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An exploratory study of predictors of late arrhythmia recurrences in patients with persistent atrial fibrillation after cardioversion

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Introduction. The existing guidelines do not contain a clear algorithm for predicting the late recurrences of atrial fibrillation (AFib).

Objectives. We have studied the predictors of late recurrence of arrhythmia in patients with persistent AFib after the restoration of sinus rhythm (SR).

Research methods. A prospective single-center study included 120 hospitalized patients with persistent AFib who underwent successful cardioversion. The recurrence of AFib was assessed in the early period after cardioversion by recording 12-channel ECG, Holter ECG monitoring and event ECG monitoring. After a nine-month period follow-up visit was performed. Baseline demographic, clinical-functional features and comorbidities were compared in group with (n = 87) and without (n = 33) late recurrences of Afib.

Results. There were no differences in demographic, anthropometric data and comorbidities. Patients with late recurrence of AFib had lower heart rate (HR) after SR recovery ($p < 0.001$). Early recurrences of AFib were found in 43 (49.4%) patients with late recurrences of arrhythmia and only in two (6.0%) without late recurrences ($p < 0.001$). Patients with late recurrences of arrhythmia had a lower average daily HR ($p < 0.001$), higher number of single atrial extrasystoles ($p = 0.001$), atrial pairs and runs ($p = 0.01$) recorded by Holter ECG monitoring.

Conclusions. Late recurrences of arrhythmia during the nine-month follow-up period were reported in 72.5% of patients. Groups of patients with and without late recurrence of arrhythmia had significant differences in the incidence of early recurrences, mean HR on SR, and the presence of atrial extrasystoles after rhythm recovery.

Keywords: persistent atrial fibrillation, atrial flutter, recurrence, predictors.

Пошукове дослідження предикторів пізніх рецидивів аритмії у пацієнтів з персистуючою фібриляцією передсердь після кардіоверсії

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Існуючі рекомендації не містять алгоритму прогнозування пізніх рецидивів фібриляції передсердь (ФП) після кардіоверсії.

Мета дослідження – вивчити предиктори пізніх рецидивів аритмії у пацієнтів із персистентною ФП після кардіоверсії.

Матеріал і методи дослідження. До дослідження включили 120 госпіталізованих пацієнтів із персистентною ФП, яким провели успішну кардіоверсію. Наявність рецидивів ФП оцінювали в ранньому періоді шляхом реєстрації 12-канальної електрокардіограми (ЕКГ), холтерівського моніторування ЕКГ (ХМ ЕКГ) та подальшого подійного моніторингу ЕКГ протягом тижня після ХМ ЕКГ, а також після 9-місячного періоду спостереження. Демографічні, клініко-функціональні особливості, супутню патологію порівнювали у групах пацієнтів з (n=87) і без (n=33) пізніх рецидивів ФП.

Результати. У порівнюваних групах не виявлено відмінностей щодо демографічних, антропометричних даних, супутніх хвороб. У пацієнтів з пізніми рецидивами ФП спостерігали нижчі показники частоти серцевих скорочень (ЧСС) після відновлення синусового ритму (p<0,001), нижча середньодобова ЧСС (p<0,001), більша кількість поодиноких передсердних екстрасистол (p=0,001), пар і пробіжок (p=0,04) за даними ХМ ЕКГ, проведеного в госпітальному періоді. Ранні рецидиви ФП було виявлено у 43 (49,4%) пацієнтів із пізніми рецидивами аритмії і у 2 (6,0%) без пізніх рецидивів аритмії (p<0,001).

Висновки. Пізні рецидиви аритмії протягом 9-місячного періоду спостереження після кардіоверсії зареєстровали у 72,5% пацієнтів. Групи пацієнтів із пізніми рецидивами аритмії та без них мали відмінності щодо частоти виникнення ранніх рецидивів, показника середньої ЧСС на синусовому ритмі, а також наявності передсердних порушень ритму після кардіоверсії.

Ключові слова: персистентна фібриляція передсердь, тріпотіння передсердь, рецидив, предиктори.

