Prognostic value of pharmacotherapy in patients with atrial fibrillation after radiofrequency ablation

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The aim of the work: to evaluate the prognostic effect of pharmacotherapy before and after radiofrequency ablation (RFA) in patients with atrial fibrillation (AF) on all-cause mortality, supraventricular arrhythmia recurrence and non-fatal cardiovascular events.

Materials and methods. Patients with paroxysmal, persistent and long-term persistent forms of AF were examined before and after RFA – isolation of pulmonary veins. The primary endpoint was patient survival, secondary – a composite endpoint of freedom from recurrence and/or non-fatal cardiovascular events for 2 years of a follow-up. Frequency and doses of pharmacotherapy were evaluated. Standard statistical procedures were used for initial data evaluation.

Results. 116 patients were consecutively enrolled in the study. In the long-term post-ablation, 23 patients (19.8 %) continued to take amiodarone, 2 patients (1.7 %) – propafenone for arrhythmic events, 38 patients (32.8 %) needed anticoagulants, and 37 patients (31.9 %) received beta-adrenoceptor blockers over the entire follow-up period. The use of RAAS inhibitors decreased from 81.0 % before the ablation to 56.0 % in the long-term period following RFA. Multifactorial logistic regression analysis showed that the prolonged (more than 3 months) anticoagulation (P = 0.032) after RFA was an independent predictor of patient survival in the two-year follow-up; doses of anticoagulants before the procedure, use and doses of beta-adrenoceptor blockers in the long-term post-ablation period were associated with the secondary endpoint.

Conclusions. RFA for AF significantly reduced the frequency of medications use in the long-term postoperatively. Independent predictors of survival were the doses of anticoagulants more than 3 months after ablation, arrhythmia recurrence and non-fatal cardiovascular events – the doses of anticoagulants before the procedure, and the use and doses of beta-adrenoceptor blockers in the long-term period after RFA.

Key words: radiofrequency ablation, atrial fibrillation, prognostic effect.
The main directions of pharmacotherapy for patients with atrial fibrillation (AF) are anticoagulation, rate or rhythm control and treatment of concomitant pathology [1]. Radiofrequency ablation (RFA) today is a leading strategy for the rhythm control for paroxysmal and persistent forms of AF in case of ineffectiveness of pharmacological antiarrhythmic therapy [1–3]. However, RFA does not exclude the pharmacological therapy administration, the anticoagulant and antiarrhythmic drug therapy is recommended to all patients within 3 months after the procedure, a significant number of patients requires a further continuation of medicinal treatment.

The relationship between the ablation efficiency and long-term endpoints and the intake of medical drugs before, in the periprocedural period and after RFA, is not sufficiently studied. Anticoagulant therapy before RFA is compulsory according to the current protocols [3] for a least 3 weeks until target values of International Normalized Ratio (INR) are reached and intracardiac thrombi are absent according to the data of transesophageal echocardiography (EchoCG). The effect of an early administration of anticoagulant drugs on the RFA outcomes is not described, but its association with the risk of stroke is statistically confirmed [4]. In its turn, a previous stroke significantly increases the risk of thromboembolic events in the post-ablation period [5]. Data from large-scale registers proved that only 23 % of patients could stop anticoagulant therapy after catheter ablation of AF on average six months following the procedure. It has also been shown that the cessation of anticoagulant therapy was associated with a risk of stroke [6].

The type and dosage of antiarrhythmic therapy before the ablation have not been previously studied on the effect in terms of mortality and morbidity in AF patients after RFA. Intense early medical control of the rhythm after ablation is associated with a decrease in the risk of all major long-term consequences including mortality, cardiovascular morbidity, symptom deterioration, etc. [7]. However, the question as for the duration of antiarrhythmic therapy after RFA and indications for its withdrawal remains open. Paroxysms are reached and intracardiac thrombi are absent according to the data of transesophageal echocardiography (EchoCG). The target values of International Normalized Ratio (INR) are studied. Anticoagulant therapy before RFA is compulsory in the periprocedural period and after RFA, is not sufficiently long-term endpoints and the intake of medical drugs before, during and after RFA procedure was performed for all patients in the study, namely isolation of pulmonary veins for paroxysmal AF and 3 additional linear ablations in the roof of the left atrium, mitral valve between mitral ring and left lower pulmonary vein and cavotricuspid isthmus for persistent AF. The primary endpoint was patient survival; the secondary endpoint consisted of freedom from recurrence and/or non-fatal cardiovascular events within a 2-year follow-up.

which complicates the decision to discontinue antirhythmic drugs.

