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THE USE OF MINERALOCORTICOID RECEPTOR ANTAGONISTS IN THE PREVENTION OF ATRIAL FIBRILLATION

Abstract

Atrial fibrillation (AF) is one of the most common cardiac rhythm disorders. Its prevalence is about 1 % in the general population and exceeds 7 % in individuals older than 60 years of age. It is known that hyperactivation of the renin-angiotensin-aldosterone system plays a key role in structural and electrical myocardial remodeling in AF. Increased activity of the renin-angiotensin-aldosterone system causes inflammation, fibrosis and oxidative stress in cardiomyocytes. Last studies suggest that most of negative effects previously explained by angiotensin-2 may be particularly caused by excessive aldosterone activity. More data about extra-adrenal hormone production (in the myocardium, the vascular wall and even the brain) have appeared, and its receptors were found far beyond the kidneys — in cardiomyocytes, endothelial cells, fibroblasts, monocytes, and macrophages. It was also shown that aldosterone has a wide profile of pathogenic effects, one of which is the stimulation of atrial myocardial fibrosis as the structural basis for AF. The discovery of new features of aldosterone suggests that blockade of mineralocorticoid receptors may prevent or slow down atrial remodeling and thereby reduce the incidence of AF. The article presents data of the world literature and the results of own studies devoted to the use of mineralocorticoid receptor antagonists in patients with AF. Modern concepts of the role of aldosterone in the arrhythmia development and the main approaches of upstream-therapy are described. The possibilities of using eplerenone and spironolactone in primary and secondary prevention of AF are discussed.

Key words: *aldosterone, renin-angiotensin-aldosterone system, atrial fibrillation, relapses, eplerenone, spironolactone*

Conflict of interests

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BP — blood pressure, ACE — angiotensin converting enzyme, ARBs — angiotensin II receptor blocker, AT — angiotensin, CI — confidence interval, LV — left ventricle, MCR — mineralocorticoid receptors, RAAS — renin-angiotensin-aldosterone system, EF — ejection fraction, AF — atrial fibrillation, CHF — chronic heart failure, BB — β-blockers

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Atrial fibrillation (AF) is one of the most common cardiac rhythm disorders. Its incidence reaches 1 % in the general population and exceeds 7 % in individuals over 60 years of age [1]. The relevance of the problem with AF is dictated not only by the high rate of thromboembolic complications associated with it and deterioration of quality of life of patients, but also by a significant increase in the risk of general and cardiovascular mortality in patients with this arrhythmia [2].

Despite the progress made in understanding the electrophysiological mechanisms of the development and maintenance of AF, the pathogenesis of this arrhythmia remains understudied. It is known [3, 4] that hyperactivation of the renin-angiotensin-aldosterone system (RAAS) plays a key role in the development of structural and electrical myocardial remodeling underlying this arrhythmia. Higher activity of RAAS contributes to the development of inflammation, fibrosis, and oxidative stress in cardiomyocytes. Studies in recent years [5, 6, 7] suggest that most of the negative effects previously explained solely by the action of angiotensin-2 (AT-2) may be partly due to excessive activity of aldosterone.

Indirect evidence on aldosterone participation in AF development was obtained as early as 2005 by P. Milliez et al. [8], who showed that patients with primary hyperaldosteronism had a 12-fold higher risk of AF compared to the general population. Information concerning the role of aldosterone in the human body has undergone significant changes in recent years [9]: there is evidence on extra-adrenal hormone production (in the myocardium, the vascular wall and even the brain), and its receptors were found far beyond the kidneys — in cardiomyocytes, endothelial cells, fibroblasts, monocytes, and macrophages. At the same time, it was shown [10] that the hormone has a wide range of various pathogenic effects, one of which is the stimulation of atrial fibrosis, which is the structural basis for the development of atrial fibrillation.

