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Risk factors, clinical and psychosomatic status in patients with chronic noncommunicable diseases during lockdown and self-isolation

A comparative study on clinical outcomes of pharmacoinvasive strategy versus primary percutaneous coronary intervention in acute myocardial infarction patients

Pharmacologic management of premature ventricular contractions in the absence of structural heart disease: estimation of positive effect duration

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Contents

Editor's Welcome

Dear colleagues!

In the 30th issue of the International Heart and Vascular Disease Journal, there are the leading article and the original articles.

The leading article section presents the original work on the assessment of behavioral risk factors, clinical and psychosomatic state in patients with chronic noncommunicable diseases during lockdown and self-isolation. This multicenter simultaneous study included 351 patients from 10 cities and 5 countries. During quarantine and self-isolation patients with noncommunicable diseases had some worsening of their clinical status requiring higher doses of medications. Most people exercised less and had worse diet during self-isolation. One in two patients with noncommunicable diseases had moderate levels of chronic stress and mild depression and anxiety.

The original article section included the study on the features of working conditions and modifiable risk factors (RF) for cardiovascular diseases among employees of locomotive crews of the metro and railways in the city of Saint Petersburg. The survey included 599 employees of locomotive crews, all of them were male, machinists and their assistants. Authors claim that the results of the study may be useful for the development of preventive programs for the Russian Railways employees.

A group of foreign authors from various countries performed a comparative study on clinical outcomes of pharmacoinvasive strategy versus primary percutaneous coronary intervention (PCI) in acute myocardial infarction patients (AMI). The study included 3073 consecutive AMI cases. Pharmacoinvasive strategy has almost equal efficacy compared with primary PCI and it represents a reasonable, non-inferior alternative when primary PCI is not readily available especially in patients presenting early after symptom onset. Other clinical study from Russia investigated features and the level of growth differentiation factor 15 (GDF-15) in patients with acute ST-segment elevation myocardial infarction at the inpatient stage of treatment. The persistence of high GDF-15 values during the in-patient treatment determined the prognosis of acute ST-segment elevation myocardial infarction.

Two original works were dedicated to the studying of various aspects of heart rhythm and conduction disturbances. One study evaluated the positive effect of the duration of pharmacologic management of premature ventricular contractions (PVC) according to ventricular ectopy analysis in the absence of structural heart disease. The study included 214 patients aged 19–45 years without structural heart disease and with class IV–V PVC. In patients without structural heart disease with a linear regression slope of ≥12 units/IEcorr the positive effect of antiarrhythmic therapy persists for 1 year or more. The second study assessed the features of atrial fibrillation (AF) in patients with arterial hypertension (AH) and extracardiac comorbidities (n=536) depending on prescribed therapy and their treatment adherence. Early verification of the AF progression risk factors and the developed personalized algorithm as a risk meter can be used to assess the prognosis of AF and the development of its complications in patients with AH in combination with extracardiac diseases.

We invite everybody to collaborate with the journal. We are waiting for your original papers, review articles, discussions, and opinions about problems, treatment and prophylaxis recommendations.

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

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LEADING ARTICLE

Risk factors, clinical and psychosomatic status in patients with chronic noncommunicable diseases during lockdown and self-isolation

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Abstract

Objective *of the current study was to investigate behavioral risk factors, clinical and psychosomatic state in patients with chronic noncommunicable diseases (NCDs).*

Materials and Methods. *This multicenter simultaneous study included 351 patients from 10 cities and 5 countries (Russia, Azerbaijan, Kazakhstan, Lithuania, Kyrgyzstan. Men and women aged 30–69 years with at least one NCD who were self-quarantining during COVID-19 were included. NCDs included arterial hypertension (HTN), coronary artery disease (CAD) with or without history of acute myocardial infarction, cancer treated with radiation and/or chemotherapy, type 2 diabetes (T2D), chronic obstructive pulmonary disease (COPD) or asthma. All patients were asked to fill special questionaries. We also performed routine physical exams that included blood pressure and heart rate measurement and body mass index calculation (BMI).*

Results. *Most patients (n=236, 68 %) had HTN, 30 % had CAD (n=103), 25 % had T2D (n=88), 12 % had COPD (n=40) and only 7 % had cancer. In general, one in four patients with at least one NCD self-isolation was associated with decreased quality of life and health. Hypertonic emergency happened in 78 patients, and 21 % required higher doses of antihypertensive medications. Angina symptoms worsened in 6 %. Among patients with T2D, 34 % required higher doses of diabetes medications. Only 5 % of patients with COPD and cancer noted any worsening of their symptoms. 138 people (40 %) stated that they had less physical activity and 34 (10 %) — that they were more active during the quarantine. 35 % (n=122) stated that they ate more often during self-quarantine and 4 % (n=14) stated that they were more successful in sticking to a diet. 55 % (n=192) stated that they had mild stress during quarantine and self-isolation; moderate level of stress was identified in 39 % (n-137) and severe stress — in 7 % (n=22) of all the respondents. 43 % (n=151) suffered from mild depression and anxiety and severe depression and anxiety were identified in 5 % (n=15) of all patients.*

Conclusion. *During quarantine and self-isolation patients with CNDs had some worsening of their clinical status requiring higher doses of medications. Most people exercised less and had worse diet during self-isolation. One in two patients with CNDs had moderate levels of chronic stress and mild depression and anxiety.*

Keywords. *Risk factors, psychosomatic status, CNDs, COVID-19 pandemic.*

Поступила: 14.01.2021 Принята: 29.03.2021

Conflict of interest: none declared.

Introduction

At the end of 2019 an outbreak of the new coronavirus disease caused by SARS-CoV-2 happened in Hubei province in China [1]. In 2020, high levels of incidence and mortality are still registered in countries where infection control measures were implemented later or only partially (Italy, Spain, USA, the UK). The status of COVID-19 pandemic varies with the largest number of cases registered in the USA, Brazil, and the UK [2, 3].

In May 2020 COVID-19 worldwide mortality rate was 7 %, in February 2021 the situation improved and the number of deaths to number of cases ratio was 2.21 %. Russia was among top 10 countries with the highest COVID-19 incidence: however, the mortality rate in early 2021 was 1.99 % [4].

During COVID-19 pandemic all countries imposed shutdowns and self-isolation according to the WHO recommendations. Elderly people and those with chronic noncommunicable diseases were at the highest risk of COVID-19 associated complications and death [5]. At that time most hospitals only admitted patients with COVID-19, thus those without COVID-19 but with CNDs had limited access to medical care. At the same time, prolonged self-isolation and total lockdown affected the quality of life and psychological state of these individuals [6].

To prevent the negative effects of the lock-down and self-isolation it is important to develop special measures that can be investigated in clinical studies of the risk factors and clinical and psychological status of patients with CNDs.

Materials and methods

This multicenter simultaneous study included 351 patients from 10 cities and 5 countries (Russia, Azerbaijan, Kazakhstan, Lithuania, Kyrgyzstan.

Men and women aged 30–69 years with at least one NCD who were self-quarantining during COVID-19 were included. NCDs included arterial hypertension (HTN), coronary artery disease (CAD) with or without history of acute myocardial infarction, cancer treated with radiation and/or chemotherapy, type 2 diabetes (T2D), chronic obstructive pulmonary disease (COPD) or asthma. Mean age was 60.6±2.4 years.

Exclusion criteria: history of psychiatric disease, severe somatic diseases including the decompensations of previously stable conditions.

Questionaries

All patients were asked to fill special questionnaire that was developed in our hospital. It included: identification information, social and demographic parameters, behavioral risk factors, including alcohol use, diet and physical activity, main disease, medications, and psychological status (levels of anxiety, depression and chronic stress) and also information on COVID-19.

The questionnaire was the main document on which this study was based.

Current smokers were identified as individuals who smoked at least one cigarette per day. Smoking status options were never smoked, used to some and current smoker.

Alcohol use was assessed using the following criteria:

— no alcohol use in the previous year

— for males: low and moderate alcohol use — <168 g of ethanol per week; sever — >168 g of ethanol per week.

Assessment of chronic stress. We used Reeder questionnaire to assess the level of chronic stress. The questionnaire included 10 questions with 5 possible answers each. It assessed 3 levels of stress: low (3.01–4 points), moderate (2.01–3 points) and severe (1–2 points) [7].

Assessment of anxiety and depression. We used European Quality of Life Questionnaire (EQ-5D) to assess the levels of anxiety and depression. The questionnaire included 5 dimensions:

1. Movement
2. Self-care
3. Everyday activity
4. Pain, discomfort
5. Anxiety, depression

Each dimension has 3 levels: no problems, some problems, and extreme problems. The questionnaire also allows the patient to self-rate the changes of his/her health over the past year [8].

Instrumental examination

We measured blood pressure and heart rate (HR) in each patient. Blood pressure reading were performed on the right hand with the standard sphygmomanometer with a patient in a comfortable seated position after at least 5 minutes of rest. Systolic blood pressure (SBP) was assessed according to the first Korotkoff sound and the diastolic blood pressure (DBP) was marked by the disappearance of the sound. Blood pressure readings were performed twice with 2–3-minute interval and the mean value was noted in the chart.

Anthropometric values included height and weight. Body mass index (BMI) was calculated as a person's weight in kilograms divided by the square of height in meters.

Data collection and investigators' training

Data were collected during the planned hospital admissions with the participation of primary care practitioners. The study took place from June to October 2021. We carried out an online training session on the study protocol and questionnaire. Some random questionaries were double checked by independent specialists. Data analysis was performed in National Research Center for Preventive Medicine in Moscow, Russia.

Statistical analysis

Data input was performed in the ACCESS MS OFFICE. Statistical analysis was performed on a personal computer (PC) using the Statistica 6 and R 3.6.1 software. Qualitative values are presented as frequencies and percentages. 95% confidence intervals (CI) are calculated using the Clopper–Pearson method and provided for the percentages. Chi-square (x2) criterion was used to compare qualitative values. Groups "before" and "after" were compared with the sign test. P-value less then 0.05 was considered statistically significant.

Results and discussion

In this multicenter simultaneous study, we investigated the changed of various behavioral risk factors, clinical and psychological status of people with at least one CND (HTN, stable angina, DM, COPD, malignancy).

It is thought that healthcare system overload together with self-isolation and lockdown played an additional role in the increased incidence of some CNDs during COVID-19 pandemic. These factors can lead to

worse risk factor control, insufficient diagnosis and treatment, untimely medical help for worsening patients [9].

In the current study there were 58% (n=205) patients from Russia and 42% (n=146) patients from other countries. Most patients had HTN 67.2% (62.1–72.1) (n=236), 29.3% (2.6–34.4%) (n=103) had stable angina (p<0.0001). 25.1% (20.6–29.9) (n=88) patients had DM; 11.4% (8.3–15.2) (n=40) had COPD and just 7.1% (4.7–10.3) (n=40) had malignancy.

At the time of the study 21.9% (17.7–26.6) (n=77) of patients had COVID-19 and recovered; 12.8% (9.5–16.8) (n=45) had complications. According to the WHO, people with one and more NCD (CVD, DM, COPD) are at a higher risk of complications and death. Adequate self-isolation and regular health monitoring reduces the risk of acquiring COVID-19 and complications in individuals with CNDs [10–15].

Analysis of social and demographic values showed that 40.7% (35.6–46.1) (n=143) had higher education, 67.2% (62.1–72.1) (n=236) were married, 15% (n=53) were widowers/widows, 6% (n=21) — divorced. Before lock-down and self-isolation 53% (47.6–58.3) (n=186) of patients had a job. During the pandemic 24.8% (20.4–29.6) (n=87) kept working the same way they used to, and 11.1% (8–14.9%) (n=39) switched to working from home and 17.1% (13.3–21.4) (n=60) temporarily stopped working and 1.7% (0.6–3.7) (n=6) lost their jobs. As such, the changes in job status were statistically significant (186 vs 120, p<0.0001).

During the lock-down we noted some worsening of CNDs in our group of patients. Hypertonic emergency happened in 78 patients, and 21% required higher doses of antihypertensive medications. Angina symptoms worsened in 6%. Among patients with T2D, 34% required higher doses of diabetes medications. Only 5% of patients with COPD and cancer noted any worsening of their symptoms. To control the spread of SARS-CoV-2 most hospitals all over the world were marked as the "red zone". Access to outpatient care become limited as well. One study analyzed hospitalization frequency in California during the rise of COVID-19 cases and determined that less people were admitted for acute myocardial infarction (MI) at that period [6]. Another study showed that when new COVID-19 cases peaked in Italy the number of MI admissions were lower and the rate of MI-associated complications and deaths was higher, although the number of coronary angiographies stayed unchanged [11]. This can mean that only the most severe patients were admitted. According to the data received from 909 hospitals in 108 countries, less invasive and non-invasive cardiac examinations were performed during COVID-19 [16, 17].

One of the aims of this study was to investigate the changes in behavioral risk factors such as smoking, alcohol use, changes in physical activity and diet. Before the pandemic 31% (n=108) patients, mostly men, used alcohol. During the quarantine there were some minor changes in the alcohol use pattern: 4% of patients stated that they used less alcohol and 2% — more alcohol. Before the pandemic 11.1% (8–14.9) of patients smoked; during the quarantine one in two smokers started to use more tobacco (p=0.0015) and 10% began to snoke less (fig. 1).

Changes in the amount of physical activity were among of the most important indicators of the influence of self-isolation. According to our results, 39.3% (34.2–44.6) (n=138) people exercised less during the

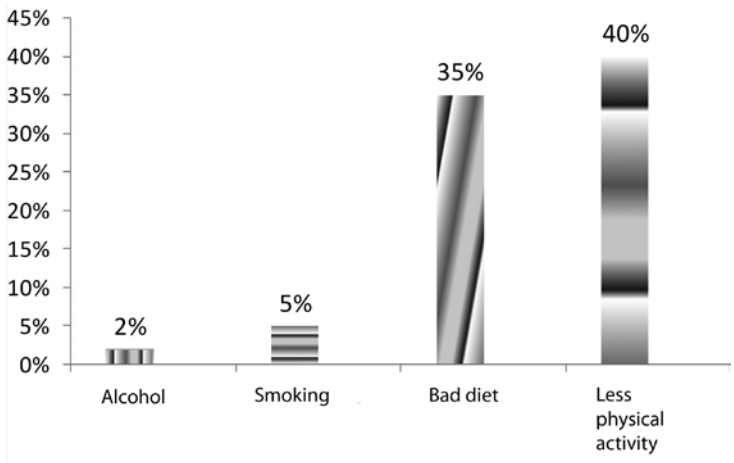

Figure 1. The rise of behavioral risk factors in patients with CNDs during quarantine and self-isolation.

