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Association of iron deficiency with atrial fibrillation recurrence after pharmacological cardioversion

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Aim. This study aims to assess the association between iron deficiency (ID) and recurrences of atrial fibrillation (AF) in patients after pharmacological cardioversion with amiodarone within 12 months.

Material and methods. The open-label, prospective, single-center study included 198 patients with non-valvular paroxysmal AF after successful pharmacological cardioversion with amiodarone. Group I included 116 patients with ID, and group II — 82 patients with normal iron status. The primary end-point of the study was the development of symptomatic AF recurrences within 12 months after the cardioversion which was estimated by the Kaplan-Meier method. The differences were considered statistically significant if p-value was <0,05.

Results. Absolute ID was found in patients of group I; anemia was revealed in 85,3% of the patients. The groups did not differ in basic clinical and demographical parameters, concomitant diseases and drug therapy. Along with that, the I group patients were older (the median was 73 (64,8-79) years old and 69 (63-75) years old, respectively, p=0,008), and their left ventricular mass was larger (the median was 145 (115-176) g and 132,5 (118,2-145) g, respectively, p=0,004). The sinus rhythm restoration in group I required less dose of amiodarone (the median was 450 (300-600) mg and 1000 (600-1200) mg, respectively, p<0,001) and less time from the start of the drug administration to the rhythm restoration (the median was 7 (3-10) and 12 (9-18) hours, respectively, p<0,001). During the 12-month follow-up period, 49 (42,2%) patients in group I and 16 (19,5%) patients in group II developed AF recurrences (p=0,0008), hazard ratio 2,64 (95% confidence interval: 1,5-4,65) (p=0,0003).

Conclusion. ID is associated with the increase of the number of symptomatic AF recurrences in patients after pharmacological cardioversion with amiodarone within 12 months.

Keywords: iron deficiency, paroxysmal atrial fibrillation, pharmacological cardioversion, amiodarone.

Relationships and Activities: none.

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Key messages

- Iron deficiency (ID) is associated with increased risk of atrial fibrillation (AF) recurrences within 12 months after pharmacological cardioversion with amiodarone.
- In pharmacological cardioversion with amiodarone, the sinus rhythm restores faster in patients with paroxysmal AF and ID.
- The sinus rhythm restoration in patients with paroxysmal AF and ID requires less dose of amiodarone.

Atrial fibrillation (AF) is one of the most common forms of cardiac rhythm disturbance, reaching 2% in population [1, 2]. Prognostically unfavorable consequences of AF include cardioembolic complications which are frequently associated with AF paroxysms [2, 3]. To date, the main risk factors for the development of AF have been established: they include arterial hypertension, ischemic heart disease, diabetes mellitus, valvular heart defects, chronic heart failure (CHF), the disorders of thyroid gland function, age and other factors [2]. Cardiomyocyte apoptosis and myocardial fibrosis, the disturbance of the regulation of Na^+ and Ca^{2+} ions in cardiomyocytes, myocardial electrical remodeling, the imbalance of cardiac autonomic regulation and inflammation play an important role [4, 5]. During last years the possible role of iron deficiency (ID) in the development of AF is discussed, however, this problem is more often considered in the context of anemia and CHF [6]. Currently, it is well known about the worsening of the forecast in patients with CHF with the presence of ID [7-9]. A possible mutual effect of CHF and ID with participation of ID is probably associated with inflammation accompanying both HCF and AF, with the increased level of hepcidin, the decreased level of ferroportin, the reduced absorption of Fe^{2+} ions in gastrointestinal tract, the disorder of erythropoesis, the development of functional and absolute ID leading to anemia which, in turn, aggravates the course of CHF and AF [6, 10]. A direct role of ID in the development and course of AF, and in influencing the restoration and maintenance of sinus rhythm remains unclear. Taking into account a wide prevalence of ID in population and the severity of AF complications, the investigation of the features of pharmacological cardioversion results and the frequency of recurrent AF paroxysms seems very interesting.

The study aims to assess the association of ID with the development of AF recurrence in patients after pharmacological cardioversion with amiodarone during 12 months.

