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Antiarrhythmic drug therapy possibilities for primary prevention of atrial fibrillation in patients with metabolic syndrome and premature atrial contractions: a prospective study

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Objective. *To estimate antiarrhythmic drug therapy possibilities for primary prevention of atrial fibrillation (AF) in patients with high risk of AF, metabolic syndrome (MS) and premature atrial contractions (PACs).*

Materials and methods. *We followed-up 305 patients aged 59 to 73 years with MS and high risk of AF development without the history AF. 156 (51, 15%) patients received basic therapy including correction of potentially*

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modified risk factors (control group), other patients received classes I–III of antiarrhythmic agents for primary prevention of AF. Every patient who was included in the trial was followed-up from 2 to 4–5 years: the endpoint was the absence or presence of AF.

Results. *Patients with MS and PACs with high risk of AF who received classes I–III of antiarrhythmic agents had AF three times less frequent compared with control group (31,54 % versus 95,51 % during antiarrhythmic and basic therapy, respectively). Positive effect of antiarrhythmic therapy for primary prevention of AF in patients with MS can be explained by the reduction or elimination of PACs, left ventricular dysfunction and signal-averaged ECG parameters improvement, P-wave dispersion and left atrial volume reduction.*

Conclusion. *The frequency of this arrythmia development reduced by three times on average during classes I–III of antiarrhythmic treatment for primary prevention of AF in patients with high risk of AF, MS and PACs.*

Key words: *Metabolic syndrome, primary prevention of AF.*

Conflicts of interest: nothing to declare.

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Introduction

International and Russian guidelines for the management of atrial fibrillation indicate that metabolic syndrome (MS) is one of the most common cause of AF development [1, 2]. Nowadays, the main AF predictors include: left atrial dilatation, mitral valve calcinosis, reduction of left ventricular ejection fraction (LVEF), transmitral flow impairment, premature atrial contractions (PACs), pathological values of signal-averaged electrocardiogram (ECG), P-wave dispersion (Pd), etc. [1, 2, 3]. During the prospective study that included complex use of AF predictors in patients with MS and assessment of the nature of PACs, the authors found criteria to identify patients with high risk of AF development without the history of AF (within 2 years after the first examination) [4, 5]. However, the use of antiarrhythmic therapy for primary prevention of AF in patients with MS, PACs and high risk of AF development have not been studied yet.

Objective

To estimate antiarrhythmic drug therapy possibilities for primary prevention of atrial fibrillation (AF) in patients with high risk of AF, metabolic syndrome (MS) and premature atrial contractions (PACs).

Materials and Methods

Prospective follow-up study included 305 patients with MS aged from 60 to 73 years (68,3±0,5 years on average). MS diagnosis based on generally accepted criteria [3]. The inclusion criteria were: sinus rhythm, PACs, I–II NYHA classes of chronic heart failure (CHF), age ⩾ 60 years with body mass index ⩾ 30 kg/m^2, the absence of AF during over 3–4 24-hour ECG monitoring more than once in 1–3 month, high or short-term risk of AF development, signed informed consent for the examination and treatment [4, 5].

The study excluded patients with acute coronary syndromes and other clinical manifestations of coronary artery disease, Wolff-Parkinson-White syndrome, sick sinus node syndrome, atrioventricular block, artificial cardiac pacemaker, ventricular tachycardia and extrasystoles (II–V classes according to B. Rayn's classification), valvular heart disease, cardiomyopathies, complete blockade of the bundle of His brunches, thyroid gland dysfunction, uncontrolled arterial hypertension, severe somatic diseases, which could affect the results of the study, patients with LVEF <45 %, left ventricular aneurism and III–IV NYHA classes of CHF [1, 2, 3]. Hypertension was diagnosed in 256 (83.93 %), diabetes mellitus in 196 (64.26 %), and chronic obstructive pulmonary disease in 53 patients (17.38 %).

The identification of high risk of AF development was determined by assessing the change in the risk index for the development of AF (RIDAF), defined by the formula:

$$RIDAF = (FiP - P \div Pd) \times (A \div B),$$

where RIDAF — risk index for the development of AF,
FiP – P — the duration of the filtered «P» wave of signal-averaged ECG (ms),
Pd — dispersion of the «P» wave (ms), defined as the difference between maximum and minimum values of the «P» wave duration during standard 12-lead ECG,

A — linear deviation of the pre-ectopic interval of PAC, corrected by the frequency of cardiac sinus rhythm contractions of over 20 PACs,

V — the number of PACs used for the study in amount per hour [4, 5].

Echocardiographic investigation of LV EF (left ventricular ejection fraction), left atrium end-diastolic volume (LA EDV), left ventricular mass index (LV MI), left ventricle diastolic dysfunction by early (E) and late (A) diastolic mitral flow velocity, estimation of FiP-P — the duration of the filtered «P» wave of signal-averaged ECG and of the Pd were mentioned earlier [5, 6]. When IRRFP decreased by 35 % or more every 1–3 months compared with baseline, we determined high risk of AF during 2-year follow-up [4, 5]. CHF class was determined by 6-minute walk test [3], mean blood pressure was calculated according to the formula:

$$MBP = (SBP — DBP) \div 3 + DBP,$$

where MBP, SBP and DBP are mean, systolic and diastolic blood pressure, respectively (mm Hg) [3].

All patients underwent basic therapy, including antihypertensive drugs, such as angiotensin-converting enzyme inhibitors (enalapril (ednyt, renitec, etc.), saluretics (indapamide, arifon, etc.), and correction of glucose blood level and lipids by the diet, hypoglycemic and hypolipidemic therapy, including statins.

Patients were followed up for 2 years. The endpoint was the presence or absence of AF. All the studies including 24-hour ECG monitoring was conducted more than once in 3–4 months, patient's condition monitoring and ECG registration — once a month. Regular monitoring of blood pressure and heart rate were performed by the patients on their own.

Statistical analysis was performed using Statistica 11.0 software and included Student's t-test and χ^2 test.

Results and discussion

305 patients were divided into two groups. Group I included 156 patients (51,15 %), who underwent basic treatment, which included only the correction of potentially modified factors without antiarrhythmic therapy (control group), patients from group II underwent antiarrhythmic therapy. Groups did not differ significantly by sex, age, clinical laboratory parameters and concomitant diseases.

We chose antiarrhythmic therapy for PACs for all patients from group II by testing its effectiveness during 24-hour ECG monitoring [3]. We used primary class II antiarrhythmic drugs and classes II and III or its combinations. The medications were prescribed in the following daily doses: propranolol 60–120 mg per day, metoprolol and atenolol — 100–150 mg per day, respectively, propafenone — 300–600 mg per day, allapinin — 50–75 mg per day, sotalol — 160–320 mg per day and amiodarone — 600–800 mg per day. The course of antiarrhythmic therapy lasted for 3–5 days and amiodarone for 8 (10) days. 24-hour ECG monitoring was performed before and after antiarrhythmic therapy, the criterion of effectiveness was over 75 % decrease in the number of extrasystoles compared with baseline and the elimination of paired and group extrasystoles [3]. If one medication was inactive, the effectiveness of each subsequent antiarrhythmic agent was determined after at least 5 elimination half-lives of the previous one [3]. At the begging of antiarrhythmic therapy, especially of the IC class, patients underwent 24-hour ECG monitoring at least once every 3–4 days for 7–14 days to exclude arrhythmogenic effect of antiarrhythmic therapy [3]. To prevent an «excess» of prolonged antiarrhythmic therapy, we prescribed it only for 3 months, and resumed in case of recurrence of extrasystoles.

33 (22.15 %) patients from group II were prescribed propranolol as long-term therapy, 47 (31.54 %) — metoprolol, 30 (20.13 %) — sotalol, 19 (12.75 %) — propafenone, 15 (10,07 %) — metoprolol + propafenone and the rest — amiodarone. PACs reoccurred in 107 (71.81 %) patients from group II by the end of the course, so antiarrhythmic therapy was resumed.

The development of paroxysmal or persistent AF within 2 years of follow-up after the first examination was noted in 149 (95.51 %) and 47 (31.54 %) patients from group I and II, respectively ($p < 0.05$). It is remarkable that patients from group II, compared with group I, during the first 3 months and after, had significant decrease in the development of AF (fig. 1). There were no deaths during the follow-up, as well heart attacks, strokes and systemic embolism. Clinical and instrumental parameters, the state of hemodynamics, the FiP-P/Pd ratio, RIDAF for groups I and II during the follow-up are presented in table 1. As we can see from the table, after inclusion in the study (baseline), there were no significant differences in all the studied parameters between groups I and II. All patients from groups I and II had significant decrease of RIDAF, FiP-P/Pd, 6-minute test values and an increase of LA EDV, LVMI, Pd, FiP-P, MBP and body mass index for 1–3 months before the development of

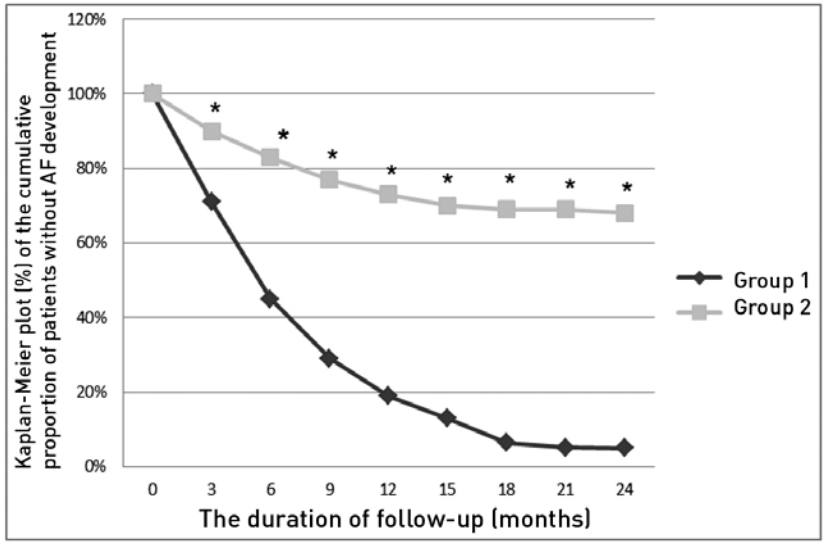

Figure 1. Kaplan-Meier plot (%) of the cumulative proportion of patients without AF development in groups I and II during two-year follow-up.
* differences are significant compared with group 1 (p < 0,05);
AF — atrial fibrillation.

AF compared with baseline, while other studied parameters did not differ significantly (table 1).

All studied parameters did not differ significantly in patients from group I without the development of AF compared with baseline. All patients from group II without AF development had significant decrease of LA EDV, Pd and MBP values and an increase of the E/A ratio, FiP-P/Pd, RIDAF and 6-minute test, other parameters did not differ significantly (table 1).

It is remarkable that all patients from group II with and without AF development, had significant decrease in the number of PACs, however, with the arrhythmia development patients from this group had significant decrease of RIDAF and without the development of this arrythmia — an increase of RIDAF compared with baseline (table 1). The absence of PACs recurrence after antiarrhythmic therapy correlated with E/A ratio (r = 0.78), RIDAF (r = 0.94), LA EDV (r = –0.86), FiP-P

Table 1. **Clinical and instrumental parameters, hemodynamic status, FiP-P / Pd ratio and RIDAF in group I and II during the follow-up (M ± m and 95 % CI of mean values[1]).**

Group	Group I n = 156			Group II n = 149		
Parameter	**A• n = 156**	**Б• n = 149**	**B• n = 7**	**A• n = 149**	**Б• n = 47**	**B• n = 102**
LVEF, %	56,84±0,77 (47–66)	58,01±0,65 (9–69)	59,14±4,12 (48–71)	57,48±0,61 (50–65)	57,37±1,17 (49–66)	59,35±1,03 (49–70)
E/A, units	0,95±0,02 (0,71–1,23)	0,78±0,01† (0,61–0,95)	0,93±0,08 (0,71–1,15)	0,93±0,01 (0,87–0,99)	0,98±0,01† (0,89–1,05)	1,07±0,01† (0,97–1,18)
LA EDV, ml/m^2	31,56±0,53 (25–39)	37,93±0,67† (29–45)	32,14±1,88 (27–37)	32,05±0,42 (27–37)	34,64±0,82† (29–39)	26,34±0,72† (29–34)
LV MI, g/m^2	134±0,9 (123–145)	137±1,0† (125–149)	134±4,2 (123–145)	135±0,8 (125–145)	138±0,4† (128–147)	135±0,1 (125–145)
FiP-P/Pd, units	2,82±0,03 (3,23–2,47)	2,11±0,01† (2,20–2,00)	2,69±0,14 (2,93–2,23)	2,79±0,04 (3,28–2,22)	2,59±0,07† (3,07–2,11)	4,22±0,09† (5,33–3,11)
RIDAF, units	8,57±0,59 (1,18–18,44)	0,10±0,08† (0,01–0,19)	7,96±2,43 (1,29–14,03)	7,94±0,58 (1,31–14,57)	0,93±0,12† (0,04–1,75)	33,16±1,82† (15,23–51,36)
PACs frequency, per hour	92±3 (52–131)	105±2† (81–131)	77±9† (56–98)	96±3 (58–142)	11±1† (3–19)	9±1† (1–17)
MBP, mmHg	117±1 (103–131)	121±1† (106–131)	119±6 (102–132)	116±1 (102–128)	118±1† (104–131)	105±1† (95–116)
6-minute test, meters	436,5±5,3 (365–510)	414,7±5,1† (355–478)	447,9±28,3 (372–516)	442,7±6,3 (368–518)	422,9±9,3† (358–489)	486,5±3,8† (445–548)
Body mass index, kg/m^2	32,9±0,2 (30,3–35,4)	34,4±0,2† (31,9–37,1)	32,7±1,0 (30,1–35,1)	33,1±0,2 (31,4–35,6)	33,9±0,4† (31,5–36,2)	33,3±0,2 (31,1–35,5)

[1] M ± m at the top of the table, 95 % of the confidence interval (CI) of average values at the bottom.
• averaged data for the duration of follow-up, A — baseline, B — 1–3 months before the development of AF; B — without the development of AF;
† with baseline (p < 0,05).

(r = –0, 79), Pd (r = –0.68), MBP (r = –0.84), increase of 6-minute walk test distance (r = 0.76) and the usage of classes II and III of antiarrhythmic drugs (r = 0.92 and r = 0.89, respectively).

Currently, it is known that the prevalence of AF in the general population is about 2 %, and the risk of AF development after 40 years is about 25 % [1, 2]. Any diseases of cardiovascular system can cause progressive «structural and/or electrical remodeling» of atrial myocardium, contributing to the development of PACs and AF [1, 2, 3]. It is remarkable that frequent PACs and/or short asymptomatic episodes of AF increase the risk of stroke and other complications [1, 2, 3, 7].

Despite the progress in identifying AF predictors, pulse palpation and ECG recording in case of irregular pulse is recommended for all patients over 65 years, and ECG monitoring, including loop recorder implantation, is indicated for patients with symptoms of heartbeat or shortness of breath [1, 2]. Therefore, determination of patients with potential risk of AF development and its primary prevention principles is an important issue in cardiology.

The study included 305 patients with MS aged from 60 to 73 years. The inclusion criteria were: sinus rhythm, I—II NYHA classes of CHF, age ⩾ 60 years, body mass index ⩾ 30 kg/m^2, no history of AF or its high risk. Each patient was followed-up for 2 years: the endpoint was the presence or absence of AF development.

MS is one of the most common cause of AF, which leads to hypertrophy and/or dysfunction of the left ventricle, dilatation of the left atrium, worsening of the spectrum of transmitral flow, etc. [1, 2, 3]. In addition, patients with MS, in most cases have «obesity paradox», which means that despite increased body mass index, they have low risk of death, heart attacks, strokes, systemic embolism and other complications [3].

We obtained similar data in this study.

Patients with MS, by the result of «oxidative stress», have diastolic Ca2 ++ overload of atrial cardiomyocytes with simultaneous activation of inward-rectifier potassium currents that lead to the induction of trigger mechanisms (delayed or early repolarization) and/or re-entry, that initially cause PACs, then atrial ectopic rhythm, and form a rotor in the posterior wall of the left atrium that leads to AF [3, 8, 9].

It is remarkable that nowadays there is no generally accepted classification, as well as international and national guidelines for the management of PACs. However, it is known that frequent (over 30 per hour of PACs), prolonged or recurrent atrial ectopic rhythm increase potential risk of AF development [4, 5, 7]. Mentioned above theoretical background is confirmed by the results of our study: AF developed in 95.51 % of patients from the control group who underwent therapy, including correction of potentially modified factors [10].

48.85 % of patients with MS and PACs underwent antiarrhythmic therapy additionally to standard therapy of potentially modified factors. 53.69 % and 23.49 % of patients with MS took II and III classes of antiarrhythmic drugs, respectively, and the rest — class IC (propafenone) to eliminate PACs. Paroxysmal or persistent AF developed in 31.54 % of patients despite antiarrhythmic therapy during 2-year follow-up, which was three times less compared with the control group. All patients who underwent antiarrhythmic therapy with and without AF, had significant decrease in the number of PACs, however, patients with AF development had significant decrease of RIDAF, and patients without AF — increase of RIDAF compared with baseline. Therefore, positive effect of antiarrhythmic therapy used for primary prevention of AF in patients with MS, should not only be assessed by the decrease in the number of PACs, but primarily by the increase of RIDAF compared baseline.

PACs did no reoccur in 28.19 % patients with MS after discontinuation of 3 months of antiarrhythmic therapy, which could be due to the elimination of its arrhythmogenic substrate [8, 9]. Elimination of atrial ectopia after discontinuation of the therapy may also be an additional criterion for determining positive effect of the therapy for primary prevention of AF in patients with MS.

Positive effect of I–III classes of antiarrhythmic agents for primary prevention of AF in patients with MS can be explained, firstly, by «atrial cardiomyopathy» prevention [11], secondly, by the decrease of unequal atrial myocardium refractoriness due to antiarrhythmic effect of the therapy, improved left ventricular function and decreased size of the left atrium [3, 9], which is confirmed by the results of this study: patients who received antiarrhythmic therapy had increased E/A, decreased LA EDV, class of CHF, hypertension, frequency of pathological Pd signal-averaged ECG values, thirdly, by antiarrhythmic and sympatholytic effects of the therapy, that improves stability of myocardial calcium transport system to damaging effect of lipid peroxidation products and/or to overloaded of cardiomyocytes by calcium ions due increased nitrogen monoxide production, accu-

mulation of protective stress proteins such as HSP70, SERCA-2a, etc. in cardiomyocytes, reduction of tumor necrosis factor activity, direct or indirect limitation of adrenergic system activation [3, 8, 9].

Antiarrhythmic therapy, apparently, «activated» the process of the atrial myocardium «remodeling» in 31.54 % of patients with MS and AF despite decreased number of PACs, and decreased atrial ectopic rhythm, probably did not contribute to its inverse regression that is confirmed by the results of this study: patients with AF had progressive left atrium dilation, impairment of the signal-averaged ECG, Pd and RIDAF values that can be explained by increased body mass index, LV MI and CHF progression. On the other hand, the absence of AF development in 4.49 % of patients from the control group can be explained by the positive effect of potentially modified factors correction on the structural and electrophysiological function of atrial myocardium, which is confirmed by the results of our study: all the studied parameters in this group of patients did not differ significantly during 2 year follow-up compared with baseline.

Conclusion

1. AF occurred in 31.54 % of patients with MS, PACs and high risk of AF development during antiarrhythmic therapy, and in 95.51 % of patients during the correction of potentially modified factors.
2. Positive effect of antiarrhythmic therapy for primary prevention of AF in patients with MS should be estimated not only by the decrease in the number of PACs but primarily by the increase of RIDAF compared with baseline.
3. The absence of PACs recurrence after antiarrhythmic therapy discontinuation can be used as an additional criterion of the effectiveness of therapy used for primary prevention of AF in patients with MS.
4. Positive effect of classes II and III of antiarrhythmic agents for primary prevention of AF in patients with MS can be explained by the improvement of left ventricular dysfunction, signal-averaged ECG, Pd values, and the decrease of left atrium volume.

Conflict of interest: None declared.

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