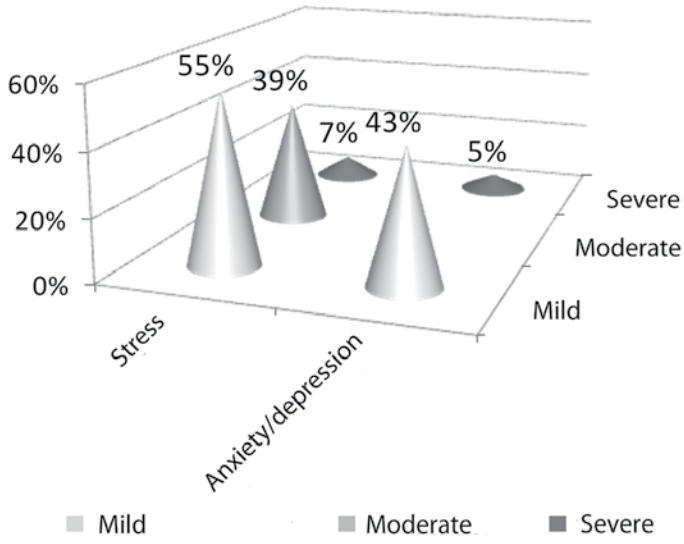

Figure 2. Changes of main psychosomatic factors in patients with CNDs

pandemic (p<0.0001); 9.7% (6.8–13.3) (n=34) had more physical activity.

Same tendency was determined when the dietary habits were assessed. 34.8% (29.8–40) (n=122) stated that they ate more during the quarantine and 4% (2.2–6.6) (n=14) stated that they, on the contrary, ate less.

These changes can be primarily explained by the way of life that the patients with CNDs are used to. All in all, 26.8% (22.2–31.7) (n=94) of patients with some CNDs noted that they felt worse and had lower quality of life during the quarantine.

It was also important for us to assess the effects of quarantine on psychologic status of the patients included (fig. 2). One in two patients with CVDs (54.7% (49.3–60), n=192) had some mild stress, moderate stress was present in 39% (33.9–44.4) cases (n=137) and 6.3% (4–9.3) patients complained on severe stress (n=22). 43% had minor depression and anxiety (n=151) and severe depression/anxiety was present in 4.3% (2.4–7) (n=15).

Undoubtfully, patients are more prone to chronic stress during the quarantine. The rate of moderate stress is rather high and that affects health status and quality of life. At the same time. one in two patients also stated that they had mild depression/anxiety during the quarantine. These conditions are reversible and don't require any addition measures. However, there is a group of individuals among these patients who are at a higher risk of further worsening of psychological status. This should be taken into consideration for the further medical management.

Conclusion

During quarantine and self-isolation patients with CNDs had mild worsening of their clinical status, more hypertonic emergencies, and requirement of higher doses of medications. Most people exercised less and had worse diet during self-isolation. On Patients with CNDs also tended to have higher levels of chronic stress and mild depression/anxiety. In general, in one in four patients with one and more CNDs quarantine and self-isolation were associated with worsening of health status and quality of life.

Conflict of interest: none declared.

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Features of working conditions and modifiable risk factors for cardiovascular diseases among employees of locomotive crews of the metro and railways in the city of Saint Petersburg

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Abstract

Objective. *To study the features of working conditions and modifiable risk factors among employees of locomotive crews depending on their place of work.*

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Materials and methods. *The survey included 599 employees of locomotive crews, all of them were male, machinists and their assistants: 313 worked in Russian Railways and 287 in Saint Petersburg Metro. All the participants answered the questionnaire on the features of working conditions and behavioral risk factors with the help of medical personnel.*

Results. *The studied groups differed with p<0.05 by working conditions. Russian Railways workers had 12-hour shift and metro employees 8-hour shift in 96 % and 81 % of cases, respectively. Machinists of Russian Railways were 4 times more likely to complain about overheating in summer and cooling in winter compared with metro workers. Moreover, machinists of Russian Railways were 7.5 times more likely to report that they were forced to repair the railways compared with metro workers. Employees of Russian Railways were 2.1 times more likely to smoke and consume excess salt, and 2.5 times more often ate irregularly (1–2 times a day) compared with metropolitan employees. Machinists of Saint Petersburg Metro had 2 times lower physical activity and 1.3 times more often ate in fast food restaurants. Workers of the Russian Railways had higher body mass index, diastolic blood pressure and fasting blood glucose level. At the same time metro workers showed higher values of waist and hip circumferences. Compared with metro workers, employees of Russian Railways over the past 12 months took a temporary disability certificate 4 times more often, visited the physician 9 times more often, and were admitted to the hospital 3 times more often. Metro employees were 8 times more likely to be suspended from driving than employees of Russian Railways.*

Conclusion. *This study showed the difference between working conditions and the presence of modifiable risk factors among workers of Russian Railways and Saint Petersburg Metro. The results may be useful for the development of preventive programs for the Russian Railways employees.*

Keywords: *locomotive crew employees, health, metropolitan, working conditions.*

Conflict of interest: none declared.

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Introduction

Passenger rail transport plays a pivotal role in communication between megacities and smaller settlements. Rail transport is usually cheaper and more convenient for passengers compared with wheeled transport. For small distances between towns, rail transport can be more convenient than aviation. In addition, rail transport can be advantageous compared to aviation in the absence of an airport in a city or regular flights between cities [1].

Transport sector has a large impact on employment. One of the features of rail transport is that representatives of various professions work in this industry [2]. However, the most valuable are workers of locomotive crews (machinists and their assistants), who directly control the traffic [3].

The work of machinists is considered stressful and is associated with various psycho-emotional stress factors. In addition, there are working conditions-related risk factors, such as: noise, vibration, temperature changes, static posture [4]. Another negative factor for metro workers is the lack of sunlight [5].

Over the last years, many publications in the literature showed the presence of modifiable risk factors among workers of locomotive crews. Such studies claim that its combined effect leads to the development of chronic noncommunicable diseases (primarily cardiovascular) that are the main cause of temporary disability and early departure of drivers and their assistants from the profession [6].

The objective of this study is to investigate the features of working conditions and modifiable risk factors among employees of locomotive crews in megacity depending on their place of work — railways and metro.

Materials and methods

The study was approved by the Intercollegiate Ethics Committee. The study was conducted in accordance with the Declaration of Helsinki Ethical Principles and Good Clinical Practices.

The study included 599 employees of locomotive crews, all of them were male, machinists and their assistants: 313 worked in Russian Railways and 287

Table 1. **Characteristics of study participants**

Place of work	Number of machinists, %	Age, years	Work experience of machinists, years	Officially married, %	Live in separate apartment%	n	
Russian railway	56.5%	34.18±10.09	11.03±10.93	47.3%	69.0%	313	599
Metro	68.4%	39.15±9.62	13.64±11.10	53.6%	60.1%	286	
p	0.79	0.071	0.18	>0.89	0.85	-	

Table 2. **The comparison of groups by the organization of working process**

Parameter		Russian railway	Metro	p	
The length of shift	8 hours	4.2%	81.1%	0.0004	0.018
	12 hours	95.8%	6.6%		
Schedule	Shifts	51.8%	91.3%	0.016	
	Rotating	48.2%	8.7%		
The beginning of the shift before 6 a.m.		23.0%	24.6%	0.90	
The end of the shift after 10 p.m.		21.7%	14.0%	0.75	
Overworking		2.6%	39.3%	0.045	
The way of getting to work	Public transport	47.6%	59.3%	0.88	
	Personal transport	39.0%	18.9%		
	On foot	13.4%	21.8%		

in Saint Petersburg Metro. The groups were comparable by age, work experience and several other characteristics (table 1). 61.9% (n=372) were machinists, half of them were officially married, over 60% lived in separate apartments. The study included only citizens of Saint Peterburg by the year 2020. The written informed consent was waived from all the study participants.

All the participants answered the questionnaire on the features of working conditions and behavioral risk factors with the help of medical personnel. This questionnaire was developed by our team earlier using the STEPS tool [7].

Based on the results of the survey, the index of adherence to healthy lifestyle (HLS) was calculated for each participant [8]. High level of adherence to HLS identified in workers with no hypodynamia, salt-free or hypo-salt diet, adequate intake of vegetables and fruits, non-smokers, and those who drink less than 168 g of alcohol less than several times a week. A satisfactory level of adherence to HLS was determined in non-smokers with the absence of any other (no more than one) component of high level of adherence to HLS. Low level of adherence to HLS was determined in smokers or those with the absence of over two components of high level of adherence to HLS.

In addition, the machinists and their assistants answered the questions if they were suspended from driving, had unscheduled requests for medical help, took a temporary disability certificate and were admitted to the hospital over the last year. With the help of medical personnel, blood cholesterol and blood glucose levels were extracted from the results of the last medical examination. Arterial blood pressure and pulse were measured during a pre-trip medical examination.

The statistical analysis was performed in Excel and Statistica for Windows software. The comparison of quantitative data was performed with Mann-Whitney U-test and of categorial data — with χ^2 method. The level of significance was set as $p<0.05$.

Results

The studied groups differed with $p<0.05$ by working conditions. Russian Railways workers had 12-hour shift and metro employees 8-hour shift in 96% and 81% of cases, respectively. 51% of Russian Railways employees and 91% of metro workers indicated that they had shift work schedule. One fifth of the respondents usually had early shift start time (before 6 a.m.) and the same number — late shift end time (after 10 p.m.). Metro employees 15 times more often overworked compared with employees of Russian Railways. On average, the journey from home to work took 1 hour, half of the respondents took public transport and less than ⅕ went to work on foot (table 2).

In general, the studied groups did not differ by the frequency of working conditions risk factors (table 3). Machinists of Russian Railways were 4 times more likely to complain about overheating in summer and cooling in winter compared with metro workers. Moreover, machinists of Russian Railways were 7.5 times more likely to report that they were forced to repair the railways compared with metro workers.

The study revealed a difference in the frequency of behavioral risk factors between studied groups

Table 3. **The comparison of groups by the presence of working conditions risk factors**

Parameter	Russian railway	Metro	p	
Noise in the cockpit	42.2%	48.4%	0.90	
Vibration in the cockpit	42.5%	46.7%	0.93	
Smell in the cockpit	34.8%	13.0%	0.52	
Cooling in winter	30.0%	7.7%	0.019	
Overheating in summer	62.9%	14.4%	0.017	0.93
The posture when driving is forced, sedentary	40.9%	31.9%	0.85	
Have been forced to repair the railways	15.0%	2.0%	0.035	
Have been forced to do a lot of movements while working	47.9%	48.2%	0.99	
Have been forced to go to work when felt unwell	42.5%	37.7%	0.74	

Table 4. **The comparison of groups by behavioral risk factors**

Parameter		Russian railway	Metro	p	
Smoking		59.3%	27.7%	0.048	
Alcohol abuse		60.7%	59.3%	0.98	
Inadequate intake of vegetables and fruits		35.1%	76.2%	0.34	
Irregular eating		59.1%	23.3%	0.040	
Consuming fatty, fried, spicy foods		89.1%	87.9%	0.97	0.099
Consuming semi-finished products, ready-made food		82.1%	85.6%	0.92	
Eating in fast food restaurants		71.2%	91.6%	0.046	
Excessive salt intake		89.3%	40.7%	0.032	
Hypodynamia		29.0%	61.9%	0.050	
index of adherence to an HLS	low	59.3%	27.7%	0.76	
	satisfactory	30.0%	63.9%		
	high	10.7%	8.4%		

Table 5. **The comparison of groups by biological risk factors**

Parameter	Russian railway	Metro	p
BMI, kg/m^2	32.86±12.10	27.47±10.56	0.022
Waist circumflex, cm	87.32±16.68	94.06±12.36	0.001
Hip circumflex, cm	92.31±16.34	96.23±15.60	0.014
Waist and hip circumflex ratio	0.95±0.17	0.98±0.12	0.001
Systolic blood pressure, mmHg	119.82±9.86	120.14±6.31	0.28
Diastolic blood pressure, mmHg	77.47±5.34	76.71±6.27	0.012
Pulse, beats per minute	72.35±7.99	75.83±4.91	0.11
Blood glucose level, mmol/l	5.23± 0.40	5.04±0.74	0.031
Blood cholesterol level, mmol/l	5.88±2.66	5.36±2.23	0.23

Table 6. **The comparison of groups by medical activity**

Parameter		Russian railway	Metro	p	
Medication intake, including vitamin and mineral complexes		31.3%	35.4%	0.93	
Considers that work has a negative impact on health		100.0%	84.9%	0.017	
Over the last 12 months	Considers that prophylactic medical examination is beneficial	73.2%	95.1%	0.31	
	Unscheduled visits to the physician	36.7%	3.9%	0.008	
	Temporary disability certificate	36.4%	8.8%	0.032	0.060
	Admission to the hospital	7.3%	0.2%	0.007	
	Ambulance call	3.5%	6.3%	0.90	
	The frequency of visits to the physician have not changed	73.2%	78.6%	0.95	
	Suspended from driving	1.4%	12.3%	0.008	

(table 4). Employees of Russian Railways were 2.1 times more likely to smoke and consume excess salt, and 2.5 times more often ate irregularly (1–2 times a day) compared with metropolitan employees. Machinists of Saint Petersburg Metro had 2 times lower physical activity and 1.3 times more often ate in fast food restaurants. High level of adherence to HLS was revealed in 1/10 of participants.

Physiological risk factors also differed between studied groups (table 5). Workers of the Russian Railways had higher body mass index (BMI), diastolic blood pressure and fasting blood glucose level. At the same time metro workers showed higher values of waist and hip circumferences. Other characteristics did not differ significantly between groups.

The study also showed a difference in the frequency of medical activities between studied groups (table 6). Compared with metro workers, employees of Russian Railways over the past 12 months took a temporary disability certificate 4 times more often, visited the physician 9 times more often, and were admitted to the hospital 3 times more often. Metro employees were 8 times more likely to be suspended from driving than employees of Russian Railways.

Discussion

The results of this research confirmed that there is a difference in the organization of the working process between Russian Railways and the metro, that was described earlier in the literature [5]. These differences were associated with the features of the technological cycle and the rhythm of the large cities; therefore, they cannot be corrected at the present stage. The only way to partially solve the problem is to change the working process of the locomotive fleet. This problem is being successfully solved by both Russian Railways and Saint Petersburg Metro.

