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Antiarrhythmic potential of aldosterone antagonists in atrial fibrillation

Rafał Dąbrowski, Hanna Szwed

Institute of Cardiology, Warsaw, Poland

Abstract

Upstream therapy is the promising issue in the treatment of atrial fibrillation (AF) especially in patients with arterial hypertension and heart failure. The possible beneficial effects of renin–angiotensin–aldosterone system blockade with ACE-inhibitors and angiotensin receptor antagonists in AF prevention have been demonstrated in experimental and clinical studies. There is growing mass of evidence, from both theoretical and experimental research studies, to suggest that upstream therapy using spironolactone or eplerenone may reduce the deleterious effect of excess aldosterone secretion and further modify the environment of AF including inhibition of atrial muscle fibrosis. It refers to patients with different forms of AF, including chronic AF. Aldosterone antagonists treatment may be a simple and valuable additional option in low-risk, hypertensive and heart failure patients in primary and secondary prevention of refractory paroxysmal and persistent AF. (Cardiol J 2012; 19, 3: 223–229)

Key words: aldosterone antagonists, atrial fibrillation

Introduction

Recent years have verified rather negatively the effectiveness of antiarrhythmic drugs in long-term prevention of atrial fibrillation (AF) episodes. One of the most relevant and promising issue is "upstream therapy" and the search for triggers of arrhythmia to treat the potential mechanisms of rhythm disturbances. Although invasive electrophysiology has made a great progress in the diagnosis and treatment of arrhythmias including AF, it is a limited option in the large population of AF patients. Its efficiency in longer perspective is still not fully established. Therefore, it seems important to search for new therapeutic methods that are inexpensive, non-invasive, well tolerated and especially may help to prevent recurrences of AF.

According to the experimental study by Wijffels et al. [1] ,,AF begets AF", after arrhythmia occurrence electrical, neurohormonal and structural remodeling begin and risk of further arrhythmia persistence increases. In the course of electrical remodeling, atrial effective refractory period (AERP) is reduced. Its association with heart rate decreases due to action potential reduction (diminution of calcium channels type L activity even up to 70%) [2]. AERP reduction creates conducive conditions of re-entry circuit formation. Reduction of repolarizations of *Ito* potassium currents and amplification of depolarization of I_{Na} and I_{NCX} currents takes place [3]. Modifications of inward rectifier potassium currents I_{K1} and nerve vagus activated currents I_{KAch}, acetylocholine dependent, have been reported [4]. The function of these currents regulates resting potential values [5]. Electrical remodeling of the sinus node is reflected by longer pauses after conversion to sinus rhythm. At the same time neurohormonal early changes occur: growing concentrations of atrial (ANP) and B-type (BNP) natriuretic peptides, angiotensin II (ANG II), aldosterone (ALD),

Address for correspondence: Rafał Dąbrowski, MD, PhD, Institute of Cardiology, 2nd Ischemic Heart Disease Department, ul. Spartańska 1, 02–637 Warszawa, Poland, tel/fax: + 48 22 844 95 10, e-mail: rdabrowski45@gmail.com

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epinephrine [6, 7]. Structural remodeling consequences are atrial enlargement, miocytes hypertrophy, contractility impairment and promotion of fibrosis. Interstitial fibrosis is a significant substrate of arrhythmia, especially in patients with congestive heart failure (HF). It's preceded by growing activity of matrix metalloproteinases and proinflammatory cytokines, like growing factor beta-1. Simultaneously more pronounced collagen I and III expression, "up-regulation" of metalloproteinases-2 and "down-regulation" of tissue inhibitor metalloproteinase-1 (TIMP-1) occur [8, 9].

Theoretical considerations of RAAS blockade in atrial fibrillation

Nakashima et al. in experimental studies demonstrated ANG II effect on atrial electrical remodeling: increased calcium channels L ion current due to activation of protein kinase C and phosphorylation of these channels [10, 11]. Additionally, inhibition of potassium currents occurs which has an adverse impact on the level of the action potential plateau and repolarization [12]. ANG II also inhibits conduction in the atrioventricular node, which can cause increased risk of ventricular arrhythmias in the mechanism of reentry [13]. Another adverse effect of ANG II is the increased release of norepinephrine from atrial sympathetic nerves through the activation of nodal AT-1 receptors and a reduction of beta-adrenergic receptors density. This is a proof of the interdependence between the adrenergic and renin–angiotensin–aldosteron-system (RAAS) [14, 15]. ANG II also activates fibroblasts and promotes the synthesis of growth factor beta-1 (TGF-beta-1). This leads to accumulation of collagen and further structural transformation of the heart. Progress of interstitial changes provoked by MAP kinase increases the risk of AF. Finally, increased expression of cardiac ANG II causes atrial enlargement and fibrosis [9]. Table 1 presents the most important mechanisms responsible for proarrhythmic actions of ANG II. Proarrhythmic effects of ANG II and ALD are sufficiently documented in experimental studies and they are responsible for structural, neurohormonal and electrical remodeling of the atria [10, 16]. High activity of ANG II and ALD promotes fibroblasts activation and collagen accumulation that lead to structural changes in the heart muscle. The role of the RAAS overactivity mechanisms in AF promotion has been sufficiently documented [9].