Previously, it was believed that the use of angiotensin-converting enzyme (ACE) inhibitors leads to persistent inhibition of aldosterone synthesis by blockade of RAAS [11]. It was later revealed that the decreased production of this hormone during therapy with ACE inhibitors is short-term, and then its concentration in the blood increases again due to the effect of the hormone escaping drug control [12]. According to some studies [5], even a combination of ACE inhibitors and angiotensin-2 receptor blockers (ARBs) is not able to adequately suppress the production of aldosterone. This is due to the availability of alternative, non-AT-2-related stimuli for its formation. It has also been proven that aldosterone is just one of several hormones linking to mineralocorticoid receptors (MCR). In some diseases, such as chronic heart failure (CHF), hypertension, acute myocardial infarction, diabetes, activation of MCR can occur under cortisol action, which in normal conditions does not have a similar effect [13].

Thus, the discovery of new features of aldosterone suggests that the blockade of MCR can prevent or slow down atrial remodeling and thus contribute to decreased AF incidence.

Currently, the use of various antiarrhythmic drugs remains the cornerstone of anti-relapse therapy for AF [14–16]. However, this strategy does not always yield the expected results: first, antiarrhythmic drugs are usually prescribed after the first episode of AF, when its substrate is already, as a rule, formed; secondly, they affect only electrophysiological processes in the myocardium (duration of the action potential and the rate of the excitation pulse), without affecting the structural substrate of arrhythmia [15]. In addition, the use of antiarrhythmic agents in order to preserve the sinus rhythm is limited by their weak efficacy and the possible development of serious side effects.

Therefore, today the attention of researchers is increasingly focused on the so-called drugs for upstream-therapy, which are able to prevent the occurrence of AF, affecting its substrate. Such drugs include ACE inhibitors, ARBs, statins, omega-3 polyunsaturated fatty acids and MCR antagonists [17–20]. Their antiarrhythmic effect is caused by several factors: prevention of structural atrial remodeling by suppressing the processes of fibrosis, inflammation and oxidative stress, improving hemodynamics by reducing blood pressure (BP) and tension of the walls of the heart chambers, as well as preventing the development or progression of coronary artery disease, which is known to be one of the most important risk factors for AF [21].

A number of studies [22–26] have shown that the use of ACE inhibitors and ARBs prevents the development of new AF cases. Retrospective analysis in SOLVD (Studies of Left Ventricular Dysfunction) [22], which included 391 patients with left ventricular (LV) ejection fraction (EF) less than 30 %, showed that the use of enalapril reduced the risk of AF from 24 % to 5.4 %, and also reduced mortality in such patients. In another large study [23], which included 1,577 patients with left ventricular systolic dysfunction which developed as a result of myocardial infarction, the use of trandolapril within 2–4 years after the onset of infarction reduced the AF rate by 55 % (hazard ratio (HR) of 0.45; p <0.01). In the Val-HeFT (Valsartan Heart Failure Trial) study [24], the addition of valsartan to standard CHF therapy resulted in a 37 % decrease in AF rate. In a large LIFE (Losartan Intervention For End Point Reduction in Hypertension) study [25], 9,193 patients with hypertension and LV hypertrophy without AF were randomized into 2 groups: in group 1 they took losartan (50 mg/day), in group 2 — atenolol (50 mg/day) as antihypertensive therapy for an average period of 4.8 years. Despite an equal decrease in BP, the rate of AF paroxysms when taking losartan was significantly lower and amounted to 6.8 cases per 1,000 people per year, whereas when receiving atenolol it was 10.1 cases (HR of 0.67; p <0.001). The incidence of stroke among patients with AF paroxysms was also significantly lower in the losartan group (HR of 0.49; p = 0.01).

The results of the VALUE (Valsartan Antihypertensive Long-term Use Evaluation) study [26] involving 15,245 patients with hypertension, where valsartan reduced the risk of new AF cases by 17 % and of persistent AF — by 32 % compared to amlodipine, are convincing.

However, the positive role of ACE inhibitors and ARBs in secondary AF prevention is unfortunately questionable. A large randomized placebo-controlled GISSI-AF [27] study investigating valsartan efficacy for secondary prevention of AF paroxysms showed that the use of this drug for 1 year was not associated with a decrease in the rate of repeated AF episodes. There was no effect of valsartan on secondary endpoints — the number of arrhythmia episodes, heart rate at the first repeated episode, the number of hospitalizations for all reasons. The results of the J-RHYTHM II study did not demonstrate the advantages of candesartan in comparison with amlodipine for the prevention of repeated AF cases during 1 year [28].