Behavioral risk factors that were revealed in machinists play an important role in the development of cardiovascular diseases (CVDs), mainly arterial hypertension and ischemic heart disease. It is disturbing that average BMI value was over 25 kg/m^2, and waist and hip circumferences ratio — over 0.9. In other words, this indicates that large number of workers has signs of general and central obesity. These indices, regardless of other risk factors, contributes to the development of chronic non-communicable diseases, that are especially important in machinists who also have working conditions risk factors for CVDs [9].

On the other hand, identified risk factors can be used as basis for the development of preventive strategy: quitting smoking, increasing physical activity, introducing the principles of healthy nutrition. It is clear that such preventive measures are impossible without the implementation of health education programs [10]. An example of such can be a corporate healthcare programs, which already exist at both Russian Railways [11] and the metro [12]. Therefore, the methods of these programs can be expanded and clarified according to the results of our study.

Russian Railways workers had higher levels of diastolic blood pressure compared with metro workers. This can be associated with higher salt intake by Russian Railways workers. It is known that high salt intake is considered as independent predictor of arterial hypertension development [13]. At the same time the reduction of salt intake can be used as preventive factor for the development of this disease [14].

The revealed difference in the medical activity between Russian Railways and metro machinists may be associated with the difference in the organization of medical support, including preventive and rehabilitative measures. The obtained data indirectly indicate that this field should be improved and developed [15]. In particular, in our opinion, it is necessary to pay more attention to education of machinists on the impact of their work on health, since behavioral risk factors the most significant according to the results of our study.

Conclusion

This study showed the difference between working conditions and the presence of modifiable risk factors among workers of Russian Railways and Saint Petersburg Metro. The results may be useful for the development of preventive programs for the Russian Railways employees. From our point of view, it is necessary to raise this question on the level of the Government of the Russian Federation. Such preventive programs should be referred to the "cost" section, and not to the "profit" section as they are now. This will help to promote active longevity programs in the workplace.

Findings

1. Employees of the locomotive crews of Russian Railways and the metro in Saint Petersburg, have different working conditions.

2 Machinists and their assistants included in our study differed by behavioral (modifiable) risk factors.

Conflict of interest: None declared.

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A comparative study on clinical outcomes of pharmacoinvasive strategy versus primary percutaneous coronary intervention in acute myocardial infarction patients

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Abstract

Objective. *To compare clinical outcomes of pharmacoinvasive (PI) strategy versus primary percutaneous coronary intervention (PPCI) in patients with AMI (acute myocardial infarction) still needs more evaluation.*

Methods. *This is a single centre, retrospective, non-randomized study comparing the two treatment strategies. A total of 3073 consecutive AMI cases were identified between 2015 and 2019.*

Results. *The pharmacoinvasive strategy group comprised of 18.5% (n=569) and primary PCI group comprised of 81.5% (n=2504) patients. The patients in PI group were younger, their mean age was 54.8± 12 years vs 56.4± 11.5 years (P<0.003) in PPCI group. Arabic speakers were 47.1% vs 40.9% (P<0.000), South Asians 25.3% vs 30.2% (P<0.018), smokers 39.9% vs 31.5% (P< 0.000) and anterior MI was 55% vs 54% (P< 0.000) in PI vs PPCI group respectively. Transradial approach was utilized in 84.4% in PI vs 75.4% (P<0.000) in PPCI group. Median door to balloon time (calculated from arrival to our hospital emergency till establishment of TIMI III flow in the culprit vessel) in PPCI group was 92 minutes. In-hospital mortality tended to be higher in PPCI vs PI as 3.6% vs 1.9% (P<0.049). LV ejection fraction was observed to be higher in PI group i-e 42.2±11% vs 40.5±11% (P<0.000) in PPCI group.*

Conclusion. *Pharmacoinvasive strategy has almost equal efficacy as compared with primary PCI and it represents a reasonable, non-inferior alternative when primary PCI is not readily available especially in patients presenting early after symptom onset.*

Keywords: *Pharmacoinvasive strategy, Primary Percutaneous Coronary Intervention, Acute Myocardial Infarction, ST-Elevation Myocardial Infarction, Thrombolysis in Myocardial Infarction, Left Ventricle.*

Conflict of interest: none declared.

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Introduction

The strategy of pharmacoinvasive (PI) therapy consists of fibrinolysis and transfer for percutaneous coronary intervention (PCI). It is not well studied as compared to primary PCI (PPCI) in patients with ST-Elevation myocardial infarction (STEMI) [1]. Primary PCI has been set as the best reperfusion option in patients with acute MI, if it is performed in a guideline directed timely fashion [2]. A large number of patients with acute MI present to those hospitals which have no facility for coronary interventions, so they receive fibrinolytics as the initial reperfusion therapy [3]. Pharmacoinvasive strategy is thought to be the treatment of choice for those communities where access to primary PCI is difficult [4]. Large scale studies comparing the efficacy and outcomes of these two strategies are still awaited [5]. The best candidates for primary PCI are those who present with cardiogenic shock, high risk of bleeding with fibrinolytic therapy, more than 3 to 4 hours after onset of symptoms or those who have very short times to be transferred to PCI capable hospital. While for initial fibrinolytic therapy are those who have low bleeding risk, present very early after onset of symptoms (<2 to 3 hours) to a non-PCI-capable hospital or who have longer transfer time to a PCI-capable hospital [6]. Many clinical trials have shown equivalence of early (3–24 hr) post-thrombolysis PCI to primary PCI in patients with STEMI [7,8].

In this study we have compared the efficacy of pharmacoinvasive strategy (PI) to primary percutaneous coronary intervention (PPCI) in those patients

who cannot readily approach for primary PCI in a timely fashion.

Material and Methods

Study Design

This is a single centre, retrospective, non-randomized, cross sectional study and did not require informed consent for data collection for this registry.

Patient Selection

Our centre is the only primary PCI-capable facility, available in the region. Patients were selected from Makkah STEMI registry and included all patients who presented with STEMI and either primary PCI or pharmacoinvasive strategy was performed.

Inclusion and Exclusion criteria

Key inclusion criteria:

i) Pharmacoinvasive strategy: Patients with acute myocardial infarction and successful reperfusion after thrombolytic therapy defined as at least 50 % ST segment resolution and improvement of chest pain.

ii) Primary PCI: Patients with acute myocardial infarction defined as having chest pain lasting more than 30 min along with ST segment elevation in 2 contiguous leads of at least 1 mm except≥ 2 mm in V2–3 or presumed new onset left bundle branch block (LBBB).

Key exclusion criteria:

There were no exclusion criteria other than standard contraindications for thrombolytic therapy and coronary angiography.

The patients were divided into two groups.

Group 1 (Pharmacoinvasive strategy group): Those patients who received thrombolytic therapy at their primary hospital and were immediately referred for routine PCI from 4 hours up to approximately 5 days.

Group 2 (Primary PCI group): Those patients who were directly shifted as acute STEMI for primary PCI. The timing of shifting was within 1–12 hours of onset of chest pain.

Study Medications

The Streptokinase, ateplase or whatever thrombolytic agent available at primary hospital was administered in the standard dosing regimen as per guidelines.

Technique for Coronary Angiography and PCI

The pimary PCI and routine PCI were performed with standard protocols by highly experienced operators. Transfemoral or transradial approach was adopted according to patient's condition. Diagnostic coronary angiography was consummated to explore infarct-related artery. Thrombus aspiration and glycoprotein's inhibitors were administered in lesions with heavy thrombus burden and/or impaired TIMI flow during or after the procedure. The operators determined the length and diameter of implanted stents.

Data Collection

Data for all patients was extracted from medical records, electronic case notes, echocardiography and angiography records. We initially aimed to compare baseline characteristics, lab findings, ejection fraction and primary in-hospital outcomes of PI strategy versus PPCI in eligible patients with acute myocardial infarction.

Statistical Analysis

Data management and statistical analysis were performed using SPSS software. Discrete variables were reported using counts and percentages and continuous variables were described by the mean and standard deviation. We evaluated differences between the PI and PPCI using the t-test or Mann-Whitney U test for continuous variables and the χ^2 test or Fisher exact test for categorical variables. $P<0.05$ was considered statistically significant

Results

Baseline Clinical Characteristics

A total of 3073 consecutive patients with STEMI who were admitted to the coronary care unit or cardiac day care unit at King Abdullah Medical City, Makkah during the period starting from January 2015 to July 2019 were analyzed. Among these patients, 569 patients (18.5 %) were assessed to be in pharmcoinvasive strategy group and 2504 patients (81.5 %) in primary PCI group. No significant difference was observed for gender, diabetics, hypertensives or for those with previous ischemic heart disease. Smokers comprised of 39.9 % vs 31.5 % of PI vs PPCI group ($P<0.001$). Among this multiethnic population, the pilgrims comprised of 33 % of total population and 17.4 % received PI while 36.2 % received PPCI ($P<0.001$). The clinical characteristics are presented in Table 1.

Infarct Related Characteristics

Larger infarct size which was defined as the higher mean value of second troponin I, was noticed to be significantly higher in primary PCI group that is 109± 234 ng/ml vs. 68± 187 ng/ml in PI group ($P<0.001$).

Table 1. **Clinical characteristics of Pharmacoinvasive Strategy vs Primary PCI**

Variables	PI N=569 (18.5%)	PPCI N=2504 (81.5%)	P Value
Age (years) Mean± SD Median (IQR)	54.8± 12 55 (47–61)	56.4± 11.5 57 (49–64)	<0.003
Gender (Male)	489 (85.9%)	2086 (83.3%)	NS
Arabic speaking	268 (47.1%)	1023 (40.9%)	<0.001
South Asians	144 (25.3%)	756 (30.2%)	NS
Pilgrims	99 (17.4%)	907 (36.2%)	<0.001
Co-morbidities			
DM	310 (54.5%)	1357 (54.2%)	NS
HTN	296 (52%)	1345 (53.7%)	NS
Smoking	227 (39.9%)	790 (31.5%)	<0.001
BMI<30	162 (28.5%)	704 (28.1%)	NS
CVA	11 (1.9%)	66 (2.6%)	NS
Dyslipidemia	89 (15.6%)	356 (14.2%)	NS
IHD	129 (22.7%)	488 (19.5%)	NS
Previous Revascularization	30 (5.3%)	184 (7.3%)	NS
Infarct Related Characteristics			
Anterior MI	312 (54.8%)	1347 (53.8%)	NS
2nd Max Troponin I level (ng/ml) Mean± SD Median (IQR)	68.8±187.8 15.5 (3–57.1)	101.9±234 44.9(12.7–121.1)	<0.001
Procedure related characteristics:			
Fluoroscopy Time Mean± SD Median (IQR)	10.2± 13.8 7.3 (4.1–12.4)	11± 9.8 8.5 (5.3–14)	<0.001
Contrast Mean± SD Median (IQR)	119.5± 65.4 110 (70–150)	132± 67.7 120 (90–160)	<0.001
Number of Stents>2	248 (43.6%) 28.4%	1285 (51.3%) 33.9%	<0.001
Critical Time Intervals			
DTA (min) Mean± SD Median (IQR)	317.5± 241.3 278 (119–459)	155± 215 77 (27–165.2)	<0.001
DTB (min) Mean± SD Median (IQR)	326.9± 244.1 291(112–475)	169.7± 217.2 92 (41–179)	<0.001

PI= pharmaco-invasive, PPCI=primary percutaneous coronary intervention, MI=myocardial infarction IQR=inter quartile range, DM=diabetes mellitus, HTN=hypertension, CVA=cerebrovascular accident, IHD=ischemic heart disease, BMI=body mass index, DTA=door to access time, DTB=door to balloon time, NS= not significant.

Procedure Related Characteristics

It was observed that transradial approach was the preferred method for transcutaneous puncture in 84.4% of patients who received PI strategy and 75.4% of PPCI (P<0.001). In PI and PPCI groups, left main stem disease was estimated to be 2.1% vs 3.1% and triple vessel coronary artery disease was observed in 18.1% vs 15% respectively. Moreover, tirofiban was utilized in 11.8% vs 27.1%, thrombus aspiration in 4.2% vs 14.1%, mean fluoroscopy time was evaluated to be 10.2± 13.8 minutes vs 11± 9.8 minutes, contrast volume as 119.5± 65.4 ml vs 132± 67.7 ml and the requirement to use more than 02 stents per procedure was 28.4% vs 33.9% in PI vs PPCI groups respectively and all these parameters were determined to be statistically significant P<0.001 (Figure 1).

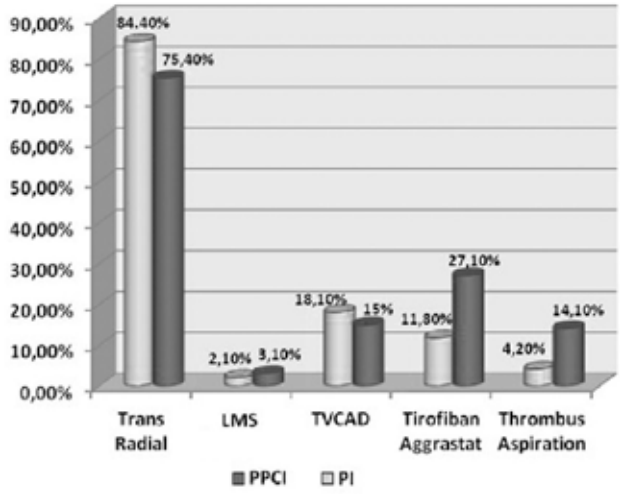

Fig. 1. Procedure related characteristics. PI= pharmaco-invasive, PPCI=primary percutaneous coronary intervention, LMS=left main stem, TVCAD=triple vessel coronary artery disease

Critical Time Intervals

As expected significant difference was observed in critical timings data between both groups. The estimated thrombolysis to balloon time was agreed and accepted to be in range from 240 minutes to 475 minutes. The median time from admission time to successful transcutaneous access, described as door to access time (DTA) was significantly shorter in the PPCI group (77 min; IQR: 27 to 165 min) as compared with the PI group (278 min; IQR: 119 to 459 min) (P<0.001). The median door to balloon time (DTB) which was defined as "the time from admission to first coronary artery intervention for primary PCI found successful in achieving TIMI III flow in an occluded culprit artery" was determined as 92 min (IQR: 41 to 179 min) for the primary PCI group and 291 min for the pharmacoinvasive strategy group (IQR: 112 to 475 min) (P<0.001).

