences did not reach statistical significance.

The assessment of CVC risk using the European Score2-Diabetes scale showed that the mean risk value in the group with T2DM and 12 somatic diseases was 23.16 ± 8.62%, while in the group with T2DM and three or more somatic diseases the risk was 1.3 times higher at 29.94 ± 13.31% ($p < 0.001$). Gender analysis of CVR showed that in the first group, CVR was comparable between men and women (23.1 ± 9.29 and 23.44 ± 8.14%, respectively). In the second group, CVR among women was 31.43 ± 12.52%, and among men—27.72 ± 14.28%.

Analysis of CVR categories shows that in the first group about 60% of patients have very high CVR. In this group, high CVR was found in onethird of patients (Table 2). In the second group, threequarters of patients had very high CVR, and one in five had high CVR. The frequency of very high CVR in the second group was significantly higher than in the first ($p = 0.015$). The opposite pattern was observed for high CVR—it was significantly more frequent in the first

Table 2. **CVR categories in two groups of patients with T2DM combined with other somatic diseases**

Indicator	Group 1	Group 2	Significance, p
Moderate risk			
Total in group	4 (3.5 %)	4 (3.6 %)	1.000
Men	1 (1.9 %)	1 (2.3 %)	1.000
Women	3 (4.9 %)	3 (4.5 %)	1.000
High risk			
Total in group	42 (36.8 %)	23 (20.9 %)	0.012
Men	22 (41.5 %)	14 (31.8 %)	0.400
Women	20 (32.8 %)	9 (13.6%)	0.012
Very high risk			
Total in group	68 (59.6 %)	83 (75.5 %)	0.015
Men	30 (56.6 %)	29 (65.9 %)	0.407
Woman	38 (62.3 %)	54 (81.8 %)	0.017

group compared to the second (p = 0.012). Moderate risk was found in up to 4% of cases in both groups, while low risk was absent.

Gender analysis of the frequency of different risk grades in the first group showed no significant differences between men and women. In the second group, the frequency of high CVR among men was twice as high as among women: 31.8% and 13.6%, respectively. The frequency of very high CVR among women was 25% higher than among men: 81.8% and 65.9%, respectively.

We also analyzed gender differences in the frequency of different CVR grades between groups. In the first group, high CVR among women was 2.5 times higher than among women in the second group (p < 0.012), while the proportion of women with very high CVR in the second group was 1.3 times higher than in the first (p < 0.017).

We analyzed the severity of parameters used to calculate CVC risk using the Score2-Diabetes scale in groups of T2DM patients combined with somatic diseases who had high and very high CVR.

At the same CVR grade, namely high CVR in the first group, the age of patients in the first group was higher than in the second group (Table 3). In the second group, the number of smokers was greater than in the first. A similar trend was observed for SBP and HDLC levels. Meanwhile, HbA1c, total cholesterol, and eGFR were comparable in both groups. The mean CVR value in the groups was comparable.

In the very high CVR category, the mean age and diabetes duration were significantly higher in the second group compared to the first (Table 4). In both groups, one in four patients with very high CVR was a smoker. In the group with T2DM and three or more

Table 3. **Comparative characteristics of parameters in individuals with high cardiovascular risk**

Parameter	T2DM with 12 somatic diseases, n = 42	T2DM with 3 or more somatic diseases, n = 23	Significance, p
Sex: m/f	22/20 (52.4 %/47.6 %)	14/9 (60.9%/39.1%)	0.606
Age	49.5 ± 5.01	45.09 ± 5.17	0.002
Age at T2DM diagnosis	45.21 ± 5.23	40.04 ± 5.41	0.001
Diabetes duration	4.45 ± 2.96	5.13 ± 2.93	0.377
Smoking	4 (9.5 %)	4 (17.4%)	0.439
SBP, mm Hg	132.83 ± 10	140.22 ± 14.77	0.039
TC	4.85 ± 1.19	5.13±0.48	0.186
HDLC	1.16 ± 0.14	1.02 ± 0.11	<0.001
HbA1c, %	7.86 ± 1	7.9 ± 1	0.878
eGFR	87.29 ± 17.65	93.91 ± 12.84	0.088
CVR	15.66 ± 2.68	14.86 ± 3.14	0.308

Table 4. **Comparative characteristics of parameters in individuals with very high cardiovascular risk**

Parameter	T2DM with 12 somatic diseases, n = 68	T2DM with 3 or more somatic diseases, n = 83	Significance, p
Sex m/f	30/38 (44.1 %/55.9 %)	29/54 (35 %/65 %)	0.315
Age	55.88 ± 5.68	58.59 ± 6.64	0.008
Age at T2DM diagnosis	49.56 ± 6.07	51.18 ± 6.07	0.105
Diabetes duration	6.09 ± 3.80	7.29 ± 3.80	0.056
Smoking	16 (23.5 %)	20 (24.09 %)	1.000
SBP, mm Hg	137.43 ± 11.93	139.7 ± 12.22	0.252
TC	5.40 ± 1.8	5.56 ± 0.97	0.512
HDLC	1.05 ± 0.16	1.03 ± 0.10	0.372
HbA1c, %	8.48±1.28	8.79 ± 1.72	0.207
eGFR	77.68±16.56	73.49 ± 14.53	0.105
CVR	28.71 ± 6.33	35.17 ± 10.89	<0.001

somatic diseases, SBP, total cholesterol, HDLC, HbA1c, and eGFR were comparable to the group with T2DM and 12 somatic diseases. Although both groups were in the very high CVR category, the mean CVR value in the group with T2DM and three or more somatic diseases was significantly higher than in the group with T2DM and 12 somatic diseases (p < 0.001).

According to Table 5, in both analysed groups, the mean TyG index was high (≥4.5), but in the group with T2DM and three or more somatic diseases it was significantly higher than in patients with T2DM and 12 somatic diseases (p < 0.001).

In the subgroups with high and very high CVR, the TyG index in the second group was significantly higher than in the first group.

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Table 5. **TyG index in groups of patients with T2DM combined with other somatic diseases**

Indicator	T2DM with 12 somatic diseases	T2DM with 3 or more somatic diseases	Significance, p
Mean TyG index	5 ± 0.35	5.14 ± 0.15	p<0.001
Subgroup with high CVR, TyG index	4.91 ± 0.51	5.09 ± 0.13	0.035
Subgroup with very high CVR, TyG index	5.06 ± 0.20	5.15 ± 0.16	0.003

Discussion

This cohort study was crosssectional in nature, and its main objective was to assess the 10-year risk of fatal and nonfatal cardiovascular complications in patients with T2DM without established CVD using the European SCORE2-Diabetes scale.