Most of the works agree with the need to minimize pharmacotherapy after catheter ablation, but clear algorithm for its prescription and withdrawal is still discussed. Therefore, the study on the effect of administration and dosage of medical drugs on the efficiency of RFA has a great practical potential.

**Aim**

The aim: to evaluate the prognostic effect of pharmacotherapy before and after RFA in patients with AF on all-cause mortality, supraventricular arrhythmia recurrence and non-fatal cardiovascular events.

**Materials and methods**

Patients were examined on the basis of the Department of Ultrasound and Clinical and Instrumental Diagnostics and Mini-invasive Interventions of the SI “Zaycev V. T. Institute of General and Emergency Surgery of the NAMS of Ukraine” (Kharkiv). Inclusion criteria were paroxysmal, persistent and prolonged persistent forms of AF requiring non-pharmacological rhythm control and preferred choice of patients for mini-invasive interventions.

The main exclusion criteria were permanent AF, age younger than 35 years old, clinical hyper- and hypothyroidism, liver failure, severe kidney function impairment (glomerular filtration rate (GFR) <30 ml/min/1.73 m²), acute coronary syndrome or recent (<3 months), left (LA) or right atrium size of >50 mm, severe arterial hypertension, systolic heart failure (HF) with left ventricular ejection fraction (LV EF) <40 % or NYHA functional class III–IV. Patients did not previously experience surgical heart interventions.

RFA procedure was performed for all patients in the study, namely isolation of pulmonary veins for paroxysmal AF and 3 additional linear ablations in the roof of the left atrium, mitral valve between mitral ring and left lower pulmonary vein and cavotricuspid isthmus for persistent AF. The primary endpoint was patient survival; the secondary endpoint consisted of freedom from recurrence and/or non-fatal cardiovascular events within a 2-year follow-up.
Patients received anticoagulant therapy for at least 3 weeks before RFA, 3 days before the procedure all of them underwent transesophageal EchoCG for atrial thrombus exclusion. Oral anticoagulant therapy was stopped 3 days before ablation and low-molecular-weight heparin was started at the INR level less than 2.0. Antiarrhythmic drugs were administered for the duration of hospitalization. Subsequent postoperative pharmacotherapy corresponded to the standard protocol [3]. Antiarrhythmic drugs were administered for a period of up to 3 months and then discontinued in patients who maintained sinus rhythm. Anticoagulant therapy was also stopped in 3 months after ablation in patients who did not have an ECG confirmed recurrence, if a thromboembolic risk was low and the CHA2DS2-VASC scale was <2. The therapy of concomitant cardiovascular pathology was provided in accordance with the current recommendations.

The frequency of use was evaluated separately for amiodarone, propafenone, group of beta-adrenoceptor blockers, renin-angiotensin-aldosterone system (RAAS) inhibitors and anticoagulants. Dosage was compared to an average group coefficient from a medium-daily dose taken for 1.0. The average daily dose was considered for inhibitors and anticoagulants. Dosage was compared to an average group coefficient from a medium-daily dose taken for 1.0. The average daily dose was considered for amiodarone – 600 mg; for propafenone – 600 mg; for bisoprolol – 5 mg, carvedilol – 25 mg, nebivolol – 5 mg, metoprolol – 50 mg; for ramipril – 5 mg, perindopril – 5 mg, lisinopril – 10 mg, enalapril – 10 mg, zofenopril – 30 mg, losartan – 50 mg, valsartan – 80 mg, telmisartan – 40 mg, candesartan – 80 mg, spironolactone – 50 mg, eplerenone – 50 mg; for rivaroxaban – 20 mg, dabigatran – 300 mg and warfarin – 5 mg.