In-Hospital Clinical Outcomes

The rate of the primary composite outcome such as mortality was not found to be significant i-e 1.9% vs 3.6% (P<0.049) for the PI and PPCI groups respectively. Also there was no significant difference in parameters like TIMI major bleeding defined as haemoglobin drop>3 g/dl, pulmonary oedema at time of presentation, intubation/ventilation, cardiogenic shock or cardiac arrest (Figure 2). Post PCI ejection fraction in PI group vs PPCI group was evaluated as

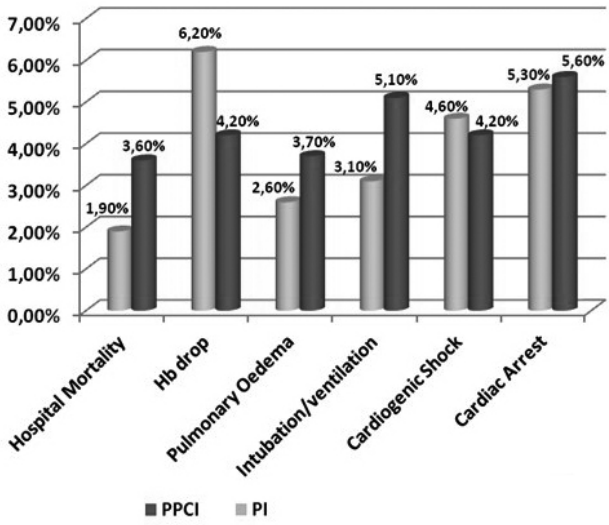

Fig. 2. In-hospital clinical outcomes. PI= pharmaco-invasive, PPCI=primary percutaneous coronary intervention, Hb drop=haemoglobin drop

Table 2. **Immediate in-Hospital outcomes**

Variables	PI N=569 (18.5%)	PPCI N=2504 (81.5%)	P Value
Post PCI EF Mean± SD Median (IQR)	42.3± 10.7 45 (35–50)	40.6± 10.6 40 (35–50)	<0.001
Length of Stay Mean± SD Median (IQR)	7.5± 9.1 4 (3–9)	5.2± 7.5 3 (2–6)	<0.001

PI= pharmaco-invasive, PPCI=primary percutaneous coronary intervention, Post PCI EF=post percutaneous coronary intervention ejection fraction), SD=standard deviation, IQR=inter quartile range

42.3± 10.7% vs. 40.6± 10.6% (P<0.001) respectively (Table 2).

Discussion

The underlying principle for the pharmacoinvasive strategy is that the initial fibrinolytic therapy is implemented for early restoration of coronary blood flow and subsequent invasive strategy applied to reopen the infarct related artery with early elective PCI. The objective to study pharmacoinvasive strategy is that despite the widespread use of primary PCI, still in our setup many areas have no timely access to primary PCI centres so pharmacoinvasive therapy would be a worth mentioning strategy for timely salvage of myocardium [9].

In the current study, we aimed to study differences in demographic data and compared immediate in-hospital outcomes between the two groups including pilgrim population and concluded that there was no major difference in terms of immediate in-hospital complications or mortality. However, it was observed that the patients receiving PPCI had lower ejection fraction (EF) which more empowers the need of timely reperfusion in the form of pharmacological reperfusion to even high risk cases.

Current study is unique in the view that we studied multiethnic population of Makkah region including pilgrims. The results are in accordance with Stars Saudi Arabia STEMI registry [15].

Although fibrinolysis can be administered in a timely fashion but it is also sometimes associated with higher rates of non-reperfusion and re-infarction that is why fibrinolysis followed by timely PCI can alleviate this risk [13]. A large meta-analysis of 7 trials showed that early PCI after fibrinolysis has been associated with a decreased risk of the combined endpoint of death and re-infarction without a significant increase in the risk of major bleeding or stroke. In fact, this meta-analysis compared rescue PCI in all studies and not primary PCI however the importance of timely reperfusion had been strongly addressed [14].

Likewise, our results are similar to FASTMI, in which patients with STEMI received PPCI and fibrinolysis followed by PCI or no reperfusion. Time to reperfusion was significantly shorter with fibrinolysis followed by PCI than by PPCI [11]. Although we did not study time to reperfusion but regarding in-hospital outcomes we observed no difference between pharmacoinvasive strategy and primary PCI [10, 11, 12]. Regarding critical timing data, our median door to balloon time for primary PCI was determined to be 92 minutes which is in accordance with AHA guidelines, O Gara et al. and ESC guidelines [6,7].

Our study depicted similar efficacy for pharmacoinvasive strategy when routine PCI was performed after thrombolysis and found that there was no difference in the composite endpoint of death, shock, congestive heart failure, or reinfarction at 30 days between the two treatment strategies [9].

Conclusion

This large observational study concludes that the patients with acute myocardial infarction who received pharmacoinvasive treatment strategy had better ejection fraction and similar immediate clinical outcomes when compared with primary PCI. With the growing number of high risk STEMI patients presenting early, pharmacoinvasive strategy seems to be a realistic alternative to reduce total ischemic time for better preservation of ejection fraction and salvage the myocardium.

Study Limitations

This non-randomized, retrospective analysis of a registry data has the usual limitations inherent to observational studies. There may be selection bias in patients in pharmacoinvasive arm because it is obvious that mostly those patients who were alive and stable after thrombolytic therapy were referred for further interventional therapy and more ill, patients with co-morbidities or those who were not fit enough to be transferred such as frail patients with high risk of mortality were excluded at primary centres from referring for interventional therapy. Follow up data is deficient which is needed for analysis of long term outcomes.

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Conflict of interest: none declared.

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Features of the Growth factor of differetiation-15 in patients with acute myocardial infarction

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Abstract

Objective *of the current study was to the clinical and laboratory features and the level of growth differentiation factor 15 (GDF-15) in patients with acute ST-segment elevation myocardial infarction (STEMI) at the inpatient stage of treatment.*

Materials and methods. *Clinical and laboratory characteristics of STEMI patients were assessed during the hospital stay; echocardiography was also performed. The prognosis of in-hospital mortality was calculated using the GRACE scale. Statistical analysis was performed using the statistical software package «Statistica 10.0 for Windows».*

Results. *The GDF-15 level increases on the first day of STEMI and correlates with the risk of in-hospital mortality according to the GRACE scale. STEMI patients with GDF-15 values≥1200 ng/ml doesn't reach the reference values during inpatient treatment. Patients with an unfavorable in-hospital outcome of STEMI were at a high risk of in-hospital mortality according to the GRACE scale with a tendency to GDF-15 concentration rise. Myocardial contractility of the left ventricle was also reduced in these patients.*

Conclusion. *The persistence of high GDF-15 values during the in-patient treatment determines the prognosis of STEMI.*

Key words: *acute myocardial infarction, GDF-15.*

Conflict of interest: none declared.

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Patients with acute ST-segment elevation myocardial infarction (STEMI) are at high risk of early complications. That leads to higher pre-hospital and in-hospital mortality. Outcomes depend on present risk factors, time when the patient started seeking medical help, access to coronary angiography (CAG), surgical treatment. Currently, STEMI is still investigated in experiments and real clinical settings.

Experiments have shown that STEMI is associated with increased levels of growth differentiation factor 15 (GDF-15) in cardiac myocytes. GDF-15 regulates late activation of macrophages, had anti-inflammatory effects, and reduces macrophage-to-foam-cell transformation. GDF-15 also has some protective effects of myocardium even before the first clinical manifestations of MI, but also increases the risk of cardiovascular disease. It can be also found in atherosclerotic plaques in MI [1].

Mimeault M. et al. (2010) have suggested that GDF-15 has the effects as antiatherogenic cytokine as it inhibits expression and activity of lipoprotein lipase and low-density lipoprotein receptors. However, the data are controversial. Low levels of GDF-15 increase the progression of atherosclerosis, and extremely high levels of GDF-15 are associated with atherosclerotic vessel damage and the development of ischemia [2].

In-hospital treatment of STEMI still needs to be investigated further, as well as risk factors and laboratory and instrumental outcome predictors.

Objective of the current study was to the clinical and laboratory features and the level of GDF-15 in patients with STEMI at the inpatient stage of treatment.

Material and methods

The current study included 150 patients with STEMI. The study was performed in accordance with the Good Clinical Practice standards and the Helsinki declaration principles. According to the 2007 Russian Society of Cardiology guidelines, STEMI diagnosis had to be determined with the clinical, ECG and laboratory markers of myocardial ischemia: troponin I, creatine kinase (CK) and creatine kinase MB (CK-MB). Inclusion criteria were age 45 and older, arterial hypertension (AH), first 24 of the disease. Exclusion criteria: type 1 and 2 diabetes, severe kidney failure, liver failure, fertile women, cancer, systemic inflammatory diseases (SIDs), infectious diseases. Physical examination included systolic and diastolic blood pressure measurements (SBP and DBP), heart rate (HR). Laboratory values included alanine transaminase (ALT), aspartate transaminase (AST), urea, creatinine, myocardial necrosis markers, electrolytes, glomerular filtration rate (GFR). Plasma levels of GDF-15 were assessed using the enzyme immunoassay. We used standard Human GDF-15/MIC-1 ELISA ("BioVendor", Czeck Republic) reactive. We also performed echocardiography to assess left atrial (LA), right atrial (RA), left ventricular (LV) sizes, LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), stroke volume (SV), ejection fraction (EF), left pulmonary artery pressure, the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave).

Patients with STEMI were examined at admission to the cardiology department and at discharge. The prognosis of in-hospital mortality was calculated using the GRACE scale (Global Registry of Acute Coronary Events scale):<126 points — low risk (<2%), 126–154 points — moderate risk (2–5%);>154 points — high risk (>5%). Statistical analysis was performed using the statistical software package "Statistica 10.0 for Windows".

Results

General clinical and laboratory characteristics of patients with STEMI are mean age 61.69±0.96 years, SBP 135.42±2.25 mmHg, DBP 81.86±1.21 mmHG, HR 81.61±1.51 beats/min. Laboratory values: ALT 45.03±2.57 Units/l, AST — 86.26±8.73 Units/l, urea 9.76±1.44 mmol/l, creatinine 84.45±2.68 mmol/l, estimated GFR 81.17±1.98 ml/min/1.73m^2. Markers of myocardial necrosis: troponin I 13.22±1.40 ng/ml, CK 320.23±35.56 U/l, MB-CK 61.63±14.92 U/l.

Echocardiography results in the general group: LA — 41.38±0.34 mm, LV ESS — 40.84±0.30 mm, LVEDS 53.43±0.29 mm, LVESV 140.70±1.81 ml, EF 46.11±0.50%, E — 50.19± 0.99 cm/s, A — 60.40± 1.12 cm/s, E/A — 0.91± 0.03, RA — 32.84± 0.21 mm, RV 29.95±0.19 mm, PA pressure 32.46± 0.59 mm Hg. These values signify reduced myocardial contractility, rise of pressure in the pulmonary artery and tendency towards the A wave rise.

All patients with STEMI that were included into our study received initial therapy including dual antiplatelet therapy, anticoagulants, beta-blockers, ACE inhibitors, statins, nitrates. Reperfusion therapy was performed before the patient was admitted to the hospital — pharmacological thrombolysis, surgical — CAG, pharmacoinvasive approach. Some patients had contraindications to thrombolytic and therapy and

CAG, including refusal to get surgical treatment, and received only initial therapy.

Assessment of laboratory markers plays a major role in determining prognosis in patients with STEMI. Retrospective studies have shown that high levels of GDF-15 are associated with higher risk of mortality and/or STEMI in patients with acute coronary syndrome (ACS). GUSTO-IV, FRISC-2, ASSENT-2, and AMI studies have investigated the role of GDF-15 in ACS patient risk stratification [3, 4] at different points of the disease [5, 6] and the length of follow-up.

In the general group of STEMI patients GDF-15 levels in the first 24 hours were 1174.3±85.2 ng/ml, at discharge — 1017.1±114.3 ng/ml ($p>0.05$). Probably, relatively short period of hospital stay was not sufficient to assess the levels of GDF-15 and further studies are required.

During the first 24 hours of STEMI GDF-15 concentration increased above normal limits. Depending on GDF-15 all the patients were divided into GDF-15<1200 and GDF-15≥1200 ng/ml groups (Figure 1). Independently of GDF-15<1200 or GDF-15≥1200 ng/ml during the first 24-hours GDF-15 levels decreased due to in-hospital treatment and the changes were statistically significant. At the same time, patients with STEMI with GDF-15≥1200 ng/ml, GDF-15 concentration hasn't reached its normal levels during the hospital stay.

In general, patients with STEMI and GDF-15≥1200 ng/ml during the first 24 hours of MI haven't reached reference values during hospital stay and that affects their prognosis.

According to Kempf T. et al. (2006), GDF-15 is protective for cardiac myocytes and the rise of its concentration is associated with the body's high cytoprotective abilities [7].

Currently special scales that assess prognosis of patients with ACS and MI at the hospital and during pre-hospital stage of treatment are available. We used GRACE scale. Depending on the risk of in-hospital mortality (low, moderate, severe) we calculated GDF-15 values at admission and discharge (Figure 2). During the first 24 after admission, in patients with STEMI the mean levels of GDF-15 increased together with the risk according to GRACE scale ($p<0.05$). At discharge GDF-15 levels was higher in patients with high risk according to GRACE than in patients at low risk. There were no statistically significant differences in the reduction of GDF-15 concentration during in-hospital treatment.

As such, patients with STEMI, who are at the high risk of in-hospital mortality according to GRACE, GDF-15 is the highest during the first 24 hours after admission and at discharge. During the hospital stay GDF-15 tended to get lower with the higher values in patients at the high risk according to GRACE.

GDF-15 concentration at admission was positively associated with GDF-15 at discharge ((r=0.42, $p<0.05$). At discharge GDF-15 correlated with RA (r=0.37, $p<0.05$) and RV (r=0.29, $p<0.05$) size, PA pressure (r=0.31, $p<0.05$). Higher levels of GDF-15 at admission (r=–0.21, $p<0.05$) and at discharge (r=-0.37, $p<0.05$) was associated with lower LVEF on echocardiography. Echocardiographic values such as decreased LVEF, dilation of right and left chambers increase the risk of cardiac failure in patients with MI at both the in-hospital and pre-hospital treatment stages.

During in-patient treatment 7 patients died (5.3%). The causes included pulmonary edema in 3 patients and cardiogenic shock in 4 patients. The patients were divided into several groups according to the hospital outcome: death or positive outcome.