The interaction between T2DM and atherosclerotic CVD has been extensively studied. Carbohydrate metabolism disorders, through direct (insulin resistance and protein glycation) and indirect (endothelial dysfunction, chronic inflammation, and oxidative stress) mechanisms, accelerate atherosclerosis and lead to adverse cardiovascular events [14].

According to the Russian PROGNOSIS IHD registry, which included 504 patients with confirmed coronary heart disease, during 7.3 years of followup, the relative risk of the primary endpoint (allcause death, fatal and nonfatal cardiovascular events) increased 1.7fold in the presence of diabetes, and 2.4fold when diabetes was combined with hypertension [15].

Overall, clinical complications of atherosclerosis contribute to increased morbidity and mortality in patients with diabetes.

Obviously, early identification of individuals with high CVR without manifest atherosclerotic CVD is important for patients with T2DM to prevent various cardiovascular events such as MI, stroke, and death. The development of the European Score2-Diabetes scale expands the possibilities for assessing CVC risk in patients with T2DM without CVD in primary care, which in turn is a significant step towards personalization of primary CVD prevention [16].

There are few studies in the literature assessing CVR in T2DM patients using the European Score2-Diabetes scale. The Score2-Diabetes scale shares some general principles with the Score2 scale developed for the general population, particularly the classification of countries into four CVR groups [17].

The new approach takes into account risk levels not only based on individual indicators but also on the region where the patient lives. For example, at the same level of risk factor severity, a patient from a lowrisk region will have a lower overall CVC risk compared with a patient from a high or veryhighrisk region [18].

According to this classification, in our cohort of T2DM patients, only 3.3% had moderate risk, and low CVR was absent altogether. This is because Russia belongs to the highCVR countries. High CVR was found in one in four patients, and the majority had very high CVR. However, this only partially explains the causes of very high CVR in the analyzed T2DM group.

The duration of diabetes, degree of glycaemic compensation, and severity of major risk factors are important in shaping CVR [19]. In our cohort, the majority of patients at the time of examination had hypertension (71.6%), hypercholesterolaemia (76.9%), low HDLC (62.5%), and high HbA1c values (only 15% of patients achieved target haemoglobin levels). Only one in five patients smoked, while mean eGFR values corresponded to mildly reduced renal function. Gender differences in the frequency of CVR grades also play a role. Among women with T2DM included in this study, high CVR was found in 23.2%, while among men it was 36.6%. Very high CVR was verified in 72% of women and 61.2% of men.

The aim of this work was to assess the risk of CVC in T2DM patients depending on the number of additional somatic diseases. The presence of additional somatic diseases, with the exception of hypertension and chronic kidney disease with excretory dysfunction, is not taken into account in CVR calculation. However, the presence of somatic diseases pathogenetically linked to diabetes may influence the cardiometabolic profile and CVR.

In the present study, in the group with three or more somatic diseases, every second patient had nonalcoholic fatty liver disease, and up to onethird had other somatic diseases (chronic cholecystitis, chronic pancreatitis, nodular goitre, urolithiasis, and chronic obstructive pulmonary disease). Most patients in the first group had two additional somatic diseases, while in the second group, one in four patients had three or four additional somatic diseases.

In the first group, the frequency of high CVR was significantly higher than in the second group, whereas the opposite trend was observed for very high CVR. With comparable severity of 5 out of 9 parameters at T2DM diagnosis, the mean age, SBP, total

cholesterol, and HbA1c in the second group were significantly higher than in the first. This is reflected in the frequency of very high CVR.

The study also assessed the relationship between the TyG index and CVR level. The TyG index is considered a surrogate marker of insulin resistance and, according to prospective studies, has prognostic significance in the development of CVE [2022].

In our study, the mean TyG index in both groups was above normal, but the combination of T2DM with a greater number of somatic diseases was associated with higher values. This pattern was observed in the subgroups with high and very high CVR. Correlation analysis revealed a significant positive relationship between the TyG index and CVR (Spearman's rho = 0.21, p = 0.023 for the first group and rho = 0.254, p = 0.007 for the second group). A similar positive correlation was found for highsensitivity Creactive protein (rho = 0.50, p < 0.001 for the first group and rho = 0.43, p < 0.001 for the second group).

Conclusion

The results of the study showed that in patients with T2DM with a mean disease duration of 57 years, about 70% have very high CVR according to the European SCORE2-Diabetes scale, because Russia, like other former USSR countries, belongs to the very highrisk region. In realworld clinical practice, T2DM is often combined with two or more additional somatic diseases, among which hypertension and nonalcoholic fatty liver disease predominate, both having a pathogenetic link with the underlying disease. The combination of T2DM with a greater number of somatic diseases is associated with more pronounced disturbances in glycaemic status, lipid metabolism, and higher SBP values, which is reflected in the overall CVC risk. Furthermore, high CVR showed a correlation with the TyG index.

Thus, the SCORE2-Diabetes scale can be used in clinical practice to develop a personalized cardiovascular prevention programme for patients with T2DM, taking into account the presence of additional somatic diseases.

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Morphological substrate of atrial fibrillation onset in euthyroid sick syndrome: an experimental study

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Atrial fibrillation (AF) is one of the most common tachyarrhythmias encountered in clinical practice. AF is associated with structural and electrical remodeling of the atrial myocardium. Atrial fibrosis, indicative of structural remodeling, is a complex multifactorial process that contributes to the initiation and maintenance of AF. Although the relationship between AF and fibrosis has been actively investigated for a considerable time in clinical and pathomorphological studies, this process is extremely complex and involves intricate neurohumoral, cellular, and molecular interactions that are not limited to the atria. The mechanisms by which atrial fibrosis contributes to

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the development of AF in euthyroid sick syndrome (ESS) remain insufficiently studied, which prompted this investigation.

Objective—to study the morphological substrate of AF onset in ESS in an experimental setting using outbred rats.

