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THE ROLE OF ALDOSTERONE IN THE DEVELOPMENT OF ATRIAL FIBRILLATION: MODERN UNDERSTANDING OF THE PROBLEM

Abstract

The literature review presents modern understanding of the role of aldosterone in the development and maintenance of atrial fibrillation. It is shown that the hormone takes part at all stages of the electrophysiological and structural atrial remodeling, contributing to the formation of the arrhythmia substrate. It was noted that negative effects of aldosterone in the myocardium are realized not only due to its high systemic production but also because of its direct synthesis in the atrial tissues. Increased expression of mineralocorticoid receptors in cardiomyocytes also play important role in the development of atrial fibrillation. It is demonstrated that hyperaldosteronemia can be a cause as well as an effect of atrial fibrillation. The episode of arrhythmia is characterized by neurohormonal activation, increased intramyocardial aldosterone synthesis and high mineralocorticoid receptor expression. This contributes to the further progression of atrial remodeling and creates conditions for the arrhythmia recurrence.

Key words: *aldosterone, atrial fibrillation, remodeling, renin-angiotensin-aldosterone system, genetic polymorphism*

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ACE — angiotensin-converting enzyme, AT2 — angiotensin 2, LV — left ventricle, MCR — mineralocorticoid receptors, RAAS — renin-angiotensin-aldosterone system, AF — atrial fibrillation

Atrial fibrillation (AF) is still 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]. Disturbed hemodynamics and thromboembolic complications associated with repeated AF episodes lead to considerable expenses on treatment, lower quality of patients' life and higher mortality [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 an undisputable fact that the development and maintenance of this arrhythmia is closely related to structural atrial changes, which are largely due to the excessive activity of renin-angiotensin-aldosterone system (RAAS) [3–5]. Higher activity of RAAS contributes to the development of inflammation, fibrosis, and oxidative stress in cardiomyocytes [3]. The pathogenic effect of RAAS hyperactivity was long associated primarily with the action of angiotensin-2 (AT2). Numerous experimental studies [6, 7] confirmed that this hormone had a number of proarrhythmic effects, such as activation of calcium currents through L-type channels, suppression of potassium flows, inhibited conduction of atrioventricular node, increased release of noradrenaline in atria, stimulation of fibrosis and systemic inflammation, etc. However, studies conducted in recent years [8–12] suggest that the majority of

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detrimental effects of RAAS, which were previously explained exclusively by the action of AT2, in fact can be attributed to the excessive activity of the end effector of the system, i. e., aldosterone.

Aldosterone role and metabolism in the body

Views on the role and metabolism of aldosterone in the body have changed considerably in recent years. According to the classic concept [13], aldosterone is an adrenal cortex hormone, the receptors of which are located in the kidneys, and its primary effect involves maintaining a constant volume of fluid in the body. However, information has been accumulated recently on the extraadrenal production of aldosterone (in the myocardium, vascular wall, adipose tissue, pancreatic cells and even brain), and its receptors were found far beyond the kidneys [14, 15]. It has been shown that the action spectrum of this hormone is not limited to influence on water-salt metabolism, but is represented by a wide variety of pathogenic effects.

RAAS serves as the principal mechanism for regulation of aldosterone secretion. Renin is synthesized in juxtaglomerular cells. It acts on angiotensinogen protein produced by the liver to form angiotensin-1, which has a poor vasoconstrictive effect. Then, under the influence of the angiotensin-converting enzyme (ACE) secreted in proximal renal tubules and lungs, angiotensin-1 turns into the potent vasoconstrictor AT2. The latter, in its turn, has a stimulating effect on the adrenal cortex, thus activating the secretion of aldosterone [16].

Along with AT2, sodium and potassium ions are the most important stimulators of aldosterone synthesis. An increase in potassium level just by 2 ppm increases the aldosterone level by 25 %. Adrenocorticotropic hormone, dopamine, endothelin, serotonin, vasopressin, and acetylcholine participate less in the stimulation of hormone synthesis. Agents inhibiting the production of aldosterone are atrial natriuretic peptide, heparin, and androgens [14, 16].