ANG II stimulates ALD synthesis in the zona glomerulosa of the adrenal cortex via ALD synthase.

Table 1. Proarrhythmic action of angiotensin II.

Activation of calcium currents through L channels
Inhibition of potassium currents
Inhibition of conduction in atrio-ventricular node
Increased release of norepinephrine from atrial sympathetic nerves
Reduction of beta-adrenergic receptors density
Systemic pro-inflammatory and hypercoagulation effects
Fibroblasts activation, increase of collagen synthesis (MAP kinase)
Cardiac hypertrophy and fibrosis
Structural remodeling of atria and ventricles
Dilatation of atria and ventricles

Other important factors stimulating ALD synthesis are corticotrophin, endothelin, adrenalin, arginine vasopressin, serotonin, nitrogen oxide and potassium concentration [17–20]. ALD enhances the effects of ANG II in part via increased transcription of AT-1 receptor and ACE, whereas ANG II may increase systemic and tissue concentrations of ALD, consistently with elevated plasma levels of both ANG II and ALD during AF [16]. ALD induces cell proliferation and myocardial fibrosis possibly due to an increase in the quantity of AT-1--receptors and enhanced local expression of the angiotensin converting enzyme [18, 21, 22]. In experimental studies, apart from its hypertensive action, ALD significantly influenced the promotion of hypertrophy, fibrosis, and necrosis of cardiomyocytes, endothelium and vessel wall cells. ALD stimulates collagen I, III synthesis and fibroblasts by activating mineralocorticoid local receptors (MR). It also promotes inflammatory processes, oxidative stress, autonomic system dysfunction, necrosis of atrial myocytes and vascular damage [18, 21–23]. ALD receptors were identified in the endothelium, left ventricle, brain, kidneys, colon, salivary and sweat glands. ALD can be synthetized locally as well in the brain, heart and blood vessels [19, 20]. Other potentially arrhythmogenic mechanisms of ALD actions include inhibition of noradrenaline reuptake, attenuation of baroreceptor activity, increase of their sensitivity to catecholamines and reduction of sinus rhythm variability. A significant loss of potassium and magnesium is also important [17, 23]. Tsai et al. [24] have measured ALD levels and expression of steroidogenesis proteins in atrial tissue, obtained from patients with and without AF during surgery. Patients with AF had increased expression of the atrial mineralocorticoid receptor as compared

Table 2. Deleterious actions of aldosterone.

Changes in myocyte electrical properties
Abnormal repolarization
Ion channel abnormalities
Baroreceptor dysfunction
Sodium retention, loss of potassium and magnesium
Catecholamine potentiation
Ventricular arrhythmias
Myocardial fibrosis and hypertrophy
Vasoconstriction
Endothelial dysfunction
Prothrombotic effects
Vascular inflammation
Oxidative stress

to patients with sinus rhythm. It is possible that the effects of ALD in the atria are not due to the amount of hormone that is generated locally, but might depend from an increased tissue expression of mineralocorticoid receptors (MR). Another study demonstrated that expression of MR is increased by sustained electrical field depolarization, and that exposure of cells to ALD activates the inward calcium and outward potassium current. In these *in-vitro* experiments, co-incubation with spironolactone (SPIR) attenuated the changes induced by exposure of atrial cells to ALD, indicating the involvement of a MR-dependent pathway. These findings help promote understanding of the cellular and electrophysiological mechanisms that might account for the beneficial effects of SPIR in the prevention of AF (Table 2) [25].