Materials and methods. The experiment was performed on 146 outbred rats. Hypothyroidism was induced by thiamazole administration, followed by restoration of euthyroidism with levothyroxine sodium under thyroid hormone level monitoring. Based on the assessment of thyroid hormone levels, the following types of hypothalamic-pituitary-thyroid axis response were identified: euthyroidism, thyrotoxicosis, and ESS. In animals with euthyroidism and ESS, the percentage of atrial fibrosis was evaluated.

Results. Regression analysis revealed that in euthyroid animals, the percentage of fibrosis in the zone of the inferior pulmonary veins had the greatest influence on the frequency of AF paroxysms ($\beta = 0.734$, $p = 0.015$). Multiple regression results demonstrated that the maximum influence on AF paroxysm frequency in ESS-1 was exerted by the percentage of fibrosis in the inferior and superior pulmonary veins (ISPV) ($p = 0.002$); in ESS-2, by fibrosis in the ISPV ($p = 0.021$) and the right atrium ($p = 0.015$); and in ESS-3, by fibrosis in the ISPV ($p = 0.023$) and the right atrium ($p = 0.040$). Fibrosis was established as a morphological substrate of AF in ESS. It was found that the atrial fibrosis area in euthyroidism was 18.8%, whereas in ESS types 1, 2, and 3 it was 36.6%, 35.8%, and 38.3%, respectively.

Conclusion. This study demonstrated that varying atrial fibrosis areas in the setting of ESS constitute a morphological substrate for the formation of re-entrant excitation circuits in AF. The fibrosis area in ESS was found to be twice as large as that in euthyroidism.

Keywords: euthyroid sick syndrome, fibrosis, atrial fibrillation, atrial remodeling, thyroid gland, thyroid hormones.

Conflict of interest: none declared.

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Introduction

Atrial fibrillation (AF) is one of the most persistent and widespread cardiac rhythm disorders. Its onset and subsequent maintenance are pathogenetically linked to structural atrial remodeling. Longterm followup of patients with AF helps to determine to what extent changes in their clinical status correspond to the degree of progression of structural changes in the atria [1, 2]. However, a close relationship between characteristic atrial alterations and the clinical picture of the disease is not observed in every case. The results of numerous clinical and experimental studies, based on repeated atrial myocardial biopsies, indicate that an increase in the percentage of fibrosis is accompanied by a higher frequency and longer duration of arrhythmia [3, 4]. At the same time, the specific mechanisms by which atrial fibrosis contributes to the development of AF in euthyroid sick syndrome (ESS) remain insufficiently investigated [5]. Given the limited number of studies on the pathogenesis of AF in ESS, we considered it appropriate to explore this issue in an experimental setting using outbred rats [6, 7].

Aim—to study the morphological substrate of AF onset in ESS in an experimental study on outbred rats.

Materials and methods

The study was performed on 146 outbred rats (50 males and 96 females) weighing 180–200 g, kept on a standard diet. The experiment consisted of four stages.

Stage 1—an electrocardiogram (ECG) was recorded in standard lead II using a PolySpectrum device for 10 minutes. The duration of ECG intervals and complexes was then assessed. Cardiac rhythm disturbances were evaluated by the average number of extrasystoles and AF paroxysms on the ECG.

Blood samples were collected from the saphenous vein into tubes containing heparin (25 IU/mL) or 3.8% sodium citrate solution. Subsequently, the levels of thyroidstimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), and reverse triiodothyronine (rT3) were measured by enzymelinked immunosorbent assay. The fT3/rT3 ratio was calculated. Normally, the optimal fT3/rT3 ratio ranges from 10 to

15, and a decrease below 10 indicates the presence of ESS. Based on thyroid hormone levels, three types of ESS were distinguished: low fT3—ESS type 1; low fT3 and low fT4—ESS type 2; high fT4—ESS type 3.

Stage 2—to induce hypothyroidism, thiamazole was administered at a dose of 2.5 mg/100 g body weight for 3 weeks. Thyroid hormone levels were then reassessed. Baseline values were: TSH—1.8±0.08 mIU/L, fT3—4.5±0.09 pmol/L, fT4—17.7±0.36 pmol/L; after achieving hypothyroidism, the corresponding values were 9.4±0.2 ($p<0.001$), 0.05±0.001 ($p<0.001$), and 0.0271±0.0006 ($p<0.001$). The baseline number of AF paroxysms per 10 minutes was 3.5±0.285 episodes, with arrhythmia duration of 13.3±0.391 seconds; in ESS1—5.6±0.320 episodes and 17.2±0.592 seconds; in ESS2—6.7±0.252 episodes and 19.2±0.691 seconds; in ESS3—7.8±0.257 episodes and 26.3±0.230 seconds.

Stage 3—to restore euthyroidism, levothyroxine sodium (Euthyrox) was given at a dose of 1.5 μg/kg for 3 weeks, followed by reassessment of thyroid hormone levels. Based on the hormone levels measured, six types of hypothalamicpituitarythyroid axis response to Euthyrox at 1.5 μg/kg were identified (Table 1).

Table 1. **Types of hypothalamicpituitarythyroid axis response to Euthyrox**

Response type	n, (%)	TSH (mIU/L)	fT4 (pmol/L)	fT3 (pmol/L)	fT3/rT3
1st—ET	42 (28.8%)	1.88 [0.24; 3.39]	17.3 [10.9: 25.7]	4.47 [2.64; 6.36]	> 10
2nd—TT	15 (10.3%)	0.023 [0.003; 0.035]	56.7 [32.9; 75.8]	12.4 [7.38; 18.42]	> 10
3rd – ST	22 (15.1%)	0.022 [0.0024; 0.0416]	18.9 [10.7; 25.7]	4.4 [2.48; 6.24]	> 10
4th—ESS1	20 (13.7%)	2.16 [0.31; 4.1]	18.8 [10.82; 25.33]	2.3 [1.81; 2.88]	< 10
5th—ESS2	24 (16.4%)	1.76 [0.43; 3.2]	9.1 [8.5; 9.79]	2.44 [2.03; 2.87]	< 10
6th—ESS3	23 (15.8%)	1.78 [0.42; 3.45]	23.62 [22.91; 24.47]	4.7 [3.11; 6.56]	< 10

Note. n (%)—number and percentage of animals studied; 1st type (ET)—first euthyroid type of hypothalamicpituitarythyroid axis response to Euthyrox; 2nd type (TT)—second (thyrotoxic) type of response; 3rd type (ST)—third (subclinical thyrotoxic) type of response; 4th, 5th, and 6th types (ESS1, ESS2, ESS3)—euthyroid sick syndrome types 1, 2, and 3, respectively. Values are presented as median [interquartile range].