Almost all aldosterone is contained in the blood in free form. Under normal conditions, its plasma concentration depends mainly on the quantity of sodium taken with food, time of the day and body position. The minimum hormone level is observed in the morning and in prone position, and the maximum level — in the afternoon and in a vertical position (sitting, standing). Low salt intake leads to increased blood concentrations of the hormone, and excessive salt intake — on the contrary, to reduced blood concentrations. Plasma level of aldosterone decreases with age [16].

Aldosterone begins to act only after being bound to special protein structures — mineralocorticoid receptors (MCR). Numerous studies have shown that these receptors are scattered all over the body: along with classical epithelial MCR located in renal cells, they are found in cardiomyocytes, endotheliocytes, salivary and sweat glands, fibroblasts, monocytes, macrophages, adipose tissue cells and neurons [15, 17]. Both adrenal mineralocorticoid hormones — aldosterone and deoxycorticosterone — have high and almost equal affinity to MCR. However, the majority of the latter is contained in the blood in inactive form. Therefore, MCR are activated primarily owing to aldosterone. MCR can also be stimulated by glucocorticoids, particularly, cortisol. Although its affinity to MCR is slightly less than that of aldosterone, the plasma level of cortisol far exceeds the concentration of aldosterone. Therefore, it is cortisone that binds MCR in some tissues (pituitary gland, myocardium) [18].

Like all corticosteroid hormones, aldosterone has two mechanisms of action [19]. Genomic, or slow, mechanism is related to intercellular penetration of the hormone molecule and its binding to nuclear receptors with subsequent stimulation of synthesis of effector proteins. Effects induced by this interaction develop in hours or days. They include myocardial fibrosis, inflammatory reactions in vascular walls, development of edema syndrome, tissue remodeling, and apoptosis of cardiomyocytes [20]. Quick, or non-genomic, route of cell signaling transduction is mediated by interaction with membrane receptors, and includes activation of various kinase cascades. As this process does not require protein synthesis, the effect develops within minutes following interaction. Examples of a non-genomic mechanism include electrical myocardium remodeling, vasoconstriction, development of oxidative stress [21].

Primary physiological effects of aldosterone consist in maintaining water-salt balance in the human body [19]. Once in the bloodstream, aldosterone interacts with MCR of epithelial cells of distal tubules and renal collecting tubules, leading on the one hand to

increased reabsorption of sodium and fluid retention, and on the other hand to enhanced excretion of potassium and magnesium. Sodium-retarding effect of aldosterone plays a key role in maintaining homeostasis in the presence of hypovolemia.

In recent years, conclusive evidence has been obtained, showing that the action spectrum of aldosterone lies far outside the limits of the narrow range of "renal" effects. Systemic or local hyperproduction of the hormone causes a number of pathological effects [19–24]:

- sodium retention, loss of potassium and magnesium;
- endothelial dysfunction;
- myocardial and vascular wall inflammatory changes;
- reduced arterial compliance;
- AT2 vasoconstrictive action potentiation;
- catecholamine action potentiation;
- increased platelet aggregation;
- increased lipids;
- dulled baroreceptor response;
- oxidative stress induction;
- impaired function of ion channels in cells and repolarization processes;
- enhanced formation of collagen in organs and tissues;
- left ventricular (LV) hypertrophy;
- LV diastolic dysfunction;
- reduced heart rate variability;
- activated tumor growth factor β1;
- impaired glucose tolerance;
- insulin resistance.

Many of these effects play a key role in the development and progression of various cardiovascular diseases, including atrial fibrillation.

Aldosterone role in AF development and maintenance

Although the role of excessive activity of RAAS in AF development is no longer in doubt, the importance of aldosterone in the development and maintenance of this arrhythmia is only just being studied. Indirect evidence of that was obtained as early as 2005 by Milliez P. et al. [25], who showed that the risk of AF in patients with primary hyperaldosteronism was 12 times higher than in the general population. Further clinical studies [26, 27] found that blood level of aldosterone increased during an AF episode and decreased following sinus rhythm restoration. Experimental data obtained later showed that the blockade of aldosterone receptors contributes to the suppression of atrial fibrosis processes and prevents AF development [28].