Data on the efficacy of these drugs in the prevention of AF and in patients without pronounced structural changes of the heart are not convincing. The ANTIPAF study, which evaluated the possibility of using ARBs for secondary prevention of AF in patients with no pronounced structural changes of the heart, did not reveal a significant difference in efficacy between olmesartan and placebo [29]. Retrospective analysis of the AFFIRM study as a whole did not demonstrate the advantages of RAAS-blocking drugs for the control of sinus rhythm, but revealed their efficacy only in patients with CHF [30].

Apparently, the use of ACE inhibitors or ARBs is effective only in reducing the rate of new AF cases. Adding them to standard antiarrhythmic drugs in patients with existing AF does not increase the chances for maintaining sinus rhythm.

Some researchers [30] explain the lack of effect of these drugs in the secondary AF prevention by the already formed arrhythmia substrate, on the one hand, and the insufficient period of treatment for the implementation of the positive drug properties, on the other hand. Another possible explanation lies in the effect of aldosterone escape: apparently, the use of only ACE inhibitors or ARBs is not enough for a complete blockade of RAAS.

Numerous evidence of the important role of aldosterone in atrial remodeling and AF development [7, 31, 32] suggests that the use of MCR antagonists may prevent the occurrence of new cases or recurrence of this arrhythmia.

Indeed, a lot of experimental data have been accumulated [33–37] on the beneficial effect of MCR antagonists on the processes of structural atrial remodeling. In experimental models of permanent AF, spironolactone reduced the severity of cardiomyocyte apoptosis, cell degeneration, atrial fibrosis and contributed to the maintenance of functional parameters, in particular, LV EF [35]. These data clearly show that the blockade of MCR is a powerful therapeutic strategy and in combination with the use of ACE inhibitors or ARBs can contribute to the preservation of atrial structure and function with AF.

In another experiment [38] preliminary administration of eplerenone prevented excessive activation of profibrotic agents, but led to a subsequent increase in the level of AT-1. At the same time, additional use of losartan prevented aldosterone-mediated atrial fibrosis.

It is reported [39] that aldosterone has a powerful proinflammatory effect on myocardium, vessels and kidneys, while MCR blockers have pronounced anti-inflammatory properties.

Thus, experimental studies confirm the view that MCR blockade in combination with AT-2 inactivation can prevent the development of structural atrial remodeling and AF occurrence. However, the results of clinical studies on this issue are few and contradictory [40].

Eplerenone in AF prevention

Eplerenone is a relatively selective MCR blocker, binding mainly to these receptors, and to a lesser extent — glucocorticoid, progesterone and androgenic receptors [41]. The efficacy of eplerenone in AF prevention is confirmed in several studies.

In CHF. Ventricular dysfunction occurring in CHF is one of the main factors of structural and electrophysiological atrial changes underlying AF. Eplerenone has demonstrated its efficacy in AF prevention in patients with CHF. A two-year prospective EMPHASIS-HF study [42] investigated the use of eplerenone in patients with confirmed CHF of II functional class with reduced LV EF (≤35 %), who were on therapy with RAAS blockers (96.5 %) and -blockers (BB) (86.7 %). The use of eplerenone as the third neurohormonal modulator for an average of 21 months was accompanied by a decreased rate of new AF cases by 42 % (p = 0.034).

In hypertension. About 70 % of patients with AF have hypertension. Having a hypotensive effect, aldosterone antagonists can contribute to better control of BP — the most important risk factor for AF. Currently, a multicenter cohort study is being conducted to assess the prevalence of primary aldosteronism among patients with hypertension and AF, as well as the role of specific treatment in the incidence of AF relapses [43].