Stage 4 of the experimental study included rats with euthyroidism and ESS types 1, 2, and 3. The animals were anesthetized with a mixture of clisazine, zolazepam, and tiletamine, and then decapitated. The heart was excised, washed free of blood, and freed from connective tissue. The objects of study were thin myocardial strips excised from the orifices of the superior pulmonary veins (SPV), from the area between the orifices of the inferior and superior pulmonary veins (ISPV), from the area between the orifices of the inferior pulmonary veins (IPV), from the wall of the right atrium (RA), and from the Bachmann›s bundle (BB). The paraffin sections obtained were stained with hematoxylin and by Van Gieson›s method with counterstaining of nuclei with hematoxylin. Under a microscope, in 10 fields of view at ×200 magnification, the type and area of fibrosis were assessed as a percentage.

Table 2 shows the number and percentage of specimens examined in euthyroidism, ESS1, ESS2, and ESS3.

Table 2. **Number and percentage of specimens examined in euthyroidism and ESS**

Parameter	ET, n (%)	ESS1, n (%)	ESS2, n (%)	ESS3, n (%)	Total, n (%)
SPV, n (%)	15 (35.7)	9 (45.0)	12 (50.0)	12 (52.2)	48 (45.7)
ISPV, n (%)	12 (28.6)	11 (55.0)	11 (45.8)	11 (47.8)	45 (44.3)
IPV, n (%)	13 (31.0)	10 (50.0)	9 (37.5)	9 (39.1)	41 (39.4)
RA, n (%)	11 (26.2)	9 (45.0)	13 (54.2)	8 (34.8)	41 (40.0)
BB, n (%)	12(28.6)	10 (50.0)	8 (33.3)	12 (52.2)	42 (41.0)
Total, n (%)	105 (30.0)	69 (49.0)	77 (44.2)	75 (45.2)	326 (42.1)

Note. n (%) ET—number and percentage of specimens examined in euthyroidism (ET); n (%) ESS1,2,3—number and percentage of specimens examined in euthyroid sick syndrome types 1, 2, and 3; n (%)—number and percentage of specimens examined from the orifices of the SPV, from the ISPV area, from the IPV area, from the RA, and from the BB.

Microscopy analysis revealed that in outbred rats, the atria exhibited perivascular fibrosis, perimuscular fibrosis, smallfocal fibrosis, and meshlike (encircling) fibrosis.

Statistical analysis

Statistical processing of the obtained results was performed using Statistica 13.3 software. For each sample, the arithmetic mean (M) and standard deviation (m) were calculated. The distribution type was assessed using the Kolmogorov–Smirnov test. To calculate statistical significance in two related groups, Student's ttest was used, while in two unrelated groups, the Mann–Whitney U test was applied. Multivariate analysis was used to identify independent predictors of atrial fibrillation recurrence. To evaluate the influence of parameters, ROC analysis with the area under the curve was employed. Threshold values for quantitative predictors were established

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based on ROC analysis at the optimal sensitivity/specificity ratio. Differences were considered significant at $p < 0.05$.

Ethical review

The experimental study was conducted in accordance with the fundamental rules set forth in the basic documents governing experiments on laboratory animals and their housing conditions (Helsinki Declaration, 2000; GOST 330442014; Rules of Good Laboratory Practice of the Eurasian Economic Union in the Field of Drug Circulation). The experimental study was approved by the Local Ethics Committee at LLC CDKI (minutes of meeting No. 823 dated 11 September 2023).

Results

Depending on the type of ESS, the results of the assessment of the percentage of atrial fibrosis are presented in three parts.

1. Results of atrial fibrosis assessment in ESS type 1.

Table 3 presents a comparative evaluation of the percentage of fibrosis in the studied atrial zones in euthyroid (ET) and ESS1 rats.

Table 3. **Percentage of atrial fibrosis in euthyroidism (ET) and ESS1 (M±m)**

Parameter	ET, (n=42)	ESS1, (n=20)	p
Fibrosis in LA between superior PVs, %	4.4±0.147	5.1±0.252	=0.006
Fibrosis in LA between superior and inferior PVs, %	3.8±0.156	12.4±0.692	<0.001
Fibrosis in LA between inferior PVs, %	3.4±0.161	4.0±0.232	=0.193
Fibrosis in RA, %	3.9±0.159	11.4±0.622	<0.001
Fibrosis in BB, %	3.8±0.112	4.8±0.188	<0.001
Total atrial fibrosis, %	18.8±0.503	36.6±1.429	<0.001
Number of extrasystoles per 10 min	10.5±0.489	15.7±1.281	<0.001
Number of AF paroxysms per 10 min	3.2±0.212	5.8±0.416	<0.001
AF duration, s	5.6±0.463	7.7±0.771	=0.016

Note. Data are presented as arithmetic mean ± standard error of the mean (M±m). ESS1—euthyroid sick syndrome with low fT3 levels.

Analysis revealed that in ET animals, the percentage of fibrosis in the ISPV zone was 14.6% lower than in the SPV zone (3.8±0.156 and 4.4±0.147, respectively, p=0.004). In the IPV zone, it was 18.2% lower than in the ISPV zone (3.4±0.161 and 3.8±0.156, respectively, p<0.001). In the RA, it was 10.7% higher than in the IPV zone (3.9±0.159 and 3.4±0.161, respectively, p=0.033). No significant differences were found between the RA and BB (p>0.05).

Analysis of the percentage of atrial fibrosis in ESS1 rats showed a significant influence of the thyroid component. It was found that fibrosis in the ISPV zone was 58.7% greater than in the SPV zone (5.1±0.252 and 12.4±0.692, respectively, p<0.001). In the IPV area, it was 67.5% lower than in the ISPV zone (12.4±0.692 and 4.0±0.232, respectively, p<0.001). In the RA, it exceeded that in the IPV zone by 64.7% (4.0±0.232 and 11.4±0.622, respectively, p<0.001). In the BB, it was 58.2% less than in the RA (11.4±0.622 and 4.8±0.188, respectively, p<0.001).