It is assumed that pathological myocardial effects of aldosterone occur not only through its systemic hyperproduction, but also because of direct synthesis of the hormone in atrial tissues. It is reported [29] that local levels of AT2 and aldosterone are higher in patients with AF as compared to individuals with sinus rhythm. Moreover, the extent of local production of RAAS products varies in different categories of patients with AF and depends on the type of underlying disease. The existence of AF in patients with mitral stenosis is associated with high levels of both local and circulating AT2 and aldosterone, while the key role in AF development in mitral insufficiency belongs to local RAAS hyperactivity [30].

By combining experimental and clinical study data, Tsai C-T et al. [31] significantly expanded the existing understanding of mechanisms of adverse effects of aldosterone. Researchers have shown that the most important negative properties of the hormone are related not even mainly to its local hyperproduction in atrial tissue, but result from excessive expression of MCR. They have demonstrated that even in equal intra-atrial aldosterone level in patients with sinus rhythm and AF, MCR expression in the latter increases considerably. In their subsequent experiments based on atrial cardiomyocytes, the authors found that the increased expression of MCR is induced by quick depolarization occurring in AF. Exposure of cells with spironolactone weakens these processes.

Reasons for increased production of aldosterone in AF remain largely understudied. It is not clear whether AF itself induces synthesis of aldosterone or, on the contrary, overproduction of this hormone "triggers" mechanisms of arrhythmia development and maintenance. Analyzing literature data and findings of own studies [26, 27], it seems that the occurrence of AF may indirectly contribute to the development of hyperaldosteronism.

In particular, it is well known [32] that an AF episode is accompanied by pronounced neurohormonal activation: increased levels of AT2 and catecholamines, which are potent stimulators of aldosterone synthesis. Increase in AT2 concentration

during an AF episode (by increasing ACE expression) and the number of its receptors leads to not only higher adrenal production of aldosterone and its higher plasma levels, but also promotes excessive intramyocardial production of the hormone.

It is interesting that the impact of AT2 on the level and activity of aldosterone is not a one-way process: the latter, in its turn, potentiates negative effects of AT2. Synergism of AT2 and aldosterone has been confirmed by many experimental studies [33]. So, when working with smooth muscle cells, negative effects caused by AT2 (oxidative stress, apoptosis) were partially mitigated by exposing the cells to spironolactone, a MCR antagonist.

Aldosterone can activate type 1a AT2 receptors by increased phosphorylation of several signaling proteins (ERK1/2, JNK, NF-kB, etc.). AT2, in its turn, can stimulate nuclear MCR receptors. Both effectors of RAAS activate a number of factors in a synergic manner, which leads to the induction of cardiac hypertrophy and fibrosis processes, systemic inflammation and hypercoagulation [34].

Thus, the development of AF in itself clearly leads to higher systemic and local production of aldosterone. In its turn, the persistence of such hyperaldosteronism promotes the occurrence of all negative effects typical for this hormone: fibrosis, inflammation, and cardiomyocyte apoptosis. This leads to further atrial remodeling, forming a substrate for AF recurrences and thereby "completing the vicious circle".

Mechanisms of aldosterone-mediated atrial remodeling

For the development of AF, a triggering mechanism (trigger) is required, and for its maintenance — a certain atrial substrate. The arrhythmia substrate forms as a result of the so-called atrial remodeling [35, 36]. Detailed mechanisms of the process have not been fully elucidated yet. At the moment, electrical (electrophysiological), contractile and structural atrial remodeling has been identified [37].

Electrical remodeling is a set of intra- and extracellular changes in the myocardium, which result in the impairment of its electrophysiological properties [37]. Changes in the functions of ion channels, transporters and receptors lead to the impairment of depolarization and post-depolarization processes, development of atrial conduction heterogeneity, and consequently, the occurrence of re-entry waves and triggering activity, predisposing to AF. Preservation of AF further contributes to the progression of electrophysiological remodeling. High atrial contraction rate in arrhythmia leads to calcium overload of the atrial myocardium, which poses a threat to cell viability and triggers a number of compensatory mechanisms aimed at reducing its intracellular flow (inactivation of L-type calcium channels). Consequently, the atrial action potential duration and effective refractory period become shorter, which contributes to AF preservation. Electrophysiological remodeling induced by AF occurs quickly (usually within several days), but at the same time it is a fast reversible process after sinus rhythm is restored [38]. Contractile atrial remodeling occurs within the same time periods as electrophysiological remodeling. Reduction in intracellular calcium concentration at a high atrial contraction rate results in decreased contractility of atrii [38].