Material and methods

The open-label, observational, prospective, single-center study included 198 patients (the median age was 71 (63,2-77) years), of them 120 (60,6%) men and 78 (39,4%) women, with paroxysmal form of AF, sequentially hospitalized to the Department of Cardiology in the Kazan Medical-Sanitary Unit in the period from 2019 to 2021 for the paroxysm development. AF was identified using the results of electrocardiography (ECG) in accordance with the current recommendations of the Ministry of Health of Russia (2020) [2]. The criteria of inclusion into the study: age >18 years, the presence of paroxysmal form of non-valvular AF, the duration of AF paroxysm not more than 48 hours at the moment of hospitalization, successful pharmacological cardioversion with amiodarone, a signed informed consent. The study does not include patients with hemoglobin level <90 g/l; valvular heart disease; hypertrophic and dilated cardiomyopathies; patients who suffered acute coronary syndrome within 1 month; clinically significant bleedings accompanied by a fall of hemoglobin level within last 6 months; stroke; patients with an active oncological disease; B_{12}-deficiency and other anemias excepting iron deficiency; patients who have no possibility to be examined during 12 months. The exclusion criteria: the development of a serious cardiovascular event in a patient (cardiovascular death, non-fatal myocardial infarction (MI), non-fatal stroke), the withdrawal of informed consent by a patient.

The anamnestic data from all the patients, including the presence of the AF symptoms at the moment of the examination and their duration, the past and concomitant diseases, taking of medications were collected; physical examination, ECG, transthoracic echocardiography (EchoCG), clinical and biochemical analysis of blood were performed. ID was identified in a decrease in the level of plasma ferritin <100 μg/l (absolute ID) or 100-299 μg/l in transferrin saturation coefficient <20% (relative ID). The reduced hemoglobin level <130 g/l in men and <120 g/l in women was estimated as a diagnostic sign of anemia according to the criteria of World Health Organization. In accordance with iron status, the patients were divided into the group of ID or the group with normal iron level.

The sinus rhythm restoration was performed by intravenous administration of amiodarone at the rate of 5 μg/kg, and if necessary, the daily dose could be up to 15 μg/kg. The dose of amiodarone and the time from the start of its administration to the sinus rhythm restoration were registered. According to the indications and current recommendations, patients were given recommendations on lifestyle modification and prescribed the necessary drug therapy. Iron sulfate drugs were prescribed to patients with identified ID.

The follow-up period was 12 months. After cardioversion, the patients visited doctors monthly on a planned basis. During each visit ECG was recorded, drug therapy was monitored and, if necessary, corrected. During entire follow-up period, the cases of the development of the symptomatic AF recurrences and adverse cardiovascular complications (cardiovascular death, non-fatal stroke, hospitalization for CHF decompensation) were registered. AF recurrences developed during the follow-up period were treated with amiodarone. All the

Table 1

Clinical and demographic characteristics of patients

Parameter	Group 1, n=116	Group 2, n=82	p
Age, years (Me [Q1; Q3])	73 (64,8-79)	69 (63-75)	0,008
Gender			0,185
Women, n (%)	75 (64,7)	45 (54,9)	
Men, n (%)	41 (35,3)	37 (45,1)	
The first time identified AF, n (%)	58 (50)	36 (43,9)	0,118
AF anamnesis <1 year, n (%)	15 (12,9)	14 (17,1)	0,450
AF anamnesis >1 year, n (%)	43 (37,1)	33 (40,2)	0,762
BMI, kg/m^2 (Me [Q1; Q3])	26,0 (24,0-27,9)	26,5 (24,5-28,9)	0,318
SAP, mm Hg (Me [Q1; Q3])	140 (130-150)	138,5 (120-145)	0,305
DAP, mm Hg (Me [Q1; Q3])	80 (80-90)	80 (80-90)	0,844
AH, n (%)	116 (100)	82 (100)	–
IHD, n (%)	36 (43,9)	48 (41,4)	0,771
MI, n (%)	13 (11,2)	18 (21,9)	0,065
CHF, n (%)	75 (64,7)	53 (64,6)	0,807
FC I, n (%)	9 (12,0)	8 (15,1)	0,808
FC II, n (%)	64 (85,3)	42 (79,2)	0,509
FC III, n (%)	2 (2,7)	3 (5,7)	0,691
FC IV, n (%)	0	0	–
DM, n (%)	47 (40,5)	30 (36,6)	0,658
Stroke, n (%)	8 (6,9)	0 (0)	0,022
COPD, n (%)	8 (6,9)	1 (1,2)	0,084
Hypothyroidism, n (%)	12 (10,3)	9 (11)	0,927

Abbreviations: AP — arterial hypertension, DAP — diastolic arterial pressure, IHD — ischemic heart disease, MI — myocardial infarction, BMI — body mass index, SAP — systolic arterial pressure, DM — diabetes mellitus, FC — functional class, AF — atrial fibrillation, COPD — chronic obstructive pulmonary disease, CHF — chronic heart failure.

patients completed the study. The primary endpoint of the study was the development of AF recurrence during 12 months.