When comparing the percentage of fibrosis in the studied zones between ET and ESS1 rats, significant differences were also found. It was revealed that in ESS1, the percentage of fibrosis in the SPV zone was greater by 14.3% (p=0.006), in the ISPV zone by 69.7% (p<0.001), in the IPV zone by 10.9% (p=0.193), in the RA by 65.6% (p<0.001), and in the BB by 17.1% (p<0.001). As can be seen from the data obtained, the most diagnostically significant finding was an almost threefold increase in the percentage of fibrosis in the ISPV zone and the RA.

To evaluate the multiple regression of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ET rats, an analysis was performed, as presented in Table 4.

Table 4. **Results of multiple regression of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ET rats**

Parameter	Number of AF paroxysms		
Multiple correlation coefficient (R)	0.910		
Coefficient of determination (R^2)	0.804		
Fisher's Ftest value	32.9		p<0.001
Fibrosis localization / Statistical indices	β	t	p
SPV, %	-0.124	-0.502	0.619
ISPV, %	-0.128	-0.356	0.724
IPV, %	0.734	2.6	0.015
RA, %	0.659	1.9	0.066
BB, %	-0.231	-0.659	0.514

Note. β—regression coefficient estimate for the variable; t—Student's ttest.

The multiple correlation coefficient (R) of 0.910 indicates a strong relationship between the num-

ber of AF paroxysms and the percentage of fibrosis in the studied atrial zones in ET rats. The leading statistical indicator is the coefficient of determination (R^2), equal to 0.804 ≈ 80.4%, which shows the proportion of variation in AF paroxysm frequency caused by the independent predictors—the atrial fibrosis zones. Fisher's Ftest (F) and the significance level are used to evaluate the regression. An Fvalue of 32.9 and a significance level (p) of less than 0.001 indicate the adequacy of the regression model.

For comparative assessment of the impact of each component of the fibrosis percentage in the studied atrial zones, standardized β coefficients (regression coefficients) were used, by the magnitude of which the influence of each fibrosis zone on the increase in AF paroxysm frequency was evaluated. According to the multiple regression results, the greatest influence on the frequency of AF paroxysms in euthyroidism is exerted by the percentage of fibrosis in the IPV zone (β = 0.734, p = 0.015).

As noted above, in ET rats, the fibrosis zone in the ISPV accounts for 3.8%, in the IPV—3.4%, and in the RA and BB—3.9% and 3.8%, respectively. These data suggest that the reduction in the percentage of fibrosis in the IPV zone compared with the ISPV, RA, and BB creates an anatomical substrate for dispersion of refractory periods and reentrant excitation. The regression coefficient assessment showed that the percentage of fibrosis in the IPV zone has the greatest influence on AF paroxysm frequency (β = 0.734, p = 0.015). Similar results have been obtained in electrophysiological studies [8]. It was noted that the effective refractory period of the atria in the IPV zone is significantly shorter (p<0.05) than in the ISPV zone, RA, and BB.

To determine the threshold values of atrial fibrosis in the SPV, ISPV, IPV, RA, and BB, ROC analysis was performed. Figure 1 presents the results of ROC analysis of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ET rats.

In euthyroidism, the threshold percentage of fibrosis area in the studied atrial zones can predict the onset or increased frequency of AF paroxysms. The studies established that the cutoff value of atrial fibrosis in the SPV zone was 4.42%, with a sensitivity of 87.5% and specificity of 75.0% (AUC = 0.935, 95% confidence interval (CI) 0.865–1.0, p < 0.05). The threshold value of atrial fibrosis in the ISPV zone was >4.07% with a sensitivity of 75.0% and specificity of 91.7% (AUC = 0.940, 95% CI 0.874–1.0, p < 0.05). The cutoff value of atrial fibrosis in the IPV zone was > 4.05% with a sensitivity of 62.5% and specificity of 95.7% (AUC = 0.938, 95% CI 0.868–1.0, p < 0.05). The threshold value of atrial fibrosis in the RA was >4.08% with a sensitivity of 81.3% and specificity of 87.5% (AUC = 0.945, 95% CI 0.882–1.0, p < 0.05). The cutoff value of fibrosis in the BB was >3.6% with a sensitivity of 93.8% and specificity of 75.0% (AUC = 0.940, 95% CI 0.874–1.0, p < 0.05).

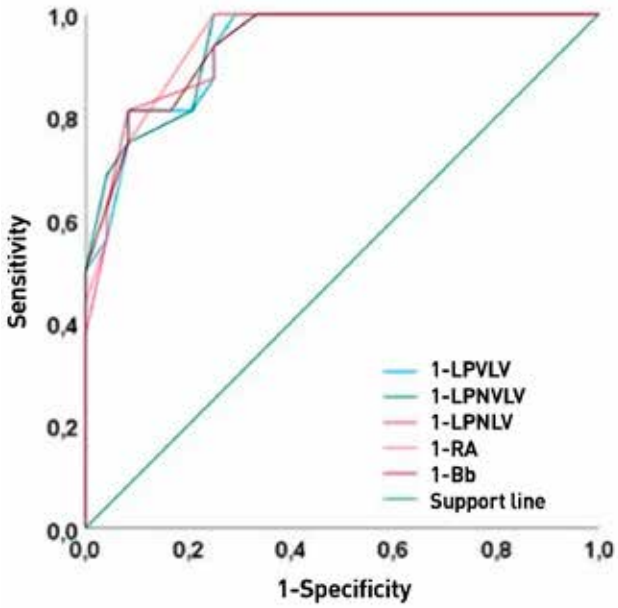

Fig. 1. ROC curves reflecting the threshold nature of the fibrosis percentage in the studied atrial zones in ET rats

Table 5. **Results of multiple regression of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ESS1 rats**

Parameter	Number of AF paroxysms		
Multiple correlation coefficient (R)	0,989		
Coefficient of determination (R2)	0,971		
Fisher's Ftest value (F)	115,4		p <0,001
Fibrosis localization / Statistical indices	β	t	p
SPV, %	0,170	0,917	0,377
ISPV, %	1,205	4,1	0,002
IPV, %	-0,181	-1,480	0,165
RA, %	-0,435	-1,483	0,164
BB, %	0,212	1,175	0,263

Note. β—regression coefficient estimate for the variable; t—Student›s ttest.