In patients with negative and positive outcomes age (65.42±4.33 years), SBP (126.66±12.29 mmHg) and DBP (78.33±7.92 mmHg) were comparable; HR

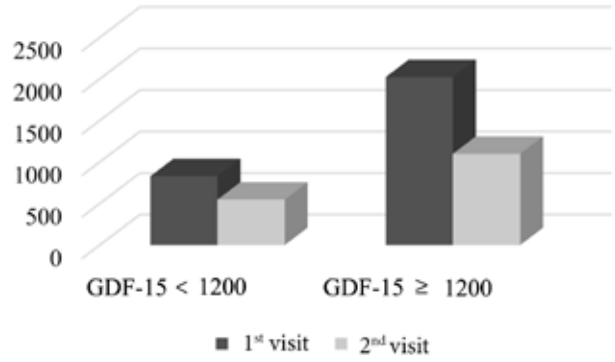

Figure 1. GDF-15 in patients with STEMI from the GDF-15<1200 and GDF-15≥1200 ng/ml groups.
P<0.05 between 1 and 2 visits in GDF-15≥1200 ng/ml group.

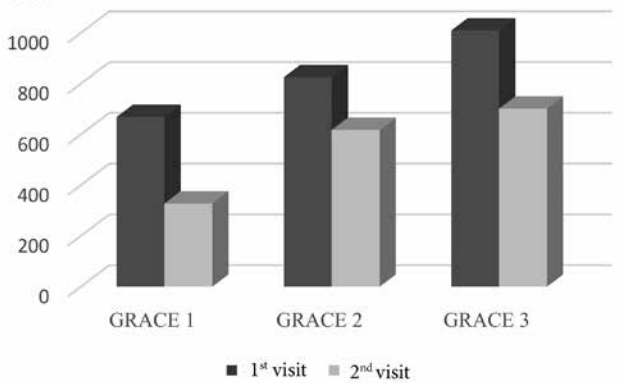

Figure 2. GDF-15 changes during the in-hospital treatment according to GRACE scale (p>0.05).

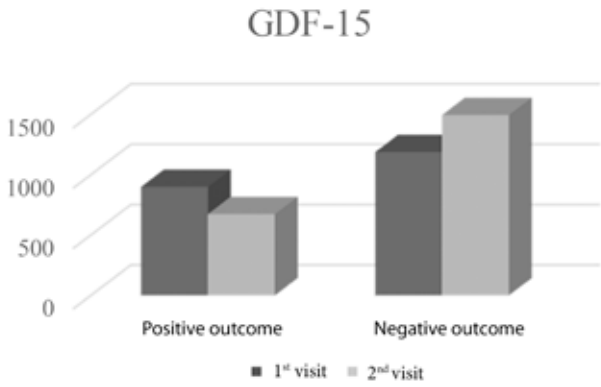

Figure 3. GDF-15 during in-hospital treatment according to outcome.
Note. Positive outcome p=0.09, negative outcome p=0.76.

(98.66±12.80 beats/min) and in-hospital mortality risk according to GRACE scale (204.28±11.48) were higher in the patients with negative outcomes (age 61.51±11.86 years, SBP 135.79±27.56 mmHg, DBP 82.01±14.70 mmHG (p>0.05), HR 80.90±17.63 beats/min, GRACE 163.36±30.63 points (p<0.05)). Patients with negative outcomes also had higher levels of ALT (74.83±21.65 U/l), AST (188.16±85.39 U/l), CK (735.16±323.99 U/l), MB-CK (95.16±41.98 U/l) compared with patients with positive outcomes (AST 98.35±8.29 U/l, ALT 48.70±2.49 U/l, CK — 368.76±33.86 U/l, MB-CK 90.77±15.49 U/l). These data confirms that the larger area of myocardium was affected patients with negative outcomes in the first 24 hours after admission.

Figure 3 shows GDF-15 values in patients with negative and positive outcomes during their hospital stay. Patients with negative outcomes had higher levels of GDF-15 that tended to increase further during in-hospital treatment. GDF-15 in patients with positive STEMI outcomes tended to decrease during in-hospital treatment.

Therefore, patients with negative outcomes have higher levels of GDF-15 that increase further during in-hospital treatment.

We didn't get any statistically significant differences in echocardiographic findings: LA 42.04±0.36 and 42.28±1.13 mm, LVESS 41.42±0.31 and 41.71±1.35 mm, LVEDS 54.01±0.30 and 53.85±1.37 mm, LVESV 77.79±1.47 and 78.00±6.60 ml, LVEDV 144.31±1.87 and 142.57±8.28 ml, EF 47.25±0.52 and 44.14±1.65 %) in patients with STEMI with positive and negative outcomes (p>0.05). Patients with negative outcomes had larger RA — 33.14±0.91 mm, RV 29.85±0.51 mm and pressure in PA — 39.28±3.88 mm compared with patients with positive outcomes — RA 33.26±0.22 mm, RV 30.35±0.19 mm, PA pressure — 33.25±0.58 mmHg (p<0.05).

As such, patients with STEMI and negative outcomes had right chambers overload, signs of pulmonary hypertension and decreased myocardial contractility.

Discussion

Assessment of changes in physical examination, laboratory and instrumental findings are crucial for determining the prognosis in STEMI. Khavinson et al (2015) state that increased levels of GDF-15 correlated with the level of LV diastolic dysfunction [9], especially in obese patients [10]. According to our results, GDF-15 increased in patients with STEMI and that was associated with reduction of LV myocardial contractility and RA and RV overload.

Conclusion

Complex assessment of GDF-15 and GRACE scale can be used to predict outcome in hospitalized patients with STEMI. Patients with the higher levels of GDF-15 during the first 24 hours after admission have larger area of myocardial damage, right chambers overload and negative prognosis of in-patient treatment.

Conflict of interest: none declared.

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Pharmacologic management of premature ventricular contractions in the absence of structural heart disease: estimation of positive effect duration

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Abstract

The objective *of this study was to evaluate the positive effect duration of pharmacologic management of premature ventricular contractions (PVC) according to ventricular ectopy analysis in the absence of structural heart disease.*

Materials and methods. *The current study included 214 patients aged 19–45 years without structural heart disease and with class IV–V PVC (Rayn B. classification (1984)). After 24-hour Holter monitoring, potentially effective antiarrhythmic agents for terminating PVC were selected. Antiarrhythmic drugs were taken for 5–7 days and a decrease in the number of extrasystoles by 75 % or more compared with baseline as well as the elimination of paired, group extrasystoles signified a positive effect. The extrasystole index (IE) and the corrected extrasystole index (IEcorr.) were calculated for all the patients before and after each administration of the drug, respectively. The follow-up duration ranged from 1 to 5 years. The endpoint was the duration of positive antiarrhythmic effect of the drugs used.*

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Results. *In 20.10 % of patients the positive antiarrhythmic effect persisted for 0.7±0.04 years, in 80.90 % — for 3.8± 0.08 years. In patients, in whom the positive effect lasted for up to 1 year, metoprolol, propranolol, sotalol were used more frequently, while class I drugs were not used at all. In patients without structural heart disease, the sensitivity, specificity, and positive prognostic value for antiarrhythmic therapy effects persistence for at least 1 year were 97, 03 %, 87.50 % and 96.08 %, respectively for a linear regression slope of ≥ 12 units/IEcorr.*

Conclusion. *In patients without structural heart disease with a linear regression slope of ≥ 12 units/IEcorr.*$_{1-10}$ *the positive effect of antiarrhythmic therapy persists for 1 year or more.*

Keywords. *PVC, duration of the positive effect of therapy.*

Conflict of interest: none declared.

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Introduction

Today, to choose the most effective treatment for frequent and stable premature ventricular contractions (PVC) various antiarrhythmics are tested. A patient receives therapeutic dosages of antiarrhythmic agent for 4–5 days and then the number and characteristics of premature complexes are assesses using the 24-hour Holter monitoring [1, 2]. The duration of positive effect is usually estimated using repeated 24–72 hours ECG monitoring once in 2–3 months. Lately, it was suggested to use the extrasystole index (EI) to assess the risk of life-threatening ventricular arrythmias (the risk is inversely proportional to the index) [3]. However, the use of this index for the estimation of positive effect in the absence of structural heart disease has not been described.

The objective of this study was to evaluate the positive effect duration of pharmacologic management of premature ventricular contractions (PVC) according to ventricular ectopy analysis in the absence of structural heart disease.

Materials and methods

The current study included 214 patients aged 19–45 years (mean age 33.5±0.95 years). Inclusion criteria were absence of structural heart disease, sinus rhythm, class IV–V PVC (Rayn B. classification (1984)) [1], complains of disrupted regular heart rhythm such as skipped beats or missed beats, congestive heart failure (CHF) NYHA I–II, informed consent for examination and treatment. Absence of structural heart disease was established after cardiac and extracardiac conditions, electrolyte imbalance, use of medications and/or toxic products (diuretics, oral contraceptive pills, alcohol abuse, etc.) that may have led to PVC were excluded. Other exclusion criteria were use of various stress-tests, invasive and non-invasive angiography, contrast-enhanced MRI [1].

All patients underwent 24–72-hour Holter ECG monitoring and echocardiographic examination using the Hitachi EUB-5500 machine. Left ventricular ejection fraction, the left atrial end-diastolic volume index (LAEDVI), left ventricular mass index (LVMI), the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave) calculations were described earlier [4, 5].

After 24-hour Holter monitoring all patients were administered cardioprotective therapy that included potassium, sedation, polyunsaturated fatty acids, etc. [4]. If the positive effects were not observed potentially effective pharmacologic antiarrhythmic agents for terminating PVC were selected. When choosing medications, the characteristics of PVC, prognosis, the presence of contraindications and possible adverse effects were taken into consideration [1, 2]. Class II antiarrhythmics were used first, and if they weren't effective — the patient was switched to class I or III; amiodarone was the last choice. We used metoprolol 50–100 mg/day, propranolol 80–160 mg/day, carvedilol 25–50 mg/day, alapinin 50–75 mg/day, moricizine 50–100 mg/day, etacizine 100–150 mg/day, sotalol 160–240 mg/day, propafenone 300–600 mg/day, amiodarone 600–800 mg/day. If the monotherapy didn't work, we used the combinations of these agents. Antiarrhythmic drugs were taken for 4–5 days (8–10 days for amiodarone). Any next agent was started at least 5 half-life periods after the previous one [1, 2]. Before and after the use of antiarrhythmic agents we performed 24-hour ECG monitoring and a decrease in the number of extrasystoles by 75 % or more compared with baseline as well as the elimination of paired, group extrasystoles signified a positive effect [1, 2]. To reduce the risk of ar-

rythmogenic affect of the medications we performed 24-hour ECG monitoring at least once in 3–4 days for 7–14 days, especially in patients taking class Ic antiarrhythmics [1, 2].

For all patients before and after taking each medication, after a half the period of its half-life, EI was calculated using the following formula:

$$EI = A \div B,$$

where EI is the extrasystole index (in units), A is the linear deviation (LD) of the corrected pre-ectopic interval (ms) for at least 20 ventricular extrasystoles, calculated separately for left and right VE, and B — analyzed ventricular extrasystole number (per hour) [3]. Corrected pre-ectopic interval over 20 extrasystoles exclude false positive result in the assessment of this indicator [3, 4]. Then the corrected ΔEI (ΔEIcorr.) was calculated according to the formula:

$$\Delta EIcorr = [(EIn - EI\ initial) \div EI\ initial] \div \sqrt{N},$$

where ΔEIcorr.n (in relative units) is the change of EI after each sequential intake of the medication compared with the initial data, EI initial — EI values before using the medication (initial data), EIn — half-life after the first, second, third dose of the medication, N — coefficient corresponding to the amount of dosses, i.e. after first intake of an antiarrhythmic medication this coefficient was "1" (ΔEIcorr.1), after second — "2" (ΔEIcorr.2), after third — 3 (ΔEIcorr.3). [3]. If amiodarone was chosen this coefficient corresponded to the days of imodarone use [3]. Due to high variability of VEs during the day [1,2], the determination of EI was carried out according to the data of 1–3-day electrocardiography monitoring.

The endpoint was the duration of positive antiarrhythmic effect of the drugs used. All examinations including 24-hour electrocardiography monitoring were performed at least once in 3–4 months, physical examination, and ECG — once per month. Regular control of blood pressure and heart rate were performed by patients at home.

Statistical analysis of obtained results was carried out using Student's t-test, chi-squared test, as well as standard software "Statistica", version 11.0.

Results

All patients were divided into two groups depending on the length of positive effects. In 43 (20.10 %) of patients the positive antiarrhythmic effect persisted for 1 year (mean 0.7± 0.04 years) (I group), in 80.90 % — for 1 year and more (mean 3.8± 0.08 years) (II group) ($p<0.05$). This division can be explained by the fact that in the absence of structural heart disease recovery of contractile force after the effective therapy is determined usually lasts for 1 year [1, 2, 6]. We haven't identified any statistically significant differences in sex, age, hemodynamics, body mass index, amount of ventricular extrasystoles in 24 hours between the two groups (Table 1). In 5 (20.83 %) and 22 (22.45 %) patients in groups I and II we identified 6–15 % PVCs in 24 hours of monitoring ($p>0.05$), in other patients — more than 15 %. In 6 (25.00 %) and 29 (29.59 %) patients in groups I and II we identified episodes of unstable ventricular tachycardia ($p>0.05$). In 11 (45.83 %) and 51 (52.04 %) patients in groups I and II we identified left ventricular premature beats, and in the other patients — right ventricular premature contractions ($p>0.05$), in 2(8.33 %) and 48 (48.98 %) — polymorphic, others — monomorphic PVCs ($p<0.05$).

Table 1. **Hemodynamic and clinical values in patients from groups I and II at baseline (M±m, 95 % confidence interval)**

Values \ Groups	Group I n= 24	Group II n= 98
Age, years	30.1±1.3 (22–43)	28.9±1.1 (20–41)
Body mass index, kg/m^2	22.3±0.4 (20–24)	21.9±0.1 (19–25)
LVEF, %	53.86±1.18 (46–59)	54.12±0.78 (45–61)
E/A, units	1.19±0.01 (1.12–1.15)	1.21±0.01 (1.17–1.24)
LAEDVI, ml/m^2	24.56±0.72 (17–31)	23.24±0.64 (18–29)
LVMMI, g/m^2	86.7±1.6 (74–99)	85.3±1.7 (72–101)
PVCs in 24 hours	18900±2450 (5870–30730)	19890±1970 (5980–32900)

Note. E/A — the ratio of peak velocity blood flow from left ventricular relaxation in early diastole (the E wave) to peak velocity flow in late diastole caused by atrial contraction (the A wave); LVEF — left ventricular ejection fraction; LAEDVI — left atrial end-diastolic volume index; LVMMI — left ventricular muscle mass index; PVCs — premature ventricular complexes.