Statistical analysis was performed using the Statistica 13.3 (StatSoft. Inc) program. The quantitative parameters were evaluated for compliance with the normal distribution using the Shapiro-Wilk criterion. In normal distribution, the data obtained are presented in the form of arithmetic averages and their standard deviations ($M\pm\sigma$). In the distribution different from normal the results were described using the median values, 25% and 75% quartiles (Me [Q1; Q3]). in normal distribution, the mean values were compared using the Student`s t-criterion, and in the cases with the absence of normal distribution, the Mann-Whitney U test was used. The statistical significance of differences in quantitative indicators with abnormal distribution was evaluated using the Kraskel-Wallis criterion. The relationship between quantitative indicators having a normal distribution was determined using the Pearson correlation coefficient, and in the absence of a normal distribution — using the Spearman's rank correlation. The nominal data were compared using Pearson's χ^2 criterion with the Yates correction or the Fisher's exact criterion. The development of AF recurrences in the investigated groups was assessed by the Kaplan-Meier method and the Cox proportional hazards model, and the likelihood-ratio test was used for comparison. The differences between parameters were considered statistically significant if the value of $p<0,05$.

The study protocol was approved by the Local Ethics Committee of Kazan State Medical University.

Results

According to the results of identification of the ID presence, the patients were divided into 2 groups. The group 1 included 116 patients with ID, of them 41 (35,3%) men and 75 (64,7%) women; the group 2 included 82 patients with normal iron status, of them

Table 2

Results of patients` blood analysis

Parameter	Group 1, n=116 (Me [Q1; Q3])	Group 2, n=82 (Me [Q1; Q3])	p
White blood cell count (×10^9/l)	7 (5,8-8,3)	7 (6,1-8,3)	0,702
Platelet count (×10^9/l)	270 (212,5-312)	267 (203,2-300,5)	0,404
Red blood cell count (×10^{12}/l)	3,9 (3,6-4,3)	4,6 (4,3-5,2)	<0,0001
Hemoglobin, g/l	107 (99,8-115)	137 (130-143,8)	<0,0001
Hematocrit, %	33 (30,6-35,4)	42 (39,9-44)	<0,0001
TIBC, µmol/l	101 (100,2-101,8)	54,3 (48,7-57,9)	<0,0001
Ferritin, ng/ml	6,6 (5,8-7,3)	57,5 (46-74,3)	<0,0001
Transferrin, g/l	8 (7,9-8,1)	3,3 (2,8-3,5)	<0,0001
TSC, %	8,2 (7,6-8,9)	37,3 (31,7-41,6)	<0,0001
NT-proBNP, pg/ml	284,0 (145,0-497,5)	258,0 (136,0-507,5)	0,737
Glucose, mmol/l	6,4 (5,3-7,9)	6,3 (5,3-7,7)	0,907
Creatinine, µmol/l	68,4 (61,0-79,8)	75,6 (61,2-84,1)	0,1574
Urea, mmol/l	5,8 (4,8-7,0)	6,4 (5,2-7,4)	0,035
Potassium, mmol/l	4,1 (4,0-4,4)	4,2 (4,0-4,4)	0,397
TSH, mU/l	1,4 (0,8-3,0)	2,0 (0,9-3,1)	0,143

Abbreviations: TSC — transferrin saturation coefficient, TIBC — total iron-binding capacity, TSH — thyroid stimulating hormone, NT-proBNP — N-terminal pro-brain natriuretic peptide.

Table 3

EchoCG data

Parameter	Group 1, n=116	Group 2, n=82	p
LVM, g (Me [Q1; Q3])	145 (115-176)	132,5 (118,2-145)	0,004
LA, ml (Me [Q1; Q3])	72,5 (65-89)	72 (62,2-77)	0,103
EF, % (Me [Q1; Q3])	58 (56-61)	58,5 (55-61)	0,999
EDS, cm (M±σ)	5,0±0,5	5,0±0,4	0,878
ESS, cm (Me [Q1; Q3])	3,3 (3,2-3,7)	3,3 (3,1-3,6)	0,475
SPAP, mm Hg (Me [Q1; Q3])	32,5 (28-40)	31,5 (28-37)	0,143
Diastolic dysfunction, n (%)	79 (68,1)	48 (58,5)	0,179

Abbreviations: EDS — end-diastolic size, ESS — end-systolic syze, LA — left atrium, LVM — left ventricular mass, SPAP — systolic pulmonary artery pressure, EF — ejection fraction.