In stable AF. The efficacy of eplerenone in maintaining sinus rhythm after catheter ablation in patients with persistent AF was studied. The results of the study [44] involving 161 patients with a long history of persistent AF (stable AF lasting from 1 year to 20 years, an average of 3.4±3.8 years) who underwent catheter ablation are presented. All patients received conventional drug therapy with ACE inhibitors or ARBs, and eplerenone was additionally administered for 55 patients. During the next 24 months of follow-up, AF relapse was detected in 47 %. In the eplerenone group, there were significantly more patients with persistent sinus rhythm (60 %) compared to the standard therapy group (40 %, p = 0.011). Analysis using multivariate Cox regression model showed that the long duration of AF (>3 years, p <0.001) and early relapses (p <0.001) significantly correlated with the rate of repeated arrhythmia episodes, and only eplerenone therapy was associated with the preservation of sinus rhythm after catheter ablation (p = 0.017).

The role of spironolactone in AF

Data on the efficacy of nonselective MCR antagonist, spironolactone, in the literature are few. A small open prospective randomized trial of SPIR-AF [45] included 164 patients with a history of AF at least 4 years ago, who were divided into 4 groups depending on the treatment prescribed: spironolactone (25 mg/day) plus BB plus enalapril, spironolactone plus BB, enalapril plus BB and only BB. The recurrence rate of AF was significantly lower in the groups of patients treated with spironolactone than in those whose treatment was limited only to BB or a combination of the latter with enalapril.

In another randomized study [46] involving 166 patients with CHF, the use of spironolactone for 6 months was associated with a lower risk of new AF cases.

Disappointing results were obtained in a study on the role of ramipril and spironolactone in the prevention of postoperative AF in patients undergoing coronary artery bypass grafting [47]. Patients of the main groups for 4–7 days before surgery were administered with ramipril at a dose of 2.5–5.0 mg/day or spironolactone 25 mg/day, and patients in the control group received a placebo. Each group consisted of approximately 150 people. Treatment continued until discharge from the hospital.

Neither ramipril nor spironolactone showed significant differences in the rate of postoperative AF compared to the placebo. It can not be excluded that the lack of effect of these drugs is due to their isolated intake. Perhaps a combination of two RAAS inhibitors is necessary for successful prevention of AF.

We conducted our own study [48], which aimed to assess the efficacy and safety of spironolactone used in addition to standard therapy in patients with recurrent non-valvular AF. The work was carried out in accordance with international standards of GCP and the requirements of the Helsinki Declaration. The study protocol and informed consent form for patients were approved by the local Ethics Committee, Institute of Emergency and Reconstructive Surgery n. a. V. K. Husak (minutes of meeting No. 11 dated 23.09.2013).

A prospective cohort open-label randomized trial was performed in 89 patients who were included with an AF episode. After restoration of sinus rhythm all patients were randomized into 2 groups: individuals in group 1 (n = 46) continued to receive standard drug therapy (ACE inhibitors/ARBs, β-blockers, statins, antithrombotics, antiarrhythmic drugs of class III), patients in group 2 (n = 43) additionally received spironolactone at a dose of 25 mg/day with subsequent titration up to 50 mg/day. The duration of treatment and follow-up was 6 months, with the primary endpoint being a relapse of AF. The secondary endpoints of the study were the time before the first arrhythmia relapse, the type of sinus rhythm restoration (spontaneously or using cardioversion), the method of cardioversion (electrical, pharmacological), changes in the structural and electrophysiological parameters of the myocardium, and the development of adverse events.

Before treatment, there were no significant differences in age, gender, severity of underlying cardiac disease, comorbid conditions, left ventricular ejection fraction, volume of the left atrium and blood aldosterone between groups (Table 1).

The duration of AF history, number and predominant type of arrhythmia episodes, EHRA score, type and dose of antiarrhythmic drugs also did not differ between groups (Table 2).