Clinical evidence for RAAS inhibitors in the prevention of atrial fibrilation

The beneficial effects of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) are mainly due to inhibition of ANG II action, with directly results in blood pressure reduction, improvement of the large vessels distensibility, reduction of hypertrophy and prevention of left ventricular remodeling. This leads to a reduction in afterload and systolic left ventricular strain. In addition, blood pressure is reduced, as well as atrial wall strain and the degree of mitral regurgitation. The amount of catecholamines in the blood and myocardium is reduced, but the concentrations of bradykinin and prostaglandins are growing. ACE-I increase parasympathetic activity and inhibits the activity of ALD [9]. It has been shown that these drugs have anti-inflammatory and antioxidant properties. In patients with permanent AF, ACE-I reduces the expression of Erk1/Erk2 protein kinases which activates the fibrosis process [16]. In retrospective, but especially in prospective studies, treatment with ACE-I reduced the recurrence of persistent and paroxysmal AF [26–29]. On the contrary the GISSI-AF prospective study revealed that one-year treatment with valsartan was not associated with a reduction in the incidence of recurrent AF [30]. ALD antagonists, ACE-I and ARB, have an additional antiarrhythmic potential and could be used in the treatment and prevention of AF. Results of experimental studies have revealed that enalapril decreases atrial fibrosis and structural remodeling and reduces the risk of AF in HF as well [31]. Analysis of 4,661 patients with AF, from a population of 682,993 patients treated for hypertension, revealed that long-term therapy with RAAS inhibitors ACE-I, ARB and beta-blockers, were associated with a lower risk for AF [32].

Potential of aldosterone antagonists in atrial fibrillation prevention: Experimental and clinical studies

All of the above mentioned mechanisms, especially electrolyte and autonomic imbalance and the severity of fibrosis, affect the environment of the arrhythmias and increase the risk of AF. Patients with primary aldosteronism have an average 12-fold higher risk of AF [33]. It was shown that ALD concentration increases during AF [34]. Plasma aldosterone-receptor expression is higher in atria of AF patients [35]. Myocardial fibrosis is particularly important in the impairment of myocardium function and as a substrate for arrhythmias. Fibrotic tissue, with a low voltage, may be a potential cause of atrial activation disturbances that may be involved in AF occurrence and maintenance [36]. Experimentally-induced fibrosis in an animal model resulted in a greater likelihood of AF [37]. Atrial tissue samples from patients with AF also showed increased fibrosis [38]. Rapidly stimulated cardiomyocytes during AF secrete substances that increase collagen and fibronectin-1 in atrial tissue by a factor of four [39]. Frequent episodes of AF exacerbate fibrosis which increases the risk of further seizures. Spatial distribution and the extent of fibrotic tissues of low voltage has a significant impact on the fibrillatory dynamics of contraction, including the location and propagation of fibrillation waves [40]. It is likely that the processes of fibrosis and remodeling contribute to the formation of

re-entry circuits sustaining arrhythmia [41]. The reduction of myocardial tissue strain and the shortening of the effective refractory period may be responsible for changes of the electrical activity. Preliminary results show that the success of pulmonary vein isolation during ablation is limited by the presence of fibrotic tissue with a low voltage or scars [42, 43]. Histological examinations confirmed the presence of fibrosis in tissues with a low voltage, but the assessment of their extent and severity is difficult [44]. Magnetic resonance imaging (MRI) with late enhancement is a good method to assess fibrosis and tissue remodeling. Marrouche at al. [45] of the University of Utah Health Sciences Center has published several reports on the role of magnetic resonance imaging in the evaluation of the anatomy of the myocardium structure in terms of prevalence of atrial fibrosis. Multivariate analysis demonstrated that the area of late enhancement of the walls of the left atrium (LA) in MRI correlates with the severity of AF. These studies suggest that the success of ablation depend on the extent of fibrosis within the atria. Scope of degenerative changes is assessed in the study of magnetic resonance delayed enhancement (DE-MRI), in which the test is performed 10 min after administration of the contrast. This allows the assessment of tissue viability and the degree of fibrosis. The UTAH scale was created to assess the degree of atrial fibrosis on the basis of DE-MRI: minimal — stage 1, < 5%, mild — stage 2, 5–20%, moderate — stage 3, 20–35%, and extensive — stage 4, > 35% [41, 45]. Excessive enhancement in the walls of the LA indicates substantial degree of fibrosis and also a high risk of AF recurrence after ablation procedure [41].

In the experimental model of myocardial infarction only SPIR caused a reduction of fibrosis within the atrial muscle and the shortening of the P wave in ECG [33]. SPIR has been shown to reverse the effects of LA remodeling by reducing atrial hyperexcitability, inhibition of vascular Ang-I/ /Ang-II conversion and attenuation of atrial fibrosis [46]. Therefore, there is enough evidence, from both theoretical and experimental research studies, to suggest that treatment of "upstream therapy" using SPIR or eplerenone may reduce the deleterious effect of excess ALD secretion and, indirectly, ANG II, and may also modify the environment of arrhythmias, including inhibition of fibrosis (Table 3).