37 (45,1%) men and 45 (54,9%) women. According to clinical and demographic characteristics, both groups were comparable to each other, and at the same time the patients with ID were older (the median age was 73 (64,8-79) years and 69 (63-75) years, respectively, p=0,008). There were no differences in gender, in the frequency of the first time identified AF and various periods of AF identification, in body mass index, arterial pressure level and the frequency of most common concomitant diseases. The prevalence of arterial hypertension, ischemic heart disease, past MI and stroke, CHF, diabetes mellitus, chronic obstructive pulmonary disease was estimated. 8 (6,9%) patients of the group 1 earlier suffered a stroke, and in the group 2 there were no patients with a stroke in the anamnesis (p=0,022). 12 (10,3%) patients of the group 1 and 9 (11%, p=0,927) patients of the group 2 had hypothyroidism (Table 1).

Before hospitalization, 38 (32,8%) patients of the group 1 and 37 (45,1%) patients of the group 2 (p=0,106) received direct oral anticoagulants. None of the patients included into the study received warfarin. There were no differences in the frequency of use of most other classes of drugs, except for blockers of the renin-angiotensin-aldosterone system and β-blockers. The group 1 patients less often received angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers — 71 (61,2%) and 72 (87,8%) patients, respectively (p<0,001). The group 1 patients also less often received and β-blockers — 21 (18,1%) patients vs 29 (35,4%) patients of the group 2 (p=0,030).

Table 4

Drug therapy in patient groups

Drugs	Group 1, n=116, n (%)	Group 2, n=82, n (%)	p
DOACs	116 (100)	82 (100)	–
ACEi/ARBs	116 (100)	82 (100)	–
β-blockers	88 (75,9)	67 (81,7)	0,420
CAs	12 (10,3)	10 (12,2)	0,859
MCRAs	1 (0,9)	0 (0)	0,862
Statins	42 (36,2)	35 (42,7)	0,440
Nitrates	21 (18,1)	13 (15,9)	0,707
L-thyroxine	12 (10,3)	9 (11)	0,927
Hypoglycemic drugs	50 (43,1)	29 (35,4)	0,344
Bronchodilators	7 (6,1)	1 (1,2)	0,185

Abbreviations: CAs — calcium antagonists, MCRAs — mineralocorticoid receptor antagonists, ARBs — angiotensin II receptor blockers, ACEi — angiotensin-converting enzyme inhibitors, DOACs — direct oral anticoagulants.