Characteristics of antiarrhythmic therapy in patients from groups I and II are presented in Table 2. According to Table 2, patients in the II group used metoprolol, propranolol and carvedilol less often compared with patients from group I.

Table 2. **Antiarrhythmic therapy in group I and II patients**

Medications	Groups of patients, n= 214	
	Group I (n= 43)	Group II (n= 171)
Metoprolol	12(27.91 %)	9(5.26 %)*
Propranolol	11(25.58 %)	8(4.67 %)*
Carvedilol	12(27.91 %)	11(6.43 %)*
Alapinin	-	19(11.11 %)
Etacizine	-	35(20.47 %)
Moricizine	-	20(11.70 %)
Propafenone	-	48(28.07 %)
Sotalol	6(13.95 %)	16(9.36 %)
Amiodarone	2(4.65 %)	5(2.92 %)

Note. * — statistical significance in p< 0,05

Changes in ΔEIcorr.$_{1-10}$ in patients form groups I and II are presented in Figure 1. According to Figure 1, patients in the II group had higher values of ΔEIcorr.$_{1-10}$ starting from the second use of antiarrhythmic agent. We identified that the rise of ΔEIcorr.$_{1-10}$ in patients from the II group after the first and second use of medications was due to increase in linear deviation (LD) of the corrected pre-ectopic interval (r=0.86) t, and after the third and following doses — due to the reduction in the number of premature contractions (r=–0.84). In patients in the groups, I and II ΔEIcorr. linear regression slope was 0.03–0.13 units/ΔEIcorr.$_{1-10}$ (mean 0.08±0.01 units/ΔEIcorr.$_{1-10}$) and 0.12–0.92 units/ΔEIcorr.$_{1-10}$ (mean 0.52±0.03 units/ΔEIcorr.$_{1-10}$) ($p<0.05$). In patients without structural heart disease, the sensitivity, specificity, and positive prognostic value for antiarrhythmic therapy effects persistence for at least 1 year were 97.03%, 87.50% and 96.08%, respectively for a linear regression slope of≥12 units/IEcorr. In patients from groups I and II the reduction of the number of PVCs compared with baseline was from 76% to 92% (mean 85±2%) and from 77% to 96% (mean 86± 1%) ($p>0.05$).

In patients from the I and II groups LVEF increased from 53.86±1.18% to 55.12±1.09% ($p>0.05$) and from 54.12±0.78% to 65.56±1.07% ($p<0.05$) respectively after one year of treatment.

Positive clinical effect from using class II antiarrhythmics in patients from the I and II groups highly correlated with linear deviation of the corrected pre-ectopic interval of PVC≥11 m/s with polymorphic PVC (r=0.88); the use of class I and III agents and the combination of class II and I agents — ≤10 m/s (r=0.84).

Discussion

Treatment of ventricular arrythmias including PVC is one of the most complicated problems as it is often associated with preventing such life-threatening conditions as ventricular tachycardia and ventricular fibrillation [1, 2, 4, 5, 6]. Despite positive prognosis of patients with PVC in the absence of structural disease, according to the B.Bigger (1984) [1] classification antiarrhythmic therapy should be started in all patients who complain on feeling arrhythmic and have worsening quality of life as well as to prevent arrythmogenic cardiomyopathy and fatal arrythmias [1, 2, 6].

One study included 214 patients aged 20–43 years (mean age 31.6±0.9 years). Inclusion criteria were absence of structural heart disease, sinus rhythm, class IV–V PVC (Rayn B. classification (1984)) [1], complains of disrupted regular heart rhythm such as skipped beats or missed beats, congestive heart failure (CHF) NYHA I–II, informed consent for examination and treatment [1]. Absence of structural heart disease was established after cardiac and extracardiac conditions, electrolyte imbalance, use of medications and/or toxic products (diuretics, oral contraceptive pills, alcohol abuse, etc.) that may have led to PVC were excluded.

13% of included patients had 6–15% and the rest had more than 15% of PVCs of the total number of ventricular complexes per day. In 28.69% episodes of unstable ventricular tachycardia were registered.

Catheter ablation of the arrythmogenic area is currently the first line therapy in patients with 15% and more PVCs, in patients in whom pharmacologic therapy is ineffective or in case of any contraindica-

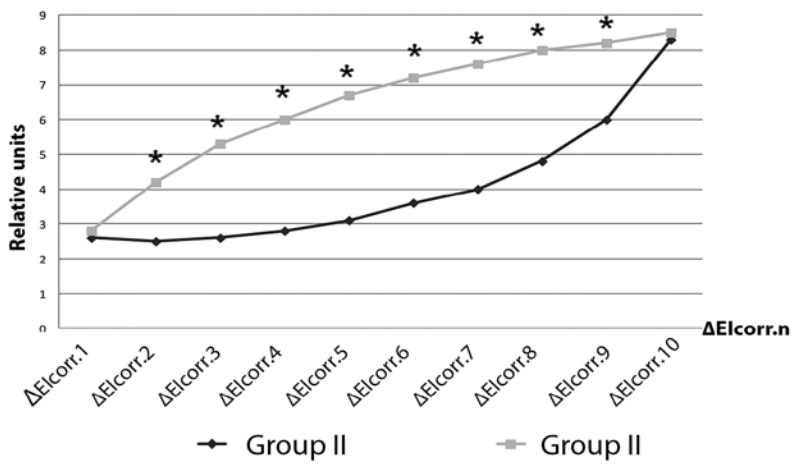

Fig. 1. ΔEIcorr. changes (means) in group I and II patients.
Note. ΔEIcorr.n (in relative units) is the change of EI after each sequential intake of the medication compared with the initial data, N — coefficient corresponding to the amount of dosses, i.e. after first intake of an antiarrhythmic medication this coefficient was "1" (ΔEIcorr.1), after second — "2" (ΔEIcorr.2), after third — 3 (ΔEIcorr.3); * — $p< 0.05$.

tions to antiarrhythmic medications [1, 2]. We based our approach to PVC therapy on this statement.

In the current study testing of antiarrhythmic therapy was performed in all patients included [1]. Class II antiarrhythmics were used first, and if they weren't effective — the patient was switched to class I or III; amiodarone was the last choice. Before and after the use of antiarrhythmic agents we performed 24-hour ECG monitoring and a decrease in the number of extrasystoles by 75 % or more compared with baseline as well as the elimination of paired, group extrasystoles signified a positive effect [1, Relative units 2]. Antiarrhythmic drugs were taken for 4–5 days (8–10 days for amiodarone). The follow-up duration ranged from 1 to 5 years. The endpoint was the duration of positive antiarrhythmic effect of the drugs used.

In 20.10 % of patients the positive antiarrhythmic effect persisted for 0.7±0.04 years, in 80.90 % — for 3.8± 0.08 years. In patients, in whom the positive effect lasted for up to 1 year, metoprolol, propranolol, sotalol were used more frequently, while class I drugs were not used at all.

Previous studies have shown that in patients with the absence of structural heart disease in whom positive effects of antiarrhythmic therapy lasted for one year or more the amount of ventricular premature beats didn't differ significantly and made up 86 % of all ventricular complexes [7]. After the most effective agent was chosen the improvement of contractile function of left ventricle lasted for 1 year and more [1, 2, 4, 5, 6].

The results of the current study were similar to the data described before.

For all patients before and after taking each medication EI was calculated as the ratio of linear deviation of the corrected pre-ectopic interval to the ventricular extrasystole number per hour [3, 4].

It was suggested to use the extrasystole index to assess the risk of life-threatening ventricular arrythmias (the risk is inversely proportional to the index) [4, 5]. The number of ventricular premature beats and EI were highly variable and, therefore, we calculated ΔEIcorr as the change of EI after each sequential intake of the medication compared with the initial data. the sensitivity, Specificity, and positive prognostic value for antiarrhythmic therapy effects persistence for at least 1 year were 97, 03 %, 87.50 % and 96.08 %, respectively for a linear regression slope of≥12 units/ IEcorr.

Previous clinical studies have shown that linear deviation of the corrected pre-ectopic interval≤10 m/s confirms the "re-entry" mechanism and/or the formation of the pathological ectopic area, and the high variability of this index — the presence of triggers [5]. Thus, after several doses of an antiarrhythmic agent in the presence of triggers, the membrane becomes less hyperpolarized that results in the rise of the corrected pre-ectopic interval and the reduction of the number of PVCs. After the depolarization, for example due to the re-entry mechanism, the fractioning of the depolarization wave occurs, then the wave splits into daughter wavelets and each of them becomes independent. This causes various corrected pre-ectopic intervals to appear of ECG. Eventually, instead of an one-way block the full blocking develops and the ectopic beats become more frequent [1, 2].

The results of our study confirm the previous data: In the presence of positive effects of antiarrhythmic agents the rise of ΔEIcorr. after the first and second use of medications was due to increase in linear deviation (LD) of the corrected pre-ectopic interval (r=0.86) and after the third and following doses — due to the reduction in the number of premature contractions (r=–0.84). Positive clinical effect from using class II antiarrhythmics in patients from the I and II groups highly correlated with linear deviation of the corrected pre-ectopic interval of PVC≥11 m/s with polymorphic PVC (r=0.88); the use of class I and III agents and the combination of class II and I agents — ≤10 m/s (r=0.84). This should be taken into consideration when choosing an antiarrhythmic agent for patients with PVC.

The persistence of the positive effect of antiarrhythmic therapy for less than a year is probably due to, first, trigger mechanisms transformation (early or late postdepolarization), for instance, to re-entry and backwards [1]. Secondly, apparently, due to reduced sensitivity to of the myocardium to antiarrhythmic agents, primarily beta-blockers, that develops because of the oxidative stress [8, 9]. Thirdly, apparently, latent myocarditis, cardiomyopathy, right ventricular arrhythmogenic dysplasia and other conditions can manifest with PVCs. In this case medications can be less effective [1, 2]. Therefore, catheter ablation is the first line treatment in these patients, especially in those with 15 % and more PVCs [1, 2, 10].

Conclusion

In patients without structural heart disease IE and ΔEIcorr. should be calculated before and after each administration of the drug when choosing the best agent. In these patients positive prognostic value for

antiarrhythmic therapy effects persistence for at least 1 year was 96.08 % for a linear regression slope of ≥ 12 units/IEcorr. One-time calculation of IE and ΔEIcorr. doesn't estimate the persistence of a positive effect of antiarrhythmic therapy. In the absence of structural heart disease the reduction of the number of PVCs doesn't determine the persistence of a positive effect of antiarrhythmic therapy.

Conflict of interest: none declared.

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Atrial fibrillation progression in middle aged patients with comorbidities

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Abstract

Objective. *To study the features of atrial fibrillation (AF) in patients with arterial hypertension (AH) and extracardiac comorbidities depending on prescribed therapy, and to access their treatment adherence.*

Materials and methods. *This observational cohort study followed up for one year 536 patients aged 45–65 years with AF (paroxysmal and persistent forms) and AH. Patients were divided into 6 groups depending on the presence of extracardiac comorbidities: 1 — AH and AF without comorbidities (n= 56) — control group; 2 — AH/AF/chronic obstructive pulmonary disease (COPD) (n= 91); 3 — AH/AF/diabetes mellitus (DM) (n= 81); 4 — AH/AF/hypothyreosis (n= 87); group 5 — AH/AF/hyperthyreosis (n=65); group 6 — AH/FP/abdominal obesity (AO) (n= 104). All the patients underwent clinical examination, anthropometry, instrumental diagnostics: electrocardiography (ECG); 24-hour Holter ECG monitoring, echocardiography (EchoCG). DNA extraction and gene polymorphisms testing were performed with polymerase chain reaction. We studied the rs1378942 and rs2200733 polymorphisms of the CSK gene of the chromosome 4q25 and rs1800795 polymorphism of the IL-6 gene of 174G/C.*

Results. *During 1-year follow-up over 50 % of patients with extracardiac diseases had an increase in the frequency of AF paroxysms by more than 20 % (DM — 76 %; COPD — 63 %; hypothyreosis — 57 %; hyperthyreosis — 64 %; AO — 58 %). The transformation into the chronic form of AF was significantly more frequent in patients with DM (p= 0.041), AO (p=0.004) and hyperthyreosis (p<0.0001). The study established statistically significant predictors of AF progres-*

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sion that interact multiplicatively: galectin-3 — the increase of which by 1 ng/l increased the risk of AF progression by 1.003 (91.0006; 1.005) (p=0.016), and matrix metalloproteinase-9 (MMP-9) — the increase of which by 1 n/ml increased the risk of AF progression by 0.16. Other predictors included: the size of left atrium (LA) (p<0.001): the increase of which by 1 cm was associated with 2.67 (91.58; 4.65) higher likelihood of AF progression, and left ventricular mass index (LVMI) — the increase of which by 1 g/m² increased the risk of AF progression by 0.9 times. When comparing the frequency of admission in patients with AF, emergency admission was significantly more frequent.

Conclusion. *Early verification of the AF progression risk factors and the development of personalized algorithms as a risk meter can be used to assess the prognosis of AF and the development of its complications in patients with AH in combination with DM, COPD, hypothyreosis, hyperthyreosis, and AO.*

Keywords: *atrial fibrillation, arterial hypertension, comorbid diseases.*

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Introduction

In recent years the prevalence of AF has increased, that cannot only be explained by higher life expectancy, heart valve disease and myocardial infarction frequencies [1]. Over 6 million people suffer from AF in Europe, and the number of patients is expected to double in the next 50 years due to increasing life expectancy of the population. AF increases the risk of stroke by 5 times and causes the occurrence of every fifth stroke [2]. Mortality, reoccurrence of stroke and disability rates are higher in patients with AF after the ischemic stroke compared with patients without AF. Accordingly, the risk of death in patients with stroke and AF is 2 times higher, and the cost of rehabilitation is 1.5 times higher [3].

The updated clinical guidelines indicate that patients with AF have increased risk of complications, especially when they are also diagnosed with AH. Up to 30–40 % of these patients are admitted to the hospital annually, 20–30 % of all strokes are associated with AF, and left ventricular dysfunction is by 20–30 % higher in among them [4]. AF develops in patients with many comorbid conditions, which can both pathogenetically contribute to the progression of AF, and independently aggravate the quality of life of patients and increase the probability of complications and sudden cardiac death. Any structural heart diseases, such as AH, chronic heart failure (CHF) can promote slow progression of structural remodeling of ventricles and atria. This process is associated with the proliferation and replacement of fibroblasts with myofibroblasts, as well as enhanced growths of connective tissue and fibrosis [5]. With the accumulation of the new data on the pathogenesis of AF, including data on the role of concomitant diseases, the division of AF to primary and idiopathic becomes questionable [6]. Thus, recent large-scale study, which included 3978 patients with AF (Euro Heart Survey), showed that only 3 % of the study participants had idiopathic or primary type of AF [7].