Analysis of the obtained data showed that the correlation coefficient R = 0.989 indicates a relationship

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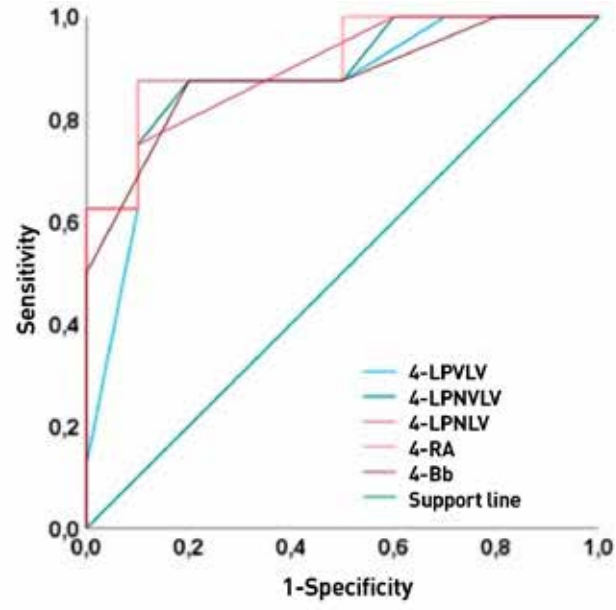

Fig. 2. ROC curves reflecting the threshold nature of the fibrosis percentage in the studied atrial zones in ESS1 rats

between AF frequency and the percentage of fibrosis in the assessed atrial regions. The coefficient of determination (R^2) = 0.971 ≈ 97.1% determines the proportion of variation in AF frequency caused by atrial fibrosis zones. The F test value of 115.4 and a significance level of $p < 0.001$ demonstrate the adequacy of the regression model. The multiple regression results revealed that the maximum influence on AF paroxysm frequency in ESS1 is exerted by the percentage of fibrosis in the ISPV ($\beta = 1.205$, $p = 0.002$).

Figure 2 presents the results of ROC analysis of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ESS1 rats.

The results of the conducted studies suggest that in ESS1, the threshold value of atrial fibrosis can predict AF paroxysms. It was found that the cutoff value of atrial fibrosis in the SPV zone was 5.1%, with a sensitivity of 87.5% and specificity of 90.0% (AUC = 0.875, 95% CI 0.699–1.0, $p < 0.05$). In the ISPV zone, it was 12.5%, with a sensitivity of 75.0% and specificity of 90.0% (AUC = 0.900, 95% CI 0.750–1.0, $p < 0.05$). In the IPV area, it was 4.2%, with a sensitivity of 77.0% and specificity of 90.5% (AUC = 0.902, 95% CI 0.755–1.0, $p < 0.05$). In the RA, it was 11.5%, with a sensitivity of 87.5% and specificity of 90.2% (AUC = 0.913, 95% CI 0.773–1.0, $p < 0.05$). In the BB, it was 4.75%, with a sensitivity of 87.2% and specificity of 80.0% (AUC = 0.881, 95% CI 0.711–1.0, $p < 0.05$).

2. Results of atrial fibrosis assessment in ESS type 2. A comparative evaluation of the percentage of fibrosis in the studied atrial zones in ET and ESS2 rats is presented in Table 6.

Table 6. **Percentage of atrial fibrosis in euthyroidism (ET) and ESS2 (M±m)**

Parameter	ET, (n=42)	ESS2 (n=24)	p
Fibrosis in LA between superior PVs, %	4.4±0.147	3.6±0.335	=0.179
Fibrosis in LA between superior and inferior PVs, %	3.8±0.156	11.7±0.649	<0.001
Fibrosis in LA between inferior PVs, %	3.4±0.161	3.5±0.152	0.506
Fibrosis in RA, %	3.9±0.159	12.4±0.599	<0.001
Fibrosis in BB, %	3.8±0.112	4.5±0.302	0.0001
Total atrial fibrosis, %	18.8±0.503	35.8±1.526	<0.001
Number of extrasystoles per 10 min	10.5±0.489	21.3±1.170	<0.001
Number of AF paroxysms per 10 min	3.2±0.212	7.6±0.520	<0.001
AF duration, s	5.6±0.463	10.6±0.477	<0.001

Note. Data are presented as arithmetic mean ± standard error of the mean (M±m). ESS2—euthyroid sick syndrome with low fT3 and low fT4 levels.

Similar data were obtained when analyzing the studied atrial zones in ESS2 rats. In the ISPV zone, the percentage of fibrosis was 68.8% higher than in the SPV zone (11.7±0.649 and 3.6±0.335, respectively, $p<0.001$). In the IPV zone, it was 69.9% lower than in the ISPV zone (3.5±0.152 and 11.7±0.649, respectively, $p<0.001$). In the RA, it exceeded that in the IPV zone by 71.7% (3.5±0.152 and 12.4±0.599, respectively, $p<0.001$). In the BB, it was 64.2% less than in the RA (12.4±0.599 and 4.5±0.302, respectively, $p<0.001$).

The results of multiple regression of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ESS2 rats are presented in table 7.

Table 7. **Results of multiple regression of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ESS2 rats**

Parameter	Number of AF paroxysms		
Multiple correlation coefficient (R)	0,982		
Coefficient of determination (R2)	0,963		
Fisher's Ftest value	82,9		p<0,001
Fibrosis localization / Statistical indices	ß	t	p
SPV, %	0,329	1,786	0,093
ISPV, %	0,451	2,6	0,021
IPV, %	-0,041	-0,353	0,729
RA, %	0,532	2,7	0,015
BB, %	-0,278	-1,440	0,169

Note. β—regression coefficient estimate for the variable; t—Student›s ttest.