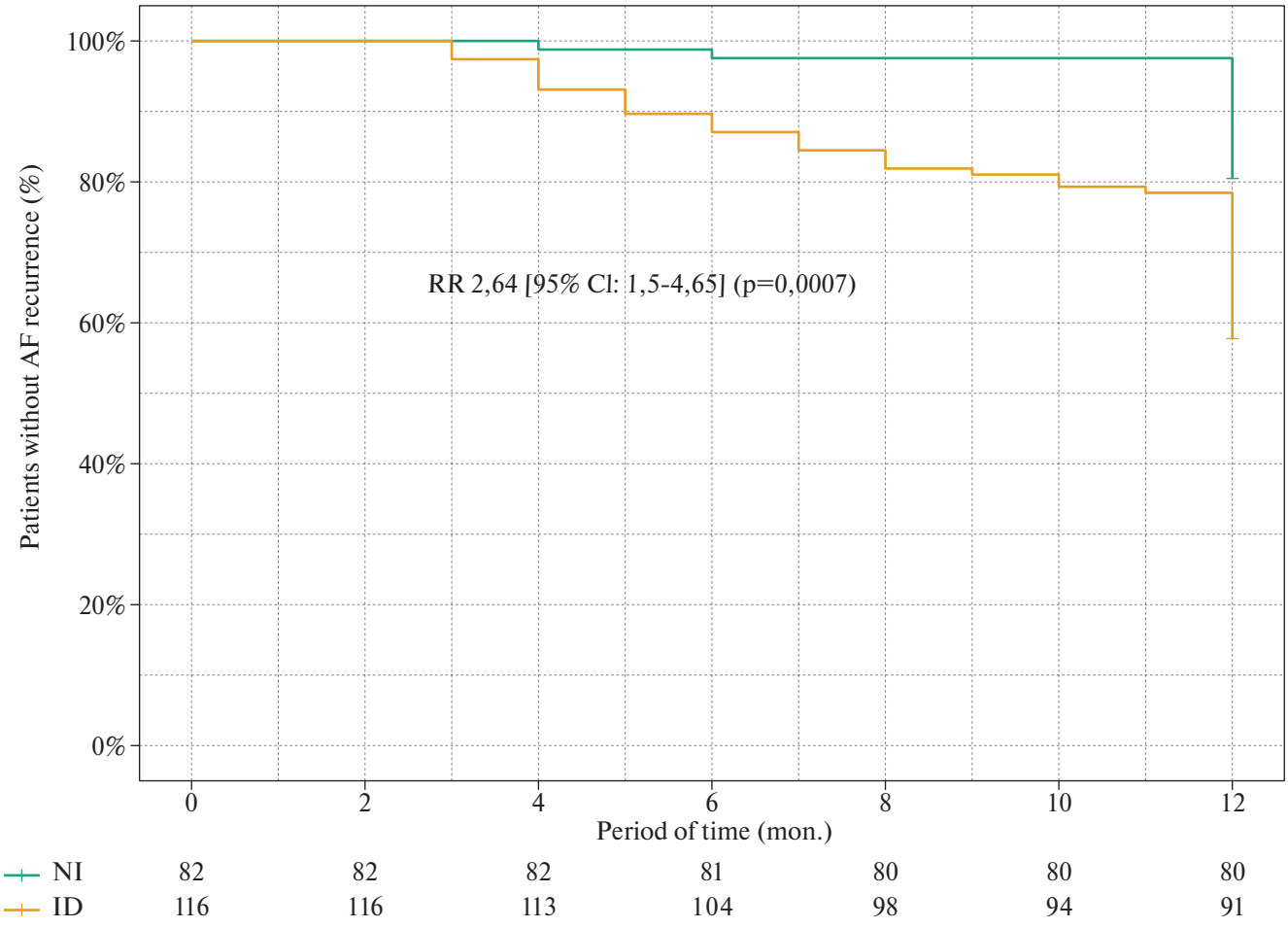

Figure 1. Development of AF recurrences in the patient group 1 and 2.
Abbreviations: ID — iron deficiency (group 1), CI — confidence interval, NI — normal iron level (group 2), RR — risk ratio, AF — atrial fibrillation.

The analyses of blood demonstrated the presence of absolute ID in almost all patients of the group 1 as well as the lower median values of red blood cell count, the level of hemoglobin, hematocrit, plasma ferritin and transferrin, transferrin saturation coefficient and higher total iron-binding

capacity (Table 2). The signs of mild anemia were found in 99 (85,3%) patients of this group. None of the group 2 patients had anemia. But the group 2 had a higher median of the plasma urea level compared to the group 1 (6,4 (5,2-7,4) and 5,8 (4,8-7,0) mmol/l), respectively, p=0,035). White blood cell count and platelet count, the levels of N-terminal pro-brain natriuretic peptide, glucose, creatinine, potassium and thyroid stimulating hormone did not differ between the groups.

A larger mass of left ventricular myocardium (LVM) was found in the patients of the group 1, using EchoCg performed at hospitalization. The median of LVM in the group 1 was 145 (115-176) g, and in the group 2 — 132,5 (118,2-145) g (p=0,004). The groups did not differ in the indicators of the left ventricular volume, end-diastolic and end-systolic sizes of the left ventricle, left ventricular ejection fraction, systolic pulmonary artery pressure and in the frequency of the occurrence of left ventricular dysfunction (Table 3).

The results of pharmacological cardioversion showed that to restore sinus rhythm, the patients of the group 1 required a significantly less dose of amiodarone (the medians of the doses were 450 (300-600) mg and 1000 (600-1200) mg, respectively, p<0,001) and less time from the start of amiodarone administration to the cessation of AF paroxysm compared to the group 2 (the medians of time were 7 (3-10) and 12 (9-18) h, respectively, p<0,001). After the cardioversion performed, all the patients received direct oral anticoagulants, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers; 88 (75,9%) patients in the group 1 and 67 (81,7%, p=0,420) patients in the group 2 received β-blockers. Antiarrhythmic drugs of I, III and IV classes did not use, except for amiodarone to stop AF recurrences. Besides, some patients receive calcium antagonists, mineralocorticoid receptor antagonists, statins, nitrates, bronchodilators, L-thyroxine, hypoglycemic and other medications (the main classes of medications prescribed to the patients in accordance with an individual clinical situation are shown in Table 4).