Introduction

Recent studies show high prevalence of arrhythmia early recurrences after pharmacological or electrical cardioversion of persistent atrial fibrillation and flutter (AFib/AFl) [1]. The likelihood of early recurrences in more than 40% of cases requires considering preventive antiarrhythmic therapy after cardioversion. Yet, evaluation of its necessity and optimal duration depends on probability of late recurrences of arrhythmia after restoration of sinus rhythm [2]. Independent on clinical symptoms, AFib/AFl is associated with potential danger of thromboembolic complications and heart failure [3]. Therefore, it is especially important to establish predictors of late recurrences of AFib/AFl. During recent years this issue has been extensively studied in patients with paroxysmal AFib after catheter ablation [4]. At the same time, attention to the predictors of Afib/AFl recurrences is now mostly related to the issue of asymptomatic arrhythmias, taking into account the diagnostic value of long-term ECG monitoring [5]. The aim of the research was to study the possible predictors of arrhythmia late recurrences in patients with persistent AFib/AFl after restoration of sinus rhythm.

Materials and methods

A single-centre study included 120 adult patients admitted to hospital with persistent AFib/AFl. The patients were recruited into the study after successful pharmacological or electrical cardioversion. The exclusion criteria were acute coronary syndrome, early postoperative AFib/AFl, relevant valvular disease, left atrial enlargement > 50 mm, left ventricular ejection fraction ≤ 40 %, permanent pacemaker, concomitant cancer, significant thyroid disease, chronic obstructive pulmonary disease, renal and/or liver failure.

Among patients recruited into the study there were 41 females (34.2%) and 79 males (65.8%) aged 26-81 years (median – 58 years). Arterial hypertension was diagnosed in 99 (82.5 %) patients, ischemic heart disease was found in 51 (43.3 %) patients, previous history of myocardial infarction – in 10 (9.2%). Previous cerebrovascular events were registered in 10 (8.3 %) and type 2 diabetes was diagnosed in 20 (15.0 %) patients, 29 (25.0 %) patients were current smokers. Demographic and anthropometric data, information about comorbidities were collected CHA_2DS_2-VASc score was calculated in all patients.

Before and after cardioversion all patients received anticoagulation therapy according to the current guidelines, as well as antiarrhythmic drugs for the purpose of restoration and maintenance of sinus rhythm.

Assessment of early recurrences of AFib/AFl was performed with 12-lead electrocardiogram (ECG), Holter ECG monitoring and event monitoring. 24-hour Holter ECG monitoring was performed three days after cardioversion, event ECG monitoring - during next seven days after Holter ECG recording. Patients undergoing event ECG monitoring were trained for its usage in case of arrhythmia symptoms appearance. In addition, patients performed ECG recordings by means of event recorders two times a day on a regular basis. Documented arrhythmia episodes with corresponding ECG signs registered by Holter or event monitoring lasting more than 30 seconds were considered as recurrences of AFib/AFl.

In total, 40 patients (33.3%) experienced early recurrence of AFib/AFl after cardioversion, while 80 (66.7%) patients didn't have registered episodes of recurrent arrhythmia.

All patients received antithrombotic and antiarrhythmic drugs after cardioversion according to the current recommendations. Participants of the study were instructed to perform out-patient 12-leads ECG recording in case of arrhythmia symptoms recurrence.

After nine-months follow-up period 12-lead ECG, 24-hour Holter monitoring and/or seven days event ECG monitoring were performed. Late recurrences of AFib/AFl were registered in 87 (72.5%) patients. In 65 (54.2%) patients AFib/AFl paroxysms were symptomatic, 22 (18/3%) participants didn't have any symptoms of arrhythmia. Among 87 patients with late recurrences, in 64 (73.5%) cases late recurrences of AFib/AFl were diagnosed by standard 12-lead ECG or using ECG event monitoring, in 23 (26.4%) – by 24-hour Holter ECG recording. Symptomatic recurrences of arrhythmia were predominantly diagnosed by

standard 12-lead ECG or event monitoring, asymptomatic AFib/AFl - by means of 24-hour ECG monitoring. I.e., using standard 12-lead ECG or event ECG monitoring, symptomatic recurrences of arrhythmia were diagnosed in 57 (65.5%) patients, asymptomatic recurrences of AFib/AFl – in seven (8.0%) cases. 24-hour Holter ECG monitoring revealed symptomatic episodes of AFib/AFl in eight (9.2%) cases and asymptomatic recurrences of arrhythmia – in 15 (17.2%) cases.

During time of the follow-up 21 (17.5%) patients have developed clinically important events. Ischemic stroke was diagnosed in two patients, three patients developed other thromboembolic complications, six patients were hospitalized due to congestive heart failure. One patient died, one experienced acute myocardial infarction, three - coronary artery bypass grafting surgery, one - coronary artery stenting procedure, permanent cardiac pacemaker implantation was performed in three patients.