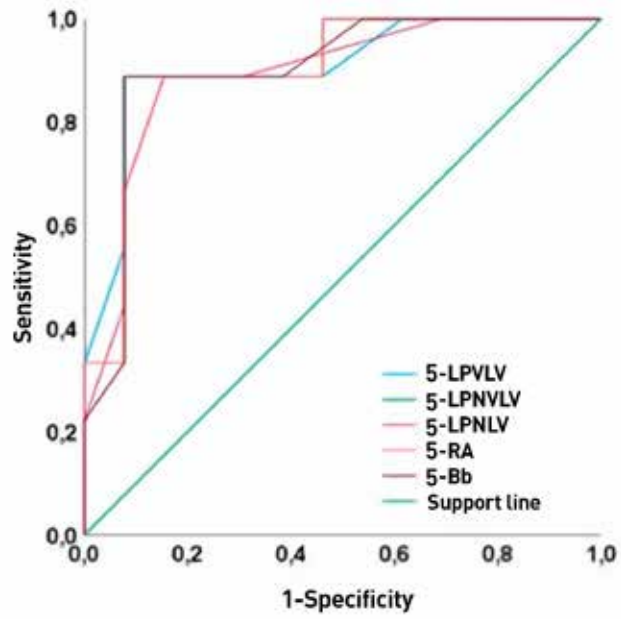

Fig. 3. ROC curves reflecting the threshold nature of the fibrosis percentage in the studied atrial zones in ESS2 rats

A correlation coefficient R of 0.982 indicates a strong relationship between AF paroxysms and the percentage of atrial fibrosis. The coefficient of determination R^2 = 0.963 ≈ 96.3% determines the proportion of variation in AF paroxysms caused by atrial fibrosis zones. Fisher's F test value of 82.9 and a significance level of p < 0.001 demonstrate the adequacy of the regression model. The multiple regression data established that the predominant influence on AF frequency in ESS2 is exerted by the percentage of fibrosis in the ISPV (ß = 0.451, p = 0.021) and in the RA (β = 0.532, p = 0.015).

The results of ROC analysis of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ESS2 rats are presented in Figure. 3.
As can be seen from the data presented, in ESS2, the threshold value of atrial fibrosis in the SPV, ISPV, IPV, RA, and BB zones allows predicting the frequency of AF. In the SPV zone, it is >3.62%, with a sensitivity of 88.9% and specificity of 92.3% (AUC = 0.906, 95% CI 0.770–1.0, p < 0.05). In the ISPV zone, it is >12.1%, with a sensitivity of 88.6% and specificity of 92.0% (AUC = 0.904, 95% CI 0.772–1.0, p < 0.05). In the ISPV zone, it is >12.1%, with a sensitivity of 88.6% and specificity of 92.0% (AUC = 0.904, 95% CI 0.772–1.0, p < 0.05). In the IPV zone, it is >3.8%, with a sensitivity of 66.7% and specificity of 90.4% (AUC = 0.893, 95% CI 0.751–1.0, p < 0.05). In the RA, it is >12.8%, with a sensitivity of 69.5% and specificity of 91.7% (AUC = 0.897, 95% CI 0.761–1.0, p < 0.05). In the BB, it is >4.6%, with a sensitivity of 77.8% and specificity of 93.2% (AUC = 0.897, 95% CI 0.764–1.0, p < 0.05).

3. Results of atrial fibrosis assessment in ESS type 3. A comparative evaluation of the percentage of fibrosis in the studied atrial zones in ET and ESS3 rats is presented in table 8.

Table 8. **Percentage of atrial fibrosis in euthyroidism (ET) and ESS3, (M±m)**

Parameter	ET. (n=42)	ESS3. (n=23)	p
Fibrosis in LA between superior PVs. %	4.4±0.147	4.2±0.216	=0.410
Fibrosis in LA between superior and inferior PVs. %	3.8±0.156	5.6±0.300	<0.001
Fibrosis in LA between inferior PVs. %	3.4±0.161	11.6±0.642	<0.001
Fibrosis in RA. %	3.9±0.159	5.9±0.425	<0.001
Fibrosis in BB. %	3.8±0.112	10.6±0.726	<0.001
Total atrial fibrosis. %	18.8±0.503	38.3±1.59	<0.001
Number of extrasystoles per 10 min	10.5±0.489	17.0±1.114	<0.001
Number of AF paroxysms per 10 min	3.2±0.212	4.2±0.286	=0.006
AF duration. s	5.6±0.463	5.7±0.377	=0.896

Note. Data are presented as arithmetic mean ± standard error of the mean (M±m). ESS3—euthyroid sick syndrome with high fT4 levels.

In the ISPV zone, the percentage of fibrosis was 23.6% higher than in the SPV zone (5.6±0.300 and 4.2±0.216, respectively, p<0.001). In the IPV zone, it was 52.2% higher than in the ISPV zone (11.6±0.642 and 5.6±0.300, respectively, p<0.001). In the RA, it was 7.7% lower than in the IPV zone (5.9±0.425 and 11.6±0.642, respectively, p<0.001). In the BB, it was 59.9% higher than in the RA (10.6±0.726 and 5.9±0.425, respectively, p<0.001).

Differences between the groups of rats with ET and ESS3 were statistically significant (p<0.05). In the ISPV zone, the percentage of fibrosis was 32.4% higher (p<0.001), in the IPV zone—69.1% higher (p<0.001), in the RA—33.9% higher (p<0.001), and in the BB—62.8% higher (p<0.001).

The results of multiple regression of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ESS3 rats are presented in table 9.

The results of regression analysis indicate that the correlation coefficient R = 0.982 points to a relationship between AF frequency and the zones and percentage of atrial fibrosis. The coefficient of determination R^2 = 0.976 ≈ 97.6% determines

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Table 9. **Results of multiple regression of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ESS3 rats**

Parameter	Number of AF paroxysms		
Multiple correlation coefficient (R)	0.988		
Coefficient of determination (R2)	0.976		
Fisher's F test value (F)	126.3		p<0.001
Fibrosis localization / Statistical indices	β	t	p
SPV. %	-0.350	-1.262	0.226
ISPV. %	0.607	2.5	0.023
IPV. %	0.155	0.481	0.637
RA. %	0.670	2.2	0.040
BB. %	-0.092	-0.326	0.749

Note. β—regression coefficient estimate for the variable; t—Student›s ttest.

the proportion of variation in AF frequency attributable to the percentage of atrial fibrosis. The adequacy of the regression model is indicated by Fisher›s Ftest value of 126.3 and a significance level of $p < 0.001$. According to the multiple regression data, it was revealed that the predominant influence on AF frequency in ESS3 is exerted by the percentage of fibrosis in the ISPV ($\beta = 2.5$, $p = 0.023$) and in the RA ($\beta = 2.2$, $p = 0.040$).

The results of ROC analysis of the number of AF paroxysms with the percentage of fibrosis in the studied atrial zones in ESS3 rats are shown in Figure 4.