The values of variables were compared using odd Student t-test, x‐quartier test, unidirectional dispersion analysis (ANOVA) and Kruskal–Wallis N-test depending on the type of variable. For comparison of groups with statistical differences according to ANOVA test, the Duncan multiple comparison test was used. The Mann–Whitney U-Test was used for comparison between groups with statistical differences based on the N-test. The survival analysis was carried out by Kaplan–Meyer method and the difference between the groups was checked with the Log-Rank test. The analysis of multifactorial logistic regression was applied for the determination of predictors for endpoints. A level of P < 0.05 was regarded as statistically significant.

Results

A total of 116 patients who meet the inclusion criteria were consecutively enrolled in the study since January 2015 to June 2018. The baseline characteristics of the patients are presented in Table 1.

All the patients used antiarrhythmic drugs before RFA. The overwhelming majority of them received amiodarone (98 patients (84.5 %)), 11 patients (9.5 %) – propafenone, as well as about one third of patients (37 patients (31.9 %)) – beta-adrenoceptor blockers. After implantation, all patients continued to take an antiarrhythmic drug for 3 months of a “blinding period”. After that, 23 patients (19.8 %) continued to take amiodarone for arrhythmic events, 2 patients (1.7 %) – propafenone and 50 patients (43.1 %) were given beta-adrenoceptor blockers over the entire follow-up period. All the patients received anticoagulation before RFA to achieve the target level of INR with a perioperative resumption of direct anticoagulant and to elongate oral anticoagulant therapy up to 3 months after the procedure. 38 patients (32.8 %) continued to take anticoagulant therapy for 2 years of the follow-up. RAAS inhibitors were prescribed to the majority of patients before ablation – 94 patients (81.0 %), 88 patients (75.9 %) continued to take drugs of this group in the acute period but their number decreased – 65 patients (56.0 %) used RAAS inhibitors up to 2 years of follow-up after RFA.

The amiodarone dosage decreased and RAAS inhibitors dosage, on the contrary, increased in an acute 3-month period after RFA. In further follow-up, the dosage of RAAS inhibitors returned to almost the ascending level (P < 0.05). The dosage coefficient of other groups of drugs was not changed significantly during the follow-up period (Table 2). A multifactorial logistic regression analysis showed that the use and doses of pharmacotherapy before RFA did not affect the following survival of AF patients. Prolonged (more than 3 months) anticoagulation (P = 0.032) after RFA was...
Table 2. Coefficient of drugs doses at the study stages

<table>
<thead>
<tr>
<th>Group of drugs</th>
<th>Before RFA</th>
<th>Within 3 months after RFA</th>
<th>Within 24 months after RFA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>1.3 ± 0.3</td>
<td>0.5 ± 0.2*</td>
<td>0.7 ± 0.4</td>
<td>*P = 0.032</td>
</tr>
<tr>
<td>Propafenone</td>
<td>1.0 ± 0.1</td>
<td>0.8 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>β-blockers</td>
<td>1.2 ± 0.3</td>
<td>1.3 ± 0.2</td>
<td>0.9 ± 0.4</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Inhibitors of RAAS</td>
<td>0.7 ± 0.4</td>
<td>1.4 ± 0.2*</td>
<td>0.8 ± 0.3**</td>
<td>*P = 0.001 **P = 0.009</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>0.8 ± 0.2</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>P &gt; 0.05</td>
</tr>
</tbody>
</table>

The values were presented as mean ± standard deviation, or number (percentage).

*, **indicator that was statistically changed at the study stages. RFA: radio frequency ablation; β-blockers: beta-adrenoceptor blockers; RAAS: renin-angiotensin-aldosterone system.

Fig. 1. Multivariate logistic regression analysis of pharmacotherapeutic predictors of survival before (A) and 3–24 months after RFA (B).

Fig. 2. Multivariate logistic regression analysis of pharmacotherapeutic predictors of freedom from recurrence and non-fatal cardiovascular events before (A) and 3–24 months after RFA (B).
an independent predictor of patient survival in the two-year study period. The use and doses of other drug groups did not affect the risk of death from any cause (Fig. 1).

The predictors of the secondary combined endpoint after RFA consisting of the absence of supraventricular arrhythmias recurrence and non-fatal cardiovascular events became the doses of anticoagulants (P = 0.017) in AF patients before the procedure. After the “blinding” post-operative period, the use and the dose of beta-adrenoceptor blockers (P = 0.028 and P = 0.23, respectively) also clearly influenced this endpoint according to the multifactorial logistic regression (Fig. 2).