Depending on the presence of late recurrences of AFib/AFl, all patients were divided into two groups. One group included 87 (72.5%) patients with late recurrences of AFib/AFl, the second - 33 (27.5%) patients without recurrences of arrhythmia. Demographic and anthropometric indicators, cardiovascular risk factors, background and concomitant pathology, laboratory data, echocardiographic parameters (Echo), as well as standard 12-lead ECG, 24-hour Holter monitoring data were compared in the study groups.

Statistical processing of the data was performed using Statistica for Windows 5.0. The variables were presented as a median (lower-upper quartiles) range for non-Gaussian distribution (verified by Shapiro-Wilk test) and compared by Mann-Whitney U test. The quality parameters were presented as absolute numbers and percentages, their frequencies between groups were compared using the Fisher test for tables 2x2 and χ^2 for larger tables.

Our study complies with the Declaration of Helsinki. The study protocol was approved by the Bioethics Committee of Shupyk National Healthcare University of Ukraine. Before the start of the study, informed consent was obtained from all of the participants.

Results

There were no significant differences regarding demographic and anthropometric data, as well as major comorbidities in the compared groups (Table 1) CHA_2DS_2-VASc score also did not differ significantly between groups of patients with and without late recurrences of AFib/AFl. CHA_2DS_2-VASc score one was found in 25 (28.74%) patients with late recurrences and in 13 (39.39%) without late recurrences of AFib/AFl, CHA_2DS_2-VASc score two in 26 (29.89%) and eight (24.24%) patients, CHA_2DS_2-VASc score > two in 21 (24.14%) and seven (21.21%) patients respectively.

A lower heart rate after restoration of the sinus rhythm and longer QTc interval were reported according to the initial standard ECG in patients with AFib/AFl late recurrences. Early recurrences of AFib/AFl were detected in 43 (49.4%) patients with late recurrences of AFib/AFL and only in two (6.0%) without late recurrences of arrhythmia (Table 2).

Table 1

Age, gender, anthropometric parameters and comorbidities in the study groups

Parameters	Variables (n (%)) in the compared groups		
	With AFib/AFl late recurrences (n=87)	Without AFib/AFl late recurrences (n=33)	P
Age, years	59 (54 - 62)	58 (47 - 62)	0.73
Male gender	54 (62.0%)	23 (69.7%)	0.52
Body mass index, kg/m^2 (median, quartiles)	29.7 (26.8-32.9)	29.5 (24.8 – 32.5)	0.44
Arterial hypertension	76 (87.3%)	26 (78.7%)	0.25
Type 2 diabetes	15 (17.2%)	5 (15.1%)	1.00
Cardiovascular embolic events	8 (9.2%)	3 (9.0%)	1.00
Ischemic heart disease	38 (43.6%)	13 (39.3%)	0.83
After myocardial infarction	8 (9.2%)	3 (9.0%)	1.00

The analysis of laboratory findings didn't reveal significant differences between compared groups. Echocardiography parameters were similar in patients with and without late recurrences of Afib/AFl as well (Table 3).

Regarding the findings of Holter monitoring during hospital period, in patients with late recurrences of arrhythmia heart rate (HR) was lower, they had more premature atrial contractions (PAC), couplets and triplets (Table 4).

Discussion

Clinical course of persistent AFib/AFl and appearance of arrhythmia recurrences after successful cardioversion may depend on atrial cardiomyopathy and development of electrical remodeling [6]. Rare appearance of arrhythmia may reflect priority of finding and avoiding special triggers, often without necessity of preventive antiarrhythmic therapy. At the same time, high probability of arrhythmia recurrence might be an additional argument to consider early radiofrequency ablation, taking into account evidence of its favorable impact on prognosis in EAST-AFNET 4 study [7].