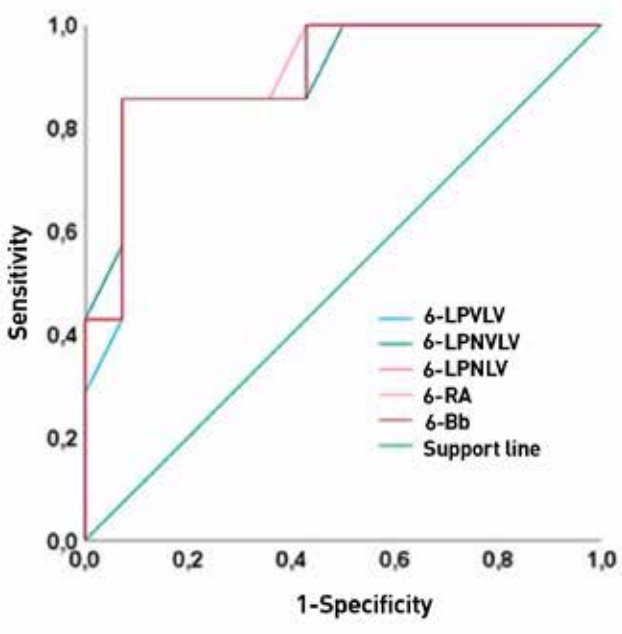

Fig. 4. ROC curves reflecting the threshold nature of the fibrosis percentage in the studied atrial zones in ESS3 rats

In the SPV zone, the threshold level of fibrosis is >4.2%, with a sensitivity of 85.7% and specificity of 78.6% (AUC = 0.903, 95% CI 0.763–1.0, $p < 0.05$). In the ISPV zone, it is >6.1%, with a sensitivity of 71.4% and specificity of 92.9% (AUC = 0.908, 95% CI 0.768–1.0, $p < 0.05$). In the IPV zone, it is >11.9%, with a sensitivity of 85.7% and specificity of 92.6% (AUC = 0.908, 95% CI 0.772–1.0, $p < 0.05$). In the RA, it is >6.4%, with a sensitivity of 85.7% and specificity of 92.1% (AUC = 0.913, 95% CI 0.783–1.0, $p < 0.05$). In the BB, it is >11.1%, with a sensitivity of 85.7% and specificity of 86.0% (AUC = 0.908, 95% CI 0.770–1.0, $p < 0.05$).

Discussion

AF is the most common cardiac arrhythmia, associated with increased cardiovascular morbidity and mortality. Its pathophysiology is based on electrical and structural remodeling occurring in the atrial myocardium [9, 10].

The thyroid gland and the heart share a common embryonic origin, with the heart being an important target organ for thyroid hormones. Various animal models and cellular studies have shown that thyroid hormones are involved in the formation of fibrosis in AF. In this article, we focused on the results of an experimental study in rats linking atrial fibrosis to AF in ESS [11].

It was noted that in both ET and ESS animals, the percentage of fibrosis in the ISPV zone was lower than in the SPV zone ($p<0.05$). In the IPV zone, the percentage of fibrosis was lower than in the ISPV zone ($p<0.05$). In the RA, the percentage of fibrosis was higher than in the IPV zone ($p<0.05$). These data suggest that the reduction in the percentage of fibrosis in the IPV zone, compared with the ISPV and RA, creates an anatomical substrate for dispersion of refractory periods and reentrant excitation in AF [12].

Regression analysis revealed that in euthyroid animals, the percentage of fibrosis in the IPV zone had the greatest influence on the frequency of AF paroxysms ($\beta = 0.734$, $p = 0.015$). Similar results have been obtained in electrophysiological studies [13]. It was noted that the effective refractory period of the atria in the IPV zone is significantly shorter ($p<0.05$) than in the ISPV zone and the RA.

Multiple regression results showed that the maximum influence on AF paroxysm frequency in ESS1 was exerted by the percentage of fibrosis in the ISPV

(p = 0.002); in ESS2, by fibrosis in the ISPV (p = 0.021) and the RA (p = 0.015); and in ESS3, by fibrosis in the ISPV (p = 0.023) and the RA (p = 0.040).

Thus, the obtained data indicate that the development of atrial fibrosis is largely responsible for the occurrence of AF in ESS. Experimental studies in rats have shown that different areas of atrial fibrosis constitute the morphological substrate for the formation of reentrant excitation circuits in AF against the background of ESS. The data also showed that the fibrosis area in ESS is twice as large as in euthyroidism.

Conclusion

Based on the experimental study, it has been shown that in ESS, fibrosis is a morphological substrate for the development of AF. The analyses performed revealed a difference in the percentage of atrial fibrosis between euthyroidism and ESS. In euthyroidism, the total percentage of atrial fibrosis was 18.8 %, whereas in ESS type 1 it was 36.6 %, in type 2—35.8 %, and in type 3—38.3 %.

Further development of both experimental models and clinical studies is required to explore the possibilities of minimally invasive diagnosis of atrial myocardial fibrosis for the early detection of the substrate for AF development and reduction of the risk of cardiovascular complications.

Conflict of interest: none declared.

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Author Guidelines

Manuscript publication rules

in the International heart and vascular disease journal

Edit from December, 2021

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Book:

Shlyakhto EV, Konradi AO, Tsyrlin VA. The autonomic nervous system and hypertension. SPb.: Meditsinskoe izdatel'stvo; 2008. Russian. Шляхто Е. В., Конради А. О., Цырлин В. А. Вегетативная нервная система и артериальная гипертензия. СПб.: Медицинское издательство; 2008. ISBN 0000 — 0000.

Chapter:

Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/ Melbourne/Auckland: Lea and Febiger; 1990. p.398 — 420. ISBN 0000 — 0000.

Russian chapter:

Diagnostics and treatment of chronic heart failure. In. National clinical guidelines 4th ed. Moscow: Silicea-Polygraf; 2011. pp.203 — 93. Russian Диагностика и лечение хронической сердечной недостаточности. В кн: Национальные клинические рекомендации. 4-е издание. М.: Силицея-Полиграф; 2011.сс.203 — 96. ISBN 0000 — 0000.

Webpage:

Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/vol14no2/1402062003014n.htm (28 May 2004)

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XIV. Journal subscription

The name of the journal in English is International heart and vascular disease journal.

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On the reception of the articles, making decisions about publication, reviews — mmamedov@mail.ru

On organizational issues (working with the site, subscription) — editor.ihvdj@gmail.com

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