Table 1. *Initial clinical characteristics of patients (m±σ, Me (Q1; Q3))*

Parameter	Control group (n = 46)	Spironolactone group (n = 43)	Significance (p)
Age, years, m±σ	62 (56; 69)	61 (55; 69)	0.9
Male, number of patients (%)	20 (44)	19 (44)	0.885
Hypertension, number of patients (%)	46 (100)	43 (100)	1.0
Heart failure I class (NYHA), number of patients (%)	12 (26.1)	10 (23.3)	0.95
Heart failure II class (NYHA), number of patients (%)	24 (52.2)	20 (46.5)	0.749
Heart failure III class (NYHA), number of patients (%)	10 (21.7)	13 (30.2)	0.5
LV EF, %	57 (52; 64)	56 (53; 63)	0.72
LA volume index, ml/m^2	28.6±4.4	29.0±5.1	0.94
Exertional angina, number of patients (%)	26 (56.5)	25 (58.1)	0.95
Exertional angina II class, number of patients (%)	16 (34.8)	14 (32.6)	1.0
Exertional angina III class, number of patients (%)	10 (21.7)	11 (25.6)	0.86
Myocardial infarction, number of patients (%)	32 (69.6)	32 (74.4)	0.786
Smoking, number of patients (%)	14 (30.4)	13 (30.2)	0.835
Diabetes mellitus, number of patients (%)	9 (19.6)	8 (18.6)	0.878
Body mass index, kg/m^2	32.1±4.8	31.8±5.2	0.95
Serum aldosterone during AF episode, pg/ml	172 (156; 198)	174 (155; 194)	0.748
Serum aldosterone level after sinus rhythm restoration, pg/ml	150 (132; 168)	148 (134; 165)	0.95
hsCRP serum level, mg/ml	4.22±0.78	4.18±0.64	0.9

Note: AF — atrial fibrillation, hsCRP — high sensivity C-reactive protein, LA — left atrial, LV EF — left ventricular ejection fraction

Table 2. *AF pattern and management in patients (m±σ, Me (Q1; Q3))*

Parameter	Control group (n = 46)	Spironolactone group (n = 43)	Significance (p)
Duration of AF anamnesis, months	24.2±6.2	22.8±4.3	p = 0.34
Number of registered episodes during the last 6 months	3 (2; 4)	3 (2; 4)	p = 1.0
Predominantly paroxysmal form of AF (spontaneous restoration of sinus rhythm), number of patients (%)	18 (39.1)	15 (34.9)	p = 0.847
Predominantly persistent form of AF (cardioversion is required for restoration of sinus rhythm), number of patients (%)	28 (60.9 %)	28 (65.1 %)	p = 0.847
EHRA II class, number of patients (%)	26 (56.5)	25 (58.1)	p = 0.953
EHRA III class, number of patients (%)	20 (43.5)	18 (41.9)	p = 0.953
Treatment with amiodarone, number of patients (%)	32 (69.6 %)	29 (67.4 %)	p = 0.991
Amiodarone average daily dose, mg	200 (200; 200)	200 (200; 200)	p = 1.0
Treatment with sotalol, number of patients (%)	14 (30.4 %)	14 (32.6 %)	p = 0.991
Sotalol average daily dose, mg	120 (80; 160)	120 (80; 160)	p = 0.934

Note: AF — atrial fibrillation

All patients received adequate concomitant drug therapy in accordance with current standards, there were no differences in the therapy between the groups. The mean dose of spironolactone in patients of group 2 at the end of the study was 37.5 (25; 50) mg/day.

For 6 months of treatment, relapses of AF were reported in 33 (71.7 %, 95 % confidence interval (CI) of 57.6 to 84.0 %) patients in group 1 and 21 (48.8 %, 95 % CI of 33.7 to 64.0 %) patients in group 2 ($\chi^2 = 3.97$; $p = 0.046$). At the same time, the absolute risk of arrhythmia relapse decreased by 22.9 % during additional spironolactone administration (95 % CI of 2.6 to 40.8 %, $p = 0.048$). Total time of follow-up was documented for 128 of arrhythmia relapses in group 1 and for 67 — group 2. The number of episodes per patient in group 2 was significantly ($p < 0.05$) lower compared to group 1 (2 (1; 2) versus 3 (2.5; 4), and the time before the development of the first relapse, on the contrary, was longer (62 (45; 78) days versus 32 (21; 45) days). Patients taking spironolactone had a higher number of cases with spontaneous sinus rhythm restoration compared to patients received standard therapy (35.8 % and 16.4 %, respectively, $\chi^2 = 8.28$, $p = 0.004$). The mean duration of AF relapse did not differ significantly between the groups.