It has been known previously that any arrhythmia tends to progress, but due to the increasing number of patients with AF in the population and the assumption that comorbid pathology is associated with such tendency, researchers have turned their attention to this problem [8]. In recent years many studies have shown the association between AF and pulmonary pathology, COPD in particular [9]. It has been proven that DM and / or AH are also associated with the development of AF [10]. Obesity is the most frequent concomitant and leading risk factor for the development of AH that contributes to the structural and functional remodeling of the myocardium, the so-called lipotoxicity phenomenon [11].

Several large studies have investigated the effect of the rs1378942 polymorphism of the CSK gene on the course of various pathological processes [12]. Studies from Japan, East Asia, and Europe have revealed the association of the rs1378942 polymorphism of the CSK gene with the development of AH and AF [13]. The role of this polymorphism of the CSK gene in the development of AH has also been confirmed in Russian Federation [14]. In addition, the role of polymorphisms rs1378942 and rs2200733 of the CSK gene of the chromosome 4q25 in the occurrence of vascular dysfunction in patients with AO was revealed [15]. However, no studies investigated common pathogenetic causes of AF, AH and AO.

Early diagnosis of the factors associated with AF progression, prescription of additional therapy for

Scheme 1

Step 1. Prospective cohort study of 308 patients with AF and AH in combination with extracardiac comorbidities. Age – 53,2 [49,5; 58] years, n=308					
AH/AF n = 56	AH/AF/DM n = 40	AH/AF/COPD n = 47	AH/AF/ hypothyreosis n = 59	AH/AF/ hyperthyreosis n = 42	AH / FP/ AO n = 64

Clinical examination (n = 308)	ECG (n=308) 24-hour Holter ECG monitoring (n=69) Treadmill cardiac stress test (n = 39)	Structural and function assessment of cardiac function– EchoCG (n = 308)	The assessment of cardiac fibrosis and remodeling markers: MMO-9, Galectin-3, NT-proBNP, inflammation markers: IL -1, IL-6, IL-8, IL-10 (n = 308)	Blood chemistry test: lipid profile, K+, glucose GFR, CRP, fibrinogen, creatinine, urea, uric acid (n = 308)	Genetic testing: polymorphism rs1378942 of the CSK gene, rs2200733 of the 4q25 chromosome and 174G/C (rs1800795) of the IL-6 gene and complex studying of the genotype frequencies andrs2200733 and rs 1378942 polymorphisms of the CSK gene of 4q25 choromosome and 174G/C (rs1800795) of the IL-6 gene (n = 167)

Comparative analysis, n = 308

secondary prevention of the arrhythmia and correct strategy for its management can slow down the progression of AF and the development of CHF that will improve not only clinical status of patients, but also their prognosis. Despite the fact that AF occurs mostly in elderly people with various manifestations of coronary heart disease, its prevalence in young and middle-aged patients with AH is constantly increasing [16]. The discussed above positions determine the objectives of this study.

Objective

To study the features of AF progression in middle-aged patients with various comorbidities.

Materials and methods

This observational cohort study followed up for one year 536 patients aged 45–65 years with AF (paroxysmal and persistent forms) and AH in combination with extracardiac comorbidities.

The first step was prospective cohort study of 308 patients with AF and AH in combination with extracardiac comorbidities from Novosibirsk Regional Clinical Cardiology Dispensary. Patients were divided into 6 groups depending on the presence of extracardiac comorbidities: 1 — AH and AF without comorbidities (n= 56); 2 — AH/AF/ COPD (n= 47); 3 — AH/AF/ DM (n= 40); 4 — AH/AF/hypothyreosis (n= 59); group 5 — AH/AF/ hyperthyreosis (n= 42); group 6 — AH/AF/AO (n= 64) (Scheme 1).

The second step was prospective cohort paired comparative study of 238 patients with AH and extracardiac comorbidities from Novosibirsk Regional Clinical Cardiology Dispensary. Patients were divided into 6 groups: 1 — AH without extracardiac comorbidities (n= 56); 2 — AH / COPD (n= 44); 3 — AH/DM (n= 41); 4 — AH/hypothyreosis (n= 28); group 5 — AH/hyperthyreosis (n= 50); group 6 — AH/AO (n=50) (Table 1). These groups were compared by all the parameters with the groups identified at the first step (Scheme 2).

Written informed consent was waived from all the participants before the study. The study was approved by the local Ethics Committee of Novosibirsk State medical University of the Ministry of health of Russia (Protocol № 147 from "18" may 2017). During the study, we followed-up patients for 1 year in order to assess the effect of comorbidities on the AF progression, the term "AF progression" was interpreted as the process of steady development of chronic form of AF from the paroxysmal

Scheme 2

Step 2. Prospective cohort paired comparative study of 238 patients with AH and extracardiac comorbidities, age – 45–60 years, n = 546					
AH n = 52	AH/DM n = 41	AH/COPD n = 44	AH/hypothyreosis n = 28	AH/hyperthyreosis n = 23	AH/AO n = 50

AH n = 52	AH/DM n = 41	AH/ COPD n = 44	AH/ hypo-thyreosis n =28	AH/ hyper-thyreosis n = 23	AH/AO n = 50		AH/AF n = 56	AH/AF/DM n = 40	AH/AF/COPD n = 47	AH/AF/hypo-thyreosis n = 59	AH/AF/ hyper-thyreosis n = 42	AH/AF/AO n =64
age 51 [45.5; 56] years, n=238							age 53.2 [49.5; 58] years, n = 308					

Comparative analysis, n = 546

AF [9]. Patients with severe stage of concomitant extracardiac pathology, heart valve pathology, systemic, oncological, acute and chronic inflammatory diseases, coronary heart disease, chronic kidney disease (CKD) above stage 3, liver pathology with impaired function, and history of strokes were excluded from the study.

All the patients underwent clinical examination, anthropometry, instrumental diagnostics: electrocardiography (ECG); 24-hour blood pressure and Holter ECG monitoring (SCHILLER, Switzerland), echocardiography (EchoCG) in accordance with the recommendations of the American Society of Echocardiography (ASE) in M and 2D modes on the Vivid 7 apparatus (General Electric, USA). All included patients underwent: standard general clinical examination; biochemical blood test, as well as determination of NT-proBNP concentration using the NTproBNP — ELISA — Best reagent kit and galectin-3 by ELISA — Bender MedSystems GmbH, (Austria), as markers of fibrosis and myocardial remodeling. DNA extraction and gene polymorphisms testing were performed with polymerase chain reaction followed by analysis of restriction fragment length polymorphism (Sibenzyme, Russia). We studied the rs1378942 and rs2200733 polymorphisms of the CSK gene of the chromosome 4q25 and rs1800795 polymorphism of the IL-6 gene of 174G/C.

Numerical data were compared using Mann-Whitney U-test, the bias of the distributions was calculated with 95 % confidence interval. Multiple group comparisons were performed using the Kruskal Wallis test. Pairwise comparison of all studied groups with the comparison group was carried out according to Dunnett's scheme, pairwise comparison of all groups was carried out using Tukey's method, to eliminate the effect of multiple pairwise comparisons, the Benjamini-Hochberg procedure was performed. To assess the dynamics of readmission, the Kaplan-Meier curves and the logrank test were used. The level of statistical significance was set up as $p<0.05$. The lower bound of the statistical significance was set as 80 %. All statistical calculations were performed in the Rstudio program (version 0.99.879 — © 2009–2016 RStudio, Inc., USA, 250 Northern Ave, Boston, MA 02210 844–448–121, info@rstudio.com) in the R language (R Core Team (2015). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/).

Results and discussion

The assessment of the AF progression was performed by the analysis of the frequency of AF episodes over the last year. It was established that over 50 % of patients with extracardiac diseases had increased frequency of paroxysms by over 20 % (DM — 76 %; COPD — 63 %; hypothyreosis — 57 %; hyperthyreosis — 64 %; AO — 58 %), and patients without concomitant diseases had less than 20 % frequency of AF paroxysms (AF/AH — 17 %). Comparative analysis revealed that the transformation of paroxysmal AF to chronic AF, which is the indicator of arrythmia progression, in patients with AO occurred after at 5.5 (3; 7) months on average ($p= 0.004$). In patients with DM — at 4 (3, 7) months, it was also significantly faster compared with the control group ($p= 0.041$), and patients with COPD, significantly more often ($p= 0.001$) had the transformation of paroxysmal AF into persistent form. The progression of the paroxysmal AF into the chronic form in patients with hyperthyroid was noted at 5.8 months (4, 5, 11) ($p<0.001$), which is also significantly faster compared with the control group.

The regression analysis was performed in order to establish factors associated with the AF progression. Univariate and multivariable regression models were used to assess AF progression risk factors. We assessed the following parameters: the stage and functional class of CHF according to NYHA, EchoCG, biochemical markers of cardiac remodeling such as: galectin-3 and NT-proBNP, biochemical parameters: C-reactive protein (CRP), cytokines, MMP-9, uric acid, GFR, fibrinogen.

Only models with $p<0.2$ significance level were selected from the one-factor model for all the predictors. The association between variables was also assessed with Spearman's correlation coefficient in order to eliminate the effect of predictors collinearity. In absolute value numbers over 0.35 indicate the presence of a relationship between predictors. We selected the predictor with the lowest achieved level of significance from the groups of related predictors in the multivariate linear regression model in the univariate logistic regression model for one predictor. Optimal linear regression models were constructed using forward and backward selection algorithms and model minimizing criterion — the Akaike information criterion (AIC). Therefore, statistically significant predictors of AF progression were revealed: with the elevation of CHF by 1 functional class ($p=0.035$) — the risk of AF progression increased by 1.36 (91.03; 1.82) times.

Table 1. **Calculation and comparison of binary indicators between groups with electrical and medical cardioversion**

Parameter	Electrical cardioversion group n = 332 n, % [95 % CI]	Medical cardioversion group n = 214 n, % [95 % CI]	Relative risk [95 % CI]	*Fisher's exact test*
AF progression (yes/no)	64 % [58 %; 71 %]	61 % [48 %; 72 %]	1.061 [0.85; 1.33]	0.65
Admission during the year	51 % [44 %; 58 %]	28 % [16 %; 37 %]	0.651 [0.54; 0.79]	< 0.001*

CI — confidence interval, * — statistically significant parameters

When constructing a multivariate logistic regression model, the full model included covariates with correlation coefficients with absolute value less than 0.5. We established the presence of related, statistically significant predictors of AF progression that function multiplicatively. These were indicators of cardiac remodeling: galectin-3, the elevation of which by 1 ng/L increased the risk of AF progression by 1.003 (91.0006; 1.005) times (p= 0.016) and MMP-9 — the elevation of which by 1 n / ml increased the risk of AF progression by 0.16 times. Other statistically significant predictors of AF progression included LA size (p<0.001): its increase by 1 cm was associated with elevation of the AF progression by 2.67 (91.58; 4.65) times and LVMI, the increase of which by 1 g/m^2 increased the risk of AF progression by 0.9 times; as well as inflammation markers — IL-6 elevation by 1 pg/1 was associated with increase of AF risk by 0.6 times.

During the assessment of emergency hospital admissions, it was established that 51 % (44 %; 58 %) of patients were urgently admitted after electrical cardioversion and 26 % (916 %; 37 %) — after medical cardioversion, p<0.001. The relative risk was 0.651 (90.54; 0.79) (Table 1).

The second step was prospective cohort paired comparative study. This stage consisted of two substages: first — 308 patients with AH and without AF with concomitant extracardiac diseases (DM, COPD, hypothyreosis, hyperthyreosis, AO) with average age of 52 (46.5; 57) years, and second — comparative analysis of the data of 238 patients with AF, AH and extracardiac diseases with the data of 308 patients with AH with extracardiac diseases without AF).

During the assessment of AH duration, it was found that patients with AF had significantly longer AH duration compared with patients without AF, except for the group of patients with COPD. The development of AF correlated with the duration of AH (r= –0.332, p= 0.044) (Table 2).

The level of MMP-9 increased in all groups of patients with AF compared with patients without AF, the level of MMP-9 also correlated with the development and progression of AF (Figure 1).

The level of serum galectin-3 in all patients with AF was significantly higher compared with patients without AF (Figure 2).

A comparative analysis of 174G/C (rs1800795) polymorphism of the IL-6 gene in patients with AH with various concomitant diseases with and without AF revealed that patients with AF more frequently had CC genotype (Table 3).