In our study, frequency of recurrences detected during first 10 days after cardioversion significantly differed in patients with and without late recurrences of AFib/AFl. It should be emphasized that an intensive search of early Afib/AFl recurrences including Holter and event ECG monitoring was used in the study, making possible to detect early recurrences in nearly half of the patients. Apart from Afib, which was asymptomatic in part of the patients, vast majority of them had atrial couplets and runs, which were established as Afib predictors, especially in patients with concomitant risk factors, such as atrial hypertension, obesity and type 2 diabetes [8]. Besides, patients with late recurrences had lower HR after cardioversion and longer QTc interval. These data generally agree with results of the previous investigations. Sinus bradycardia is a recognized general predictor of subclinical AFib/AFl recurrence [9], while QTc prolongation may predict recurrence of AFib after radiofre-

Table 2

Parameters of the in-hospital ECG in the study groups

Parameters	Variables (median (lower-upper quartiles))		
	With late recurrences of AFib/AFl (n=87)	Without late recurrences of AFib/AFl (n=33)	p
HR during SR, per minute	60 (58 - 66)	65 (63 - 70)	<0.001
PQ, sec	0.18 (0.16-0.20)	0.18 (0.16-0.18)	0.10
QTc, sec	0.40 (0.38-0.44)	0.38 (0.36-0.42)	0.004
Early recurrences of AFib/AFL (n, %)	43 (49.4%)	2 (6.0%)	<0.001

Note: HR – heart rate; SR – sinus rhythm

Table 3

The in-hospital echocardiography parameters in patients with and without late recurrence AFib/AFl

Parameters	Variables (median (lower-upper quartiles))		
	With late recurrence of AFib/AFl (n=87)	Without late recurrence of AFib/AFl (n=33)	p
RV size, cm	2.4 (2.3-2.6)	2.4 (2,2-2,6)	0.32
LA size, cm	4.1 (3.8-4.4)	4.0 (3.6-4.3)	0.19
Ascending aorta size, cm	3.1 (3.0-3.4)	3.1 (3.0-3.3)	0.93
IVS thickness, cm	1.15 (1.05-1.3)	1.1 (1.0-1.2)	0.19
LVPW thickness, cm	1.1 (1,0-1,2)	1.1 (1.0-1.2)	0.21
LV end-diastolic diameter, cm	5.0 (4.7-5.3)	5.0 (4.8-5.2)	0.72
LVEF, %	60 (56-60)	60 (56-60)	0.43

Note: RV - right ventricle; LA - left atrium; IVS - intraventricular septum; LVPW - left ventricular posterior wall; LV – left ventricle; LVEF – left ventricular ejection fraction.

Table 4

Parameters of 24-hour Holter monitoring during hospital period after cardioversion in the study groups

Parameters	Variables (median (lower-upper quartiles))		
	With late recurrence of AFib/AFl (n=87)	Without late recurrence of AFib/AFl (n=33)	p
Minimum HR, beats/min	50 (45-55)	53 (49-56)	0.08
Mean HR, beats/min	68 (59-74)	71 (69-75)	<0.001
Maximum HR, beats/min	100 (93-106)	102 (98-113)	0.06
≥500 PAC per 24 hours	34 (39.1%)	3 (9.1%)	0.001
Atrial couplets and triplets	67 (77.0%)	19 (57.6%)	0.04
Short runs of supraventricular tachycardia	35 (40.2%)	9 (27.3%)	0.21

Note: PAC - premature atrial contractions

quency catheter ablation compared to patients without recurrent arrhythmia [10]. In earlier studies, patients with late recurrences of AFib/AFl had lower minimum, mean and maximum HR, more frequently detected episodes of early recurrent arrhythmia and atrial ectopic rhythms [11]. It is obvious that detection of late AFib/AFl predictors makes necessary to consider long-term preventive antiarrhythmic therapy and/or radiofrequency catheter ablation procedures.

In conclusion, more than two thirds of the patients with persistent Afib/AFl had late recurrences of arrhythmia during nine-months follow-up after successful cardioversion. Groups of patients with and without late recurrences of arrhythmia had significant differences regarding frequency of early recurrences, as well as heart rate, presence of atrial couplets and runs. Early 24-hour Holter and event ECG monitoring should be systematically implemented to increase detection of early recurrences of arrhythmia, including silent episodes.

Study limitations

Certain limitations of our study were non-inclusion of patients with significantly reduced left ventricular ejection fraction and severe dilatation of left atrium. This made possible to avoid influence of irreversible mechanical and electrical remodeling caused by long-term episodes of Afib/AFl. Besides, many patients used amiodarone before and after cardioversion, but the decision on choice of the antiarrhythmic therapy and its duration was not based on the unified algorithm. It is not possible to exclude that amiodarone might be prescribed more often in patients with Afib/AFl early recurrences, taking into account the data of the early period after cardioversion. Nevertheless, this didn't influence the probability of late arrhythmia recurrence.

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