Goette at al. [34] demonstrated that AF occurrence results in an increase in ALD concentration, and 2 days after cardioversion its level declines with the reduction of aldosterone–renine index and mean heart rate. In an experimental study, atenolol, lisinopril and SPIR effects were evaluated for 3 months after heart infarction. Only SPIR generated a reduction of atrial fibrosis and a reduction of P wave activity in ECG [47]. These two factors are among the risk factors for AF episode occurrence. Thus, it is logical that the up-stream therapy with SPIR can further diminish a potentially harmful effect of ALD and indirectly, ANG II, modifying the setting of possible occurrence of arrhythmia. Arterial hypertension is present in approximately 70% of AF patients. SPIR, having antihypertensive properties, may have contributed to a better control of hypertension, which can be of importance in its antiarrhythmic action. In some patients it may be either alternative, i.e. supplementing or concomitant therapy. Eplerenone, a novel selective ALD antagonist may be a valuable alternative for a wider implementation of such a therapy in case of SPIR side effects, especially gynecomastia occurrence.

Table 3. Possible beneficial effects of aldosterone antagonists (spironolactone, eplerenone) in prevention of atrial fibrillation.

Shortening of the P wave in ECG
Reduction of atrial hyperexcitability
Prevention of vascular endothelium changes and oxidative stress
Attenuation of atrial fibrosis, reduction of type I and III procolagen synthesis
Attenuation of volume overload of the left atrium
Stabilization of electrolyte concentration (potassium) and autonomic balance
Antihypertensive properties
Reduction of pre-load
Prevention of cardiac remodeling: reduction of the dimensions of the left atrium and both ventricles
Improvement of left ventricular function and ejection fraction
Prevention of refractory paroxysmal and persistent atrial fibrillation

Sub-analysis of the EMPHASIS study (eplerenon in patients with mild systolic HF, NYHA II, ejection fraction < 35%) indicated that the eplerenone treatment can prevent first AF or atrial flutter episode. In the study, 1,364 patients received eplerenone at a dose of 25–50 mg, and 1,373 patients received a placebo. The study was terminated after 21 months because of the 37% reduction in the combined end point: 24% reduction in cardiovascular death and 42% reduction in hospitalization [48]. After 2 years of observation, newly-detected AF occurred in 2.7% of patients treated with eplerenone compared with 4.5% receiving placebo [49]. Single

center, prospective, randomized SPIR-AF study included patients (n = 164) with recurrent, paroxysmal or persistent AF, who did not responded to treatment with conventional class I and III antiarrhythmic drugs or were intolerant to them. The study demonstrated a reduction of AF episodes during 12 months of treatment with SPIR and a beta-blocker therapy, compared with enalapril and a beta-blocker or the beta-blocker drug without the use of antiarrhythmic drugs [50].

Prevention of left ventricle and atrial remodeling in patients with chronic atrial fibrillation: RAAS blockade

In chronic disease states such as arterial hypertension and HF, AF may be a consequence of pathological modulation of intercellular signals [51, 52]. Longer lasting AF causes structural changes within the atria leading to increased activity of dipeptidyl peptidase IV, and an increase in the expression of ANG-converting enzyme and ALD. At the same time the levels of bradykinin decreases [16]. The results of experimental studies in dogs with HF (rapid ventricular pacing for 5 weeks) showed that administration of enalapril reduces atrial fibrosis and heart remodeling and reduces the risk of AF occurrence in HF, which indicates the role of the RAAS system in remodeling of the atria [31]. In another study in dogs undergoing rapid ventricular pacing to induce HF, administration of enalapril resulted in decreases in conduction heterogeneity and reduced AF duration and degree of fibrosis within the atria [55]. Potentially beneficial effects of ACE-I and ARB is to prevent adverse changes within the ion channels, stabilization of electrolyte concentration, prevention of overloading the cells with calcium ions and reduce the degree of atrial wall stretch, end-diastolic pressure reduction in the left ventricle and the prevention of cardiac fibrosis [21]. Chronic AF is a permanent arrhythmia which in longer period promotes electrical and structural remodeling of atria and ventricles [53, 54]. AF itself perpetuates the development of structural atrial alterations by the increased expression of angiotensin converting enzyme, number of AT-1-receptors in cardiomyocytes and ALD action. ANG II and ALD promote the activation of fibroblasts and collagen accumulation, which lead to atrial structural and electrical remodeling [18]. Lack of the hemodynamically effective systole of atria synchronized with the systole of ventricles and a chaotic rhythm of ventricles result in the volumetric overload of the cardiac chambers, reduced diastolic filling and reduced stroke volume. These changes are followed by a decrease in renal perfusion, activation of the RAAS and adrenergic systems, increased vasopressin, ANG II and ALD secretion. ALD concentrations are elevated in patients with persistent AF [34]. Long lasting AF leads to interstitial fibrosis, monocytic infiltration, degeneration and atrophy of atrial myocytes, atrial and ventricular remodeling and, finally, to HF. Reports suggests that suppression of RAAS activity by ACE-inhibitors may inhibit atrial and ventricular remodeling [10, 55]. SPIR may prevent cardiac remodeling via the ACE, epidermal growth factor receptor (EGFR), extracellular signal-regulated kinases (ERK) pathway, nicotinamide adenine dinucleotide phosphate oxidase, lectin-like oxidized low-density lipoprotein receptor-1 and Rho-kinase pathways [56]. SPIR has an early gene-regulatory effect independent of MR. The affected genes encode a large number of signaling proteins and receptors, including immunoinflammatory response genes, apoptosis and antiapoptosis genes. The results indicate that SPIR affects genes controlled by the transcription factors NF-kappaB, CEBPbeta and MYC [57]. SPIR protects from caspase-3 activation induced by serum deprivation in contrast to the selective MR antagonist, eplerenone, that is non-protective. Progesterone, hydrocortisone and dexamethasone all protect human umbilical vein endothelial cells from serum-deprivation induced caspase-3 activation, whereas ALD and dihydrotestosterone had no effect. SPIR displayed agonist activity only to the progesterone receptor. SPIR and progesterone, but not eplerenone, inhibited mitochondrial cytochrome c release and cleavage of nuclear poly (ADP-ribose) polymerase (PARP) by a NO-independent mechanism and increased cell viability. This effect is likely mediated by the agonist properties of SPIR toward the progesterone receptor [58].