If arrhythmia persists for over 7 days, contractile remodeling transforms into structural remodeling, when different disturbances in myocardial cell and tissue structures occur [38]. At the cellular and tissue levels, structural remodeling is expressed as apoptosis, cellular degeneration, inflammatory changes, fibroblast proliferation, and at the macrolevel — as atrial hypertrophy and dilation. Many structural changes are irreversible and, ultimately, result in the development of permanent AF.

Role of aldosterone in electrical atrial remodeling

Numerous studies have shown that aldosterone is the most important mediator in electrical atrial remodeling. Mechanisms of such an effect are under discussion. Some assume that one of them is mediated through non-genomic effect of the hormone, i. e., the oxidative stress induction. Aldosterone directly stimulates the formation of reactive oxygen intermediates in the myocardium, which leads to the destruction of membrane components, with formation of lipid peroxidation products [10].

The other, more complex route is mediated by hyperproduction under the exposure of nuclear factor kappa B (NF-kB) aldosterone [39, 40]. This protein is one of the main transcriptional agents responsible for adaptive responses of cells. It represents the family of cytoplasmic proteins, which, when stimulated, pass into the free state, moving

to the nucleus where they exhibit activity binding to promoters of over 100 genes. NF-kB plays an important role in cellular proliferation, apoptosis, inflammatory and autoimmune responses, as it regulates the expression of genes involved in these processes. One of the important effects of NF-kB is its participation in regulating the function of ion channels. Stimulated formation of this protein under the influence of aldosterone leads to disturbed transmembrane ion fluxes, thus contributing to electrical atrial remodeling [40, 41].

Aldosterone-dependent electrical atrial remodeling can also be caused by calcium overload of cardiomyocytes. In the study conducted by Lalevée N. et al. [42], aldosterone increased calcium flux through T-type ion channels, without affecting L-type ion channels. This resulted in the overloading of cardiomyocytes with calcium, inducing the electrical atrial remodeling. The effect of aldosterone on calcium metabolism in cardiomyocytes was also confirmed by Sakamuri S. S. et al. [43]. The authors showed that the use of MCR antagonists can prevent the calcium overload of cardiac cells. This information helps explain the ineffectiveness of calcium channel blockers in preventing electrical remodeling and understand why the drugs failed in the clinical studies on AF prevention: they block L-type calcium channels, while aldosterone acts through T-type channels, i. e., the so-called escape phenomenon occurs.

Calcium metabolism disorders caused by aldosterone can, in turn, trigger a chain of other pathologic processes. In the section of human atrial cells, it was demonstrated that tachy-induced overload of atrial cells with calcium causes oxidative stress, cellular degeneration and mitochondrial dysfunction in them. It leads further to cellular apoptosis and contractile dysfunction [44].

Thus, the role of aldosterone in the induction of electrophysiological disorders in atrial cells is now obvious. However, it should be noted that electrical remodeling is a complex and multifactorial process, and despite all the studies conducted in this area, there are still more questions than answers. It is hard to say whether the findings of said studies can be fully extrapolated to the general population of patients with AF. In some publications, the effect of aldosterone on electrical remodeling processes was assessed only on the basis of cellular models, while the majority of patients enrolled in the conducted clinical studies had valvular AF (developed with an underlying severe mitral or aortic valve condition) and were subject to surgical intervention. At the same time, mechanisms of the effect of this hormone on electrophysiological processes in the myocardium in non-valvular AF remain unclear.

Aldosterone role in structural atrial remodeling

At the tissue level, structural atrial remodeling manifests itself in several processes: myocardial fibrosis, inflammatory changes, cardiomyocyte hypertrophy and apoptosis [45]. Current studies confirm that aldosterone participates in these processes [19].