In order to identify the pathogenetic mechanisms of spironolactone antiarrhythmic effect, we analyzed its effect on the main clinical and laboratory determinants of the disease. For 6 months of treatment, patients of group 2 showed a significant ($p < 0.05$ compared to baseline values and $p < 0.05$ compared to group 1) reduction of LV hypertrophy signs (thickness of the interventricular septum, LV myocardium mass index) and improvement of diastolic LV function (reduction in E/Em). LV myocardium mass index was also decreased in group 1, but this decrease was less pronounced than in group 2.

Positive changes during the follow-up period was noted in some indicators of myocardium electrophysiological state. Thus, patients in group 2 showed a significant ($p < 0.05$) decrease in the mean daily number of supraventricular and ventricular premature beats, dispersion of the P-wave and the registration rate of late atrial potentials.

Experimental studies show that aldosterone has a proinflammatory effect on myocardium, vessels and kidneys, while MCR blockers have pronounced anti-inflammatory properties. However, there are virtually no similar data obtained in clinical studies. We analyzed the effect of spironolactone on blood highly sensitive C-protein, a universal marker of inflammation. The baseline level of this protein did not differ significantly between groups. After 6 months of therapy, no significant changes in its concentration were observed in any of the groups.

The question about the effect of specific therapies with MCR antagonists on blood aldosterone is

of particular interest. Initially, this indicator did not differ between groups. The use of spironolactone for 6 months led to a decrease in the concentration of the hormone from baseline level (from 148 (134; 165) pg/ml to 124 (98; 138) pg/ml, p <0.05 compared to baseline values and p <0.05 compared to group 1). At the same time, in patients of group 1 who did not receive MCR antagonists, aldosterone level, on the contrary, increased significantly (from 150 (132; 168) pg/ml to 164 (146; 178) pg/ml, p <0.05).

During spironolactone administration, the frequency of adverse events requiring treatment discontinuation (hyperkalemia, orthostatic hypotension) was 12 % (95 % CI of 4.4 to 22.6 %). We did not observe any significant renal impairment and increased risk of gender-related side effects during 6 months of drug administration.

Thus, the use of spironolactone for 6 months as part of antiarrhythmic therapy was associated not only with significant reduction in the risk of AF relapses, but also with regression of LV hypertrophy, improvement in diastolic function, a decrease in the dispersion of the P-wave, ectopic atrial and ventricular activity and in the incidence of late atrial potentials. Our study did not reveal obvious effects of spironolactone on the volume of the left atrium and markers of inflammation: the decrease in these indicators during drug therapy did not reach statistical significance. It is noteworthy that the use of spironolactone for 6 months was associated with a decrease in plasma aldosterone, while the lack of MCR blockade led to its progressive increase, apparently due to the effect of the escape of aldosterone from therapy with ACE inhibitors and ARBs.

Currently, a randomized placebo-controlled INSPIRE-AF study (Inhibition of Aldosterone to Reduce Myocardial Diffuse Fibrosis in Patients with Paroxysmal and Persistent Atrial Fibrillation) is being conducted to assess the efficacy of spironolactone taken at a dose of 25 mg/day for 12 months in patients with paroxysmal and persistent AF with preserved LV EF [49]. The primary endpoint of this study is the reduction of myocardial fibrosis, determined by magnetic resonance imaging. The effect of the drug on the rate of AF relapses, quality of life of patients and laboratory markers of collagen metabolism will also be evaluated.

Currently, the study IMPRESS-AF (Improved exercise tolerance in patients with PReserved Ejection fraction by Spironolactone on myocardial fibrosiS in Atrial Fibrillation), dedicated to the assessment of spironolactone effect on exercise tolerance, quality of life and diastolic function of the heart in patients with symptomatic AF and preserved LV EF is on active phase [50]. This study involves 250 patients, who were randomized to receive spironolactone at a dose of 25 mg/day or a placebo for 2 years. Interestingly, the study includes patients with permanent AF. The primary endpoint is an improvement of exercise tolerance after 2 years of follow-up. Secondary endpoints include changes in quality of life (according to EQ-5D and the Minnesota Living with Heart Failure Questionnaire), LV diastolic function, and hospitalization for any reason.

Thus, the role of aldosterone antagonists in AF has not yet been definitively determined. Further clinical studies will determine the need to include this group of drugs in the treatment protocols for patients with AF.

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