Experimental and clinical studies showed a beneficial effect of ALD receptors antagonists on the inhibition of heart and arterial remodeling in arterial hypertension [59, 60]. The RALES landmark study showed a significant reduction of the morbidity and risk after 24 months of blocking ALD receptors by SPIR among patients with severe HF [61]. In patients after myocardial infarction, SPIR and potassium canrenoate treatment resulted in the reduction of type I and III procolagen synthesis and inhibition of left ventricular dilation [62, 63]. Dilated left atria and fibrosis may be a direct consequence of left ventricle dysfunction and hemodynamic atrial overload. In the study by Milliez et al. [47], SPIR, an ALD antagonist, was introduced

three months after myocardial infarction, when atrial remodeling had developed. The effect of the treatment was insignificant after one month of therapy, but SPIR reduced the fibrosis of dilated atria in the course of HF. Apart from fibrosis inhibition, an important factor may be the attenuation of volume overload of the LA, electrolyte and autonomic balance stabilization. It is possible that ALD, apart from influencing indirectly on the AF development, may exert a further augmented action on the remodeling of atria and ventricles in the vicious circle mechanism according to the statement that "AF begets AF" [1, 64]. Long lasting AF leads to atrial and ventricular remodeling followed by HF, so early prevention with an ALD antagonist, SPIR or eplerenone, may be justified. SPIR has been shown to reverse the effects of LA remodeling by reducing atrial hyperexcitability, inhibition of vascular Ang-I/Ang-II conversion and attenuation of atrial fibrosis [65]. In an experimental study, three groups of dogs (n = 21) had right atrial pacing for 6 weeks. The group was given SPIR one week before, and during, the atrial pacing. Myolisis, atrial fibrosis and dilatation were all significantly increased and these changes were inhibited by SPIR. SPIR treatment reversed the increased expression of caspase-3, bax, calpain I and MMP-9 and the decreased level of Bcl-2, calpastatin and TIMP-1, induced by chronic atrial pacing [66]. SPIR can prevent vascular changes and oxidatative stress [67]. Eight genes have been identified whose expression is regulated by ALD, and which are involved in the process of remodeling the left atria and the regulation of vascular tone [68]. Clinical reports show that long lasting therapy with SPIR at 25 mg/day may result in a significant reduction of the dimensions of the LA and both ventricles in patients with chronic AF. In a meta-analysis of 19 randomized trials evaluating the treatment of ALD antagonists, SPIR, eplerenone, or potassium kanreonate of heterogeneous groups of patients with left ventricular dysfunction, 20% reduction in overall mortality and 3.1% improvement in left ventricular ejection fraction was observed [69]. Results of the study using an experimental model of heart infarct in rats showed that eplerenone, added to irbesartan, caused the improvement of left ventricular function and inhibited its remodeling [70]. Patients with chronic heart failure (n = 51), NYHA class I–III, ejection fraction < 40%, were randomized to treatment of SPIR, candesartan