Table 2. **Clinical indicators in patients with or without AF**

Parameters	AF and AH n= 308 Median [IQR]	AH without AH n= 238 Median [IQR]	Difference [95 % CI]	Mann–Whitney U test
Age, years	56 [53; 60]	50 [45; 56]	6 [2; 11]	0.005*
Total cholesterol, mmol/l	5.02 [4.16; 6.04]	5.85 [5; 6.95]	0.76 [0.04; 1.45]	0.034*
LDL-cholesterol, mmol/l	2.42 [2.13; 3.02]	3.45 [2.65; 4.5]	0.98 [0.33; 1.58]	0.005*
Potassium, mmol/l	4.0 [3.8; 4.2]	4.4 [4.23; 4.47]	0.3 [0.15; 0.5]	< 0.001*
GFR, ml/min	57.9 [50.32; 70.7]	78.0 [64; 90]	9 [3; 25.99]	0.014*
IL-6, pg/ml	8.4[1.48;9.35]	4.3 [0.96; 10.93]	0.3 [0.33; 1.67]	0.004*
MMP-9, ng/ml	437.0[313.25; 659.3]	362.0 [205.3; 493.1]	73 [0.33; 1.49]	0.005*
NT-proBNP, pg/ml	101.36 [94.92; 116.7]	87.99 [33.5; 134.2]	33.71 [1.48; 59.58]	0.047*
Galectin, ng/ml	52.80 [13.99; 100.33]	14.05 [7.06; 14.76]	38.04 [5.77; 57.24]	< 0.001*
Systolic blood pressure, mmHg	154 [145; 165]	168 [158.25; 178.25]	13 [4; 22]	< 0.001*
End-diastolic volume, cm	5.8 [5.3; 6.2]	5.6 [5.27; 5.73]	0.3 [0.1; 0.5]	0.062*
Left ventricular diastolic dysfunction, (E/A, ms)	1.44 [1.2;1.6]	0.6 [0.4;0.8]	0.84 [0.75;0.9]	0.003*
AH duration, years	5 [4; 7]	3 [2; 5.25]	2 [1; 3]	< 0.001*

CI — confidence interval, IQR — interquartile range, * — statistically significant parameters

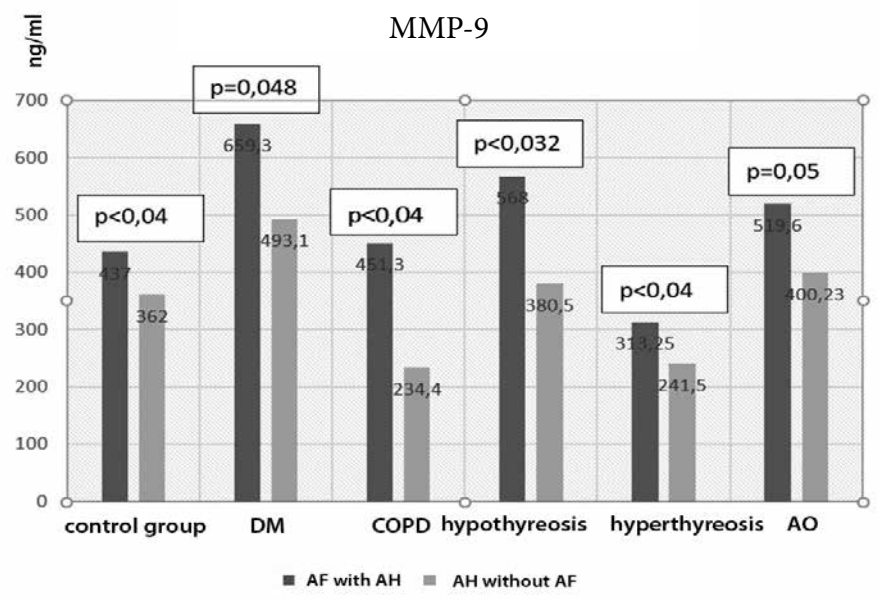

Figure 1. The level of matrix metalloproteinase-9: p — the level of significance compared with groups without AF

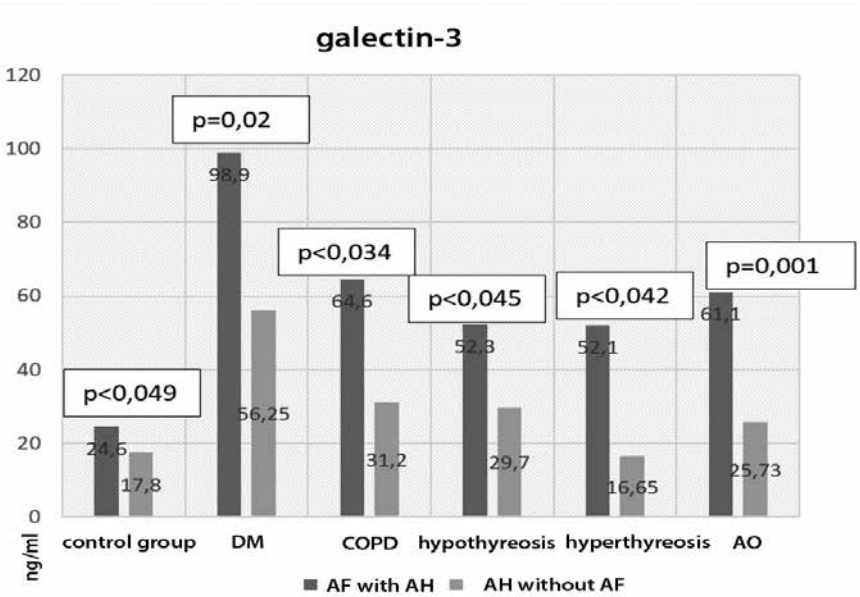

Figure 2. The level of galectin-3: p — the level of significance compared with groups without AF.

Table 3. **Genetic determinants in patients with AH and with or without AF**

Parameters	AH and AF n= 164	AH without AF n= 188	Fisher's exact test
rs2200733 polymorphism of the 4q25 chromosome CT CC	46 % [18 %; 67 %] 54 % [38 %; 87 %]	51 % [28 %; 71 %] 49 % [29 %; 60 %]	0.883
rs1378942 polymorphism of the CSK gene AA AC CC	51 [35 %; 62 %] 45 % [18 %; 47 %] 4 % [18 %; 47 %]	38 % [22 %; 47 %] 50 % [23 %; 71 %] 12 % [7 %; 26 %]	0.424
174G/C (rs1800795) polymorphism of the IL-6 gene CG CC GG	79 % [38 %; 97 %] 21 % [18 %; 35 %] 14 % [18 %; 47 %]	30 % [18 %; 57 %] 46 % [21 %; 62 %] 4 % [1 %; 7 %]	< 0.003*

* — statistically significant parameters

Table 4. **The development of complications in patients with AH and with or without AF**

Parameters	AH and AF n=308 n, % [95% CI]	AH without AF n= 238 n, % [95% CI]	RR [95% CI]	Fisher's exact test
Admission during 1-year follow-up	25, 47% [34%; 60%]	17, 94% [74%; 99%]	0.499 [0.37; 0.68]	< 0.001*
Cardioembolic strokes during 1-year follow-up	21% [12%; 33%]	6% [1%; 26%]	3.736 [0.52; 26.95]	0.073
CHF+/–	91% [80%; 96%]	89% [67%; 97%]	1.019 [0.85; 1.23]	> 0.999

CI — confidence interval, RR — relative risk, * — statistically significant parameters

A comparative analysis of cardioembolic strokes, CHF progression and all-cause emergency hospital admission during 1-year follow-up depending on the presence of AF was performed. Only emergency hospital admission differed significantly, and the incidence of cardioembolic strokes tended to increase in AF patients — 11.2% versus 1.6% in patients without AF (Table 4).

The comparative analysis of the frequency of all-cause hospital admission in patients with AH with extracardiac pathology, depending on the presence of AF during 1-year follow-up revealed that patients with AF combined with hyperthyreosis, AO and DM were admitted more frequent compared with patients without AF.

The development of personalized algorithms for the formation of risk groups for the development of complications and progression of AF in patients with AH and extracardiac diseases was performed with various statistical methods, where logistic regression model was superior to others. It was established that groups with hypothyreosis, DM and AO correlated with the progression of AF. According to Pearson correlation coefficient the functional class of CHF correlated with the progression of AF, which also correlates with total cholesterol, low density lipoproteins and rs1378942 polymorphism of the CSK gene.

In the multivariate logistic regression model, the following statistically significant predictors of AF progression were identified (corresponds to 1 unit (U) of the indicator measurement): the elevation functional class (NYHA) of CHF by 1 U increased the risk of AF progression by 25.49 (5.05; 377.32) times (p= 0.002), end-diastolic volume — by 0.13 (0.02; 0.65) times (p= 0.025), ejection fraction — by 0.87 (0.76; 0.97) times (p= 0.027), glucose — by 0.29 (0.09; 0.71) times (p= 0.017), CRP — by 0.41 (0.19; 0.74) times (p=0.009). The predictors of cardioembolic stroke included total cholesterol, the elevation of which by 1 U increased the risk of cardioembolic stroke by 0.72 [0.55; 0.92] times, and triglycerides — by 1.27 [1.02; 1.59] times. No statistically significant predictors of CHF progression were identified, although in the univariate model, statistically significant indicators included: the LA size, the enlargement of which by 1 cm increased the risk of CHF progression by 5.04 (1.80; 16.18) times, and NT-proBNP — by — 1.01 (1.00; 1.02) times.

The final result of the personalized algorithms for the formation of risk groups for the development of complications and progression of AF was tested with comparative analysis and mathematical calculation, and the key parameters of the optimal logistic regression model were: functional class (NYHA) of CHF, LVMI, LA size, end-diastolic volume and galectin-3 (Table 5).

Findings

1. The duration of AH (p= 0.001), and its combination with DM (p= 0.041) and AO (p= 0.004) were prognostically negative in patients with AH and AF.

2. The study showed the prognostic value of fibrosis and remodeling biomarker such as galectin-3 and MMP-9, as well as inflammation markers — IL-6, IL-8 and IL-10, in the AF development and progression in patients with AH and extracardiac diseases.

3. Rs1378942 polymorphism of the CSK gene and 174G / C (rs1800795) of the IL6 gene were associated with the risk of AF reoccurrence in patients with AH and DM, COPD, hyperthyreosis and AO. The increase of CC genotype was found in patients with AF during the comparative analysis of 174G / C (rs1800795) of

Table 5. **Optimal logistic regression model of the AF progression**

Predictor	RR [95% CI]	p
Optimal logistic regression model		
CHF (NYHA)	1.4 [0.93; 2.13]	0.013*
LVMI	0.99 [0.97; 1]	0.014*
Left atria size	3.07 [1.74; 5.63]	<0.001*
End-diastolic volume	7.85 [2.39; 35.88]	0.002*
Galectin-3	1.002[0.76; 1.004]	0.009*

CI — confidence interval, * — statistically significant parameters

IL-6 gene in patients with AH and various comorbidities with and without AF.

4. Personalized algorithm for the formation of risk groups for the development of complications and progression of AF in patients with AH and extracardiac diseases was developed and tested. This method is based on the determination of galectin-3, MMP-9, pro- and anti-inflammatory cytokines levels, the E / A index, LVMI, LA size assessment, and the determination of genotypes of polymorphism rs1378942 of the CSK gene and 174G / C (rs1800795) of the IL-6 gene.

Conflict of interest: none declared.

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The section contains the disclosure by all authors of possible relations with industrial and financial organizations that may lead to a conflict of interest in connection with the material presented in the manuscript. It is desirable to list the sources of funding for the work. If there is no conflict of interest, it is written: "Conflict of interest is not declared." Information on the existence of a conflict of interest should also be reflected in the Conflict of interest section at the end of the article.

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Example of design:

The study was carried out in accordance with the standards of good clinical Practice (Good Clinical Practice) and the principles of the Helsinki Declaration. The study Protocol was approved by the Ethical committees of all participating clinical centers. Prior to being included in the study, written informed consent was obtained from all participants.

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The absence of an information file or incomplete text (not containing the above items) is the basis for refusal to accept the manuscript for consideration.

IV. Manusctipt submision check-list

Since the main file of the manuscript is automatically sent to the reviewer for» blind review», it should not contain the names of the authors and institutions. The file contains only the following sections:

1. Article title
2. Summary with key words
3. List of abbreviations
4. Text
5. Acknowledgements (if any)
6. List of references
7. Tables, figures (if they can be embedded in the text of Word format).

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List of abbreviations — when compiling a list of abbreviations to the article, including text, tables and figures, only those used by the author 3 or more times are included. Usually shrink often used in manuscripts of the terms (e.g., hypertension, CHF FC) and title of clinical trials (SOLVD, TIMI, HOPE).

The first reference to an abbreviation is always accompanied by the full spelling of the abbreviated concept, and the abbreviation is indicated in brackets. For example, blood pressure (BP); heart rate (HR). Capital letters are more often used to denote abbreviations. If abbreviations are used only in tables and figures, and are not used in the text, they should not be included in the list of abbreviations, but should be given a transcript in the note to the table or figure. The summary of the article, as a separate document, is subject to the same rules as the article (abbreviations are made when they are used 3 or more times).

Abbreviations should be generally accepted and understandable to the reader, in accordance with the generally accepted norms in the scientific literature. Undesirable abbreviations that coincide in writing with others that have a different meaning.

Abbreviations in the list of abbreviations are written in alphabetical order, separated by commas, in solid text, using "dash". **Example of design:** BP-blood pressure, HR-heart rate.

Text — the text of the manuscript of the original works should be structured: Introduction, Material and methods, Results, Discussion and Conclusion. The text of reviews and lectures can be unstructured.

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However, to print in the journal (at the stage of creating a layout) graphics, diagrams and drawings are required in electronic form in the formats "MS Excel", "Adobe Illustrator", "Corel Draw", "MS PowerPoint", photos with a resolution of at least 300 dpi.

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These files are referred to as additional files. Figures should not repeat the materials of the tables.

Tables should contain the compressed, necessary data. Each table is placed at the end of the text (after the list of references) with the number, name and explanation (note, abbreviations).

The tables should clearly indicate the dimension of the indicators and the form of data (M±m; M±SD; Me; Mo; percentiles, etc.). All figures, totals and percentages should be carefully verified, and also correspond to the mention in the text. The explanatory notes are given below the table, if necessary. The footnotes must be in the following order: *, †, §, ||, ¶, #, **, †† etc.

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The bibliographic description contains the names of the authors up to three, after which, for domestic publications should indicate "et al.", for foreign — "et al." When citing articles from journals indicate in the following order the output: the name and initials of the authors, the name of the source, year, volume, number, pages (from and to). When citing articles from the collections indicate the output: name, initials, title, title of the collection, place of publication, year of publication, page (from and to).

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tient with chronic heart failure and complete left bundle branch block. Russ J Cardiol. 2011;6:4–8. Russian. Барт Б. Я., Ларина В. Н., Бродский М. С., и др. Ремоделирование сердца и прогноз больных с хронической сердечной недостаточностью при наличии полной блокады левой ножки пучка Гиса. Российский кардиологический журнал. 2011;6:4–8. doi:10.15829/1560-4071-2011-6-4-8.

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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The author prepares the following documents to upload the manuscript to the site:

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3. The manuscript must pass the primary selection: the Editorial Board has the right to refuse publication or send comments to the article, which must be corrected by the Author before reviewing.

— checking the completeness of the manuscript: if you do not comply with the requirements of the Rules for the authors to complete the manuscript or its design, the Editors have the right to refuse to publish or in writing to require to send the missing materials or to correct the version already downloaded to the site.

— Manuscripts are checked in the "Antiplagiat" system. The originality of the manuscript should be at least 75 %. We expect manuscripts submitted for publication to be written in an original style that involves new thinking without the use of previously published text. Manuscript with originality below 75 % shall not be admissible.

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7. If the reviewer makes a conclusion about the possibility of publication of the article and does not make significant corrections, the article is given to the expert on statistics and after a positive report is accepted for further work.

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X. After the publication in the journal

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3. We expect the authors of the articles to actively make efforts to bring the results of their research to the public, namely: to have a personal page on the Internet (personal page), to monitor and update your profile ORCID and RecsearcherID, to involve colleagues in their work through social networks.

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XIV. Journal subscription

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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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