During 12-month follow-up period, symptomatic recurrences of AF were recorded in 49 (42,2%) patients in the group 1 and in 16 (19,5%) patients in the group 2 (p=0,0008). The risk ratio of the development of AF paroxysms in the patients with ID was 2,64 (95% confidence interval: 1,5-4,65) (p=0,0003). The results of the Kaplan-Meier analysis are shown in Figure 1. Taking into account the differences between the groups of the patients in age and past stroke, we performed the Cox regression analysis with inclusion of age and stroke in anamnesis as correction co-variants. In view of these corrections, a relative risk of the development of AF recurrences in the patients with ID was 3,08 (95% confidence interval: 1,74-5,47) times (p<0,0001). For the follow-up period, there have been no cases of hospitalization for decompensation of CHF, cardiovascular death, non-fatal MI or non-fatal stroke.

Discussion

To date, quite a large amount of information has been accumulated concerning the negative mutual influence of AF and CHF on each other development and course, that forms as though a vicious circle [6]. The effect of CHF on the development of AF paroxysms after cardioversion in patients with ID would have been assumed. In our study, CHF was identified in almost 65% of patients but there were no differences in the frequency of its occurrence in both groups. Both groups did not differ between each other in the main characteristics, except for those parameters which are determined by the presence of ID and its symptoms. In 85,3% of the patients in the group 1 anemia as a result of ID was revealed, that naturally affected the decrease in the values of red blood cell count, and the levels of hemoglobin and hematocrit in clinical analysis of blood. According to existing data, the prevalence of ID increases with age [2], and in our study the patients of the group 1 were older than in the group 2. The review of Sutil-Vega M, et al. (2019) provided the data on a larger LVM in patients with ID [11]. The similar data were obtained in EchoCG performed to the patients of the group 1. In turn, the lower level of urea we revealed in the patients with ID requires further special investigation of the kidney function in patients with different iron status. Thus, we may say about sufficient comparability of both groups between each other for most parameters which are not caused by the wide prevalence of anemia in the group 1. A key distinguishing factor was the presence or absence of ID. ID was associated with the requirement of a less dose of amiodarone and less time needed for the sinus rhythm restoration in pharmacological cardioversion. The obtained results indicate the necessity of further investigation of the influence of ID on the effectiveness of antiarrhythmic therapy. The drug therapy received by the patients after cardioversion does not differ between both investigated groups. 12-month follow-up for the patients showed a great difference in the development of AF recurrences. According to the results of our study, ID is associated with the increased frequency in AF recurrences more than 2,6 times, increasing the risk of their development during 1 years after cardioversion. Currently, there is no certain explanation of the relationship between ID and amiodarone

influence on the sinus rhythm restoration and with further development of AF recurrences we revealed. To some extent, the obtained results can be determined by the influence of ID on the decrease in the production of adenosine triphosphate, the impairment of the control of cellular Ca^{2+}, the development of mitochondrial dysfunction and damage to mitochondrial DNA, oxidative and nitrosative stress, inflammation, autonomic dysfunction, the acceleration of cardiomyocyte apoptosis and myocardial remodeling [12, 13]. It is believed that the dispersion of the P wave of the electrocardiogram can be considered as a simple and reliable marker of the development of AF paroxysms [14]. Simsek H, et al. (2010) showed the relationship between ID with increase in P wave dispersion and myocardial function disorder, that may contribute to the development of AF paroxysms [15]. Thus, a number of changes in cardiomyocytes, caused by ID, may affect both the results of cardioversion and development of AF recurrences.

A certain limitation of our study is a small number of included patients and the assessment of the presence of ID only in the inclusion of patients into the study. In addition, in the study antiarrhythmic drugs of I, III and IV classes were not used for long-term therapy.

Conclusion

The results we obtained indicate the association of ID with decreased ability to maintain sinus rhythm and increased number of symptomatic AF recurrences in patients within 12 months after pharmacological cardioversion with amiodarone. To determine the role of ID as a prognostic factor of the effectiveness of cardioversion and development of AF paroxysms, further investigations on a larger group of patients are needed. New data may influence the existing approaches to the management of patients with AF.

According to the results of open-label, observational, prospective study, ID is associated with the increased frequency of AF recurrences during 1 year after pharmacological cardioversion with amiodarone.

Pharmacological cardioversion in patients with AF paroxysm and ID requires less doses of amiodarone and less time for sinus rhythm restoration.

Relationships and Activities: none.

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