There is more and more information available, showing that aldosterone is a key mediator for atrial fibrosis [46, 47]. Myocardial fibrosis is a pathologic process characterized by the destruction of the normal structure of cardiomyocytes and subsequent excessive deposition and accumulation of extracellular matrix proteins (collagens and fibronectins), which form the basis of connective tissue, in the destructed cardiomyocytes.

Underlying molecular mechanisms of this phenomenon are not entirely clear. Some assume that the trigger effect of aldosterone in myocardial fibrosis processes is implemented through a number of ways. Firstly, the hormone has a direct growth-stimulating impact on fibroblasts, and in this case the excessive expression of intramyocardial MCR plays the most important role in the implementation of profibrotic effects. The interaction between aldosterone and MCR leads to the stimulated production of types 1A and 3A collagen, transforming growth factor β1, alpha-type smooth muscle myosin and other fibrotic agents. In long-term and persistent hyperaldosteronism, the accelerated proliferation of collagen- and fibronectin-producing fibroblasts is observed. Eventually, it leads to the pronounced stimulation of perivascular fibrosis processes in intramyocardial vessels of atrii [48].

The other mechanism consists in the effect of aldosterone on the fibrinolysis system. It has been proven that the hormone affects a number of plasminogen inhibitors and activators, in particular, type 1 plasminogen activator inhibitor (PAI-1) and tissue-type plasminogen activator (t-PA) [49, 50]. Distortion of the PAI-1/t-PA ratio leads to the development of imbalance in the fibrinolysis system and coagulation system. It is well known [50] that PAI-1 and

t-PA are synthesized primarily by the vascular endothelium. Hyperaldosteronism-induced endothelial dysfunction results in disturbed participation of the endothelium in the regulation of fibrinolysis processes and the activation of myocardial fibrosis. The inhibitory action of aldosterone on the fibrinolysis system also promotes fibrosis processes. By suppressing the production of plasmin from plasminogen, aldosterone contributes to the accumulation of the extracellular matrix.

The fibrosing effect of the hormone can be mediated by the induction of inflammation, arteriolar necrosis and cardiomyocyte apoptosis [50]. Substitutive fibrosis processes develop subsequently in place of dead cells.

There is also a number of other potential, but less studied mechanisms. Rombouts K. et al. [51] say that aldosterone can inhibit the activity of collagenase, an enzyme participating in collagen catabolism processes. S. Johar et al. [52] demonstrate that aldosterone is a mediator of AT2-induced atrial fibrosis, while the use of spironolactone inhibits these effects of AT2.

Along with fibrosis, inflammatory changes in the atrial myocardium also play a role in the genesis of the structural remodeling of atrii. It is noted that AF often develops in patients after coronary artery bypass graft surgery, with the maximum incidence observed on day 2 or 3 following the surgery and coincides with peak blood concentrations of inflammatory markers (C-reactive protein, leucocytes, and interleukins). The level of C-reactive protein and incidence of arrhythmia episodes are substantially reduced by preventive application of glucocorticosteroids and other drugs having anti-inflammatory action in patients who underwent cardiac surgery and unoperated patients with AF [53]. This hypothesis has also been confirmed histologically [54]: microscopy of atrial issue in patients with AF often reveals inflammatory infiltration even when there are no other organic heart diseases.

It has been shown that aldosterone potentiates local inflammation processes in the endothelium of small and medium coronary vessels, as well as in perivascular areas of the myocardium. Even physiological concentrations of aldosterone in MCR-expressing cardiomyocytes cause rapid increase in the activity of genes involved in inflammation processes [55].

Pro-inflammatory effect mechanisms of the hormone are diverse [56]. First of all, the induction of inflammation is started by reactive oxygen intermediates. It is well known that the formation of hydrogen superoxide and peroxide leads to the activation of various pro-inflammatory transcription factors — protein-1 activator, NF-κB, etc. The activation of the latter subsequently results in the formation of different adhesion molecules, chemokines and inflammatory cytokines. In the experiment, systemic administration of aldosterone increased NADPH oxidase concentrations in macrophages, heart, vessels and kidneys [57]. *In vitro*, aldosterone activated chemoattractant lymphocyte factor, interleukin-16, antigen-4 associated with cytotoxic T-lymphocytes (CTLA4) and other inflammation mediators [58]. *In vivo*, aldosterone administration in rats increased the cardiac expression of intercellular adhesion molecules, cyclo-oxygenase-2, osteopontin and led to inflammatory changes in arteries involving perivascular macrophages. At the same time, the administration of MCR blockers in animals prevented such an inflammatory reaction. In kidneys, the administration of aldosterone caused perivascular leucocytic infiltration and increased expression of osteopontin and interleukins 1 and 6 [59].

Thus, there is no doubt about the role of aldosterone in the genesis of inflammatory changes in the myocardium.

While the effect of aldosterone on atrial tissues is only just being studied, the fact that this hormone is a key factor of structural ventricular remodeling is no longer in doubt [39]. Ventricular hypertrophy and fibrosis occurring in this case result in the increased stiffness of the left ventricle, the development of its diastolic dysfunction, subsequent hemodynamic atrial overload and occurrence of conditions for AF development.

There is no doubt that aldosterone takes part in the development of LV hypertrophy. It has been shown that aldosterone concentration in patients with hypertension significantly correlates to the mass index of its myocardium [39]. In patients with aldosterone-secreting adenomas, LV hypertrophy, which is reversible following tumor resection, is observed [59].

One of the best understood pathogenetic mechanisms of the development of LV hypertrophy against the background of hyperaldosteronism is associated with the hypertensive effect of the hormone. Sodium retention and increased circulatory

volume as a result of excessive production of aldosterone naturally leads to a rise of blood pressure, LV overload and compensatory gain in its myocardial weight [19].

However, there is emerging evidence that the hormone can stimulate hypertrophy processes, irrespective of the extent of its hypertensive effect. According to Tomaschitz A. et al. [60], aldosterone level in patients with mild and moderate hypertension who had LV hypertrophy was significantly higher than in patients with a comparable degree of hypertension but without LV hypertrophy. In experimental studies, aldosterone in the presence of sodium chloride stimulated myocardial fibrosis and hypertrophy, irrespective of blood pressure level [61].

By interacting with epithelium receptors of baroreflex areas, aldosterone contributes to their hyposensitization and impairment of blood pressure control mechanisms [61]. In this way, the hormone can modulate local sympathetic cardiac activity and indirectly affect the development of LV hypertrophy. Genetic factors affect the rate and degree of myocardial hypertrophy development as well. There is evidence that the gene responsible for aldosterone synthesis belongs to the group of genes, the expression of which determines the polygenic inheritance of LV hypertrophy [60].

With respect to the stimulating effect the hormone has on hypertrophy processes, the expected question arises whether such an effect is limited to the ventricular myocardium, or covers atrii as well. This question was answered in the experimental work by Reil J.-C. et al. [11], where osmotic minipumps, which supply aldosterone at a rate of 1.5 mg/h, were implanted subcutaneously in 11 rats of the treatment group. The control group included 9 native rats. Standard electrocardiogram, AF inductivity and atrial pressure were analyzed in the animals following 8 weeks of observation *in vivo*. Then, isolated hearts were assessed for LV function and atrial conduction, and epicardial mapping was performed. Histologic examination of tissues was also conducted. The results showed that neither systolic, nor diastolic LV function, as well as atrial pressure, changed in the animals that received aldosterone. At the same time, longer P-wave, increased overall time of atrial activation, and impaired local conduction were observed in them. Histologic differences consisted in the development of hypertrophy of atrial cardiomyocytes and their fibrosis in the treatment group. This model proves conclusively that aldosterone has a direct effect on the atrial myocardium, including hypertrophy processes therein.

Aldosterone synthase gene polymorphism as a risk factor for AF

As is known, the most common causes of AF are ischemic heart disease and hypertension, and, rarer, valvular heart disease [1]. However, sometimes clinicians have to deal with family cases of arrhythmia or observe early onset of the disease in the absence of clear cardiac and extracardiac causes, which allows suspecting the genetic nature of the disease [62].

There is now data showing that the primary genetic determinant of non-familial AF forms is polymorphism of the RAAS genes [63]. The role of the terminal effector of the system, i. e., aldosterone, in the development and progression of myocardial remodeling is also determined to a considerable extent by genetic factors. In particular, the key enzyme participating in synthesis of the hormone is aldosterone synthase, for the primary structure of which the *CYP11B2* gene is responsible. Polymorphism of the fifth region of the gene has been examined most of all. The DNA region in the regulatory area of the *CYP11B2* gene where cytosine (C) in the -344th position is replaced with thymine (T) is designated as genetic marker C(-344)T. There are 3 potential genotypes of this fragment: C/C, C/T, T/T [64].

Some assume that the activity of aldosterone, and hence the intensity of its pathogenic effects, may depend on polymorphism of C(-344)T. According to recent studies [65, 66], the presence of T-allele (rs1799998 polymorphism) is associated with hypertension, chronic kidney disease and cardiac hypertrophy.

Data on the interrelation between C(-344)T polymorphism and AF development still remains contradictory. Amir R. E. et al. [67] examined the relationship between different genotypes of the enzyme and the risk of AF in 178 patients with LV systolic dysfunction. Arrhythmia was diagnosed in 57 (32 %) patients. The genetic study found that -344 CC genotype is a potent predictor of AF: almost half (45 %) of the patients with this genotype had arrhythmia, while in individuals with -344 TT and TC types it was reported cumulatively only in 27 % of cases ($p = 0.02$). Multivariate

regression analysis has shown that, after age and the size of the left atrial, -344 CC genotype was the most potent independent predictor of AF (odds ratio: 2.59, 95 % CI: 1.68–3.98, p = 0.02).

Other researchers, in contrast, have found a relationship between the presence of T-allele of aldosterone synthase C(-344)T gene and the development of AF. Sun X. et al. [68] did not find any significant impact of the gene polymorphism on the risk of AF development or recurrence. ACE (I/D) genotype has become the determining genetic factor for the development of arrhythmia. According to these and some other researchers [69], C(-344)T polymorphism in the aldosterone synthase gene is not directly related to the risk of AF, but is associated with the development of structural atrial remodeling.

Convincing results have been obtained in the meta-analysis that included 2,758 patients with AF from six different studies [69]. The authors found that the presence of C-allele in C(-344)T gene of *CYP11B2* substantially increases the risk of AF (odds ratio: 1.26, 95 % CI: 1.11–1.42, p = 0.0002).

Finally, a recent large-scale meta-analysis of 12 studies involving 5,466 patients confirmed that C(-344)T polymorphism with presence of T-allele (rs1799998) is closely related to a higher risk of AF in the general population (odds ratio: 1.29, 95 % CI: 1.08–1.54, p = 0.005), and its highest predictive value is typical for East Asians and individuals with hypertension and heart failure [66].

Still, the ambiguity of the available information on the contribution of aldosterone synthase C(-344) T gene polymorphism to the development of AF makes it necessary to conduct further studies in this area.

Conclusion

The excessive activity of aldosterone undoubtedly plays a role in the development and maintenance of AF. The hormone takes part in all the stages of electrophysiological and structural atrial remodeling, promoting the formation of arrhythmia substrate. The occurring disorders are not only the result of hemodynamic changes in cardiac chambers, but also the consequence of the direct action of aldosterone on the atrial myocardium.

The adverse myocardial effects of the hormone occur not only through its systemic hyperproduction, but also because of direct synthesis of the hormone in atrial tissues. Increased expression of MCR plays a major role in the development of AF.

Hyperaldosteronism can be a cause as well as the effect of AF. An episode of arrhythmia is characterized by pronounced neurohormonal activation, accompanied by an increase in intramyocardial synthesis of aldosterone and expression of its receptors. This contributes to further atrial remodeling, by creating conditions for arrhythmia recurrences and thereby "completing the vicious circle".

The data obtained helps to shed light on AF development mechanisms and the role of aldosterone in them. Further study of pathogenic effects of the hormone and their pathways may contribute to the discovery of new therapeutic approaches to the treatment of arrhythmia.

Conflict of interests

The authors declare no conflict of interests.

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