Discussion

In our study, we determined the peculiarities of pharmacotherapy as well as the relationship between the use of drugs and the long-term prognosis for AF patients before and after RFA. First 3 months after RFA of AF are considered the “blinding” period, which is not included in the evaluation of the procedure efficiency [9]. Besides, anticoagulant and antiarrhythmic agents are obligatory in accordance with the approved guidelines [3]. In this regard, we did not take into account the treatment results of the AF patients during the first 3 months after RFA.

The total frequency of antiarrhythmic drug use expectedly decreased in our study, less than one third of the patients continued to take one of the drugs for a long time which coincided with the total level of arrhythmic events in these patients. Wherein, the doses of beta-adrenoceptor blockers administrated for the long-time post-operatively were associated with the absence of recurrences and non-fatal cardiovascular events. Meanwhile, the use of amiodarone and propafenone and their doses at all stages of the study in no way affected the prognosis of AF patients. Shanyha G. et al. [10] in a large analysis also showed that antiarrhythmic therapy after catheter ablation was not associated with an increased risk of general mortality, but the authors noted that the safety of the drug administration could be achieved only in the condition of careful patient selection for the procedure. The short-term use of antiarrhythmic therapy after RFA showed the efficiency in the prophylaxis of early supraventricular arrhythmia recurrence in the work [11], but it did not lead to a reduction in the risk of late recurrences. The data of major studies concerning prognostic effects of long-term use of antiarrhythmic drugs and their doses on non-fatal cardiovascular events after RFA of AF have not been found.

Our study did not find an association between the administration and dosage of RAAS inhibitors both before and after RFA and the risk of AF recurrences and cardiovascular events within 2-year follow-up. Taebjee M. H. et al. [12] in their study also revealed no correlation between the use of RAAS modulators and the long-term results of the catheter ablation for AF. However, patients who used this group of drugs were older, more likely to suffer from concomitant cardiovascular diseases, so the lack of difference compared with the control group was regarded by the authors as a positive result indicating the leveling of negative consequences by RAAS inhibitors in high risk patients. Antiarrhythmic therapy in our study covered all AF patients before RFA and in the acute period after the procedure. The existing studies coincide in the opinion as for the need of anticoagulants administration during the “blinding” post-operative period after RFA for AF [6]. Direct anticoagulants were used during the selection of patients for the study in peri-procedural period for the time of hospitalization, anticoagulant therapy continued after discharge from the hospital both with warfarin and a group of non-vitamin K antagonist oral anticoagulants, predominantly the latter. Trujillo T. C. et al. [13] in a large meta-analysis showed the same efficiency and safety of direct anticoagulants and vitamin K antagonists, but the authors noted that direct anticoagulants had more predictable beginning and completion of activity, therefore they had advantages in patients at risk factors of bleeding. Recently, data on the safety of continuous or minimally interrupted use of non-vitamin K antagonist oral anticoagulants in peri-procedural period have been under active consideration [14]. With reference to many works, the administration of longer anticoagulant therapy (more than 3–6 months) after RFA should be individual, based on the efficiency of the procedure and score according to the CHA2DS2-VASc scale.

Anticoagulant therapy both before and after RFA for AF prevents the thromboembolic events, of which the most common is a stroke at different times after the procedure and this is backed by strong facts [4–6,14,15]. However, our results regarding the effects of anticoagulant drugs dosage at different stages on general mortality, the procedure efficiency and thromboembolic events are new and require further research.

Conclusions

1. RFA for AF significantly reduced the frequency of antiarrhythmic drugs, RAAS inhibitors and anticoagulants administration in the long-term post-operative period.
2. Dose of anticoagulant drugs in case of their use in 3 months after ablation influenced the AF patient survival for 2 years after RFA.
3. The dose of anticoagulants before RFA as well as the use and dose of beta-adrenoceptor blockers in the long-term post-ablation period were independent predictors of arrhythmia recurrences and non-fatal cardiovascular events.

Perspective for further research. It is suggested to examine the effect of pharmacotherapy on RFA for AF prognosis in the long-term post-operative period to optimize the selection of patients for the procedure as well as develop recommendations for adjusting AF medical therapy before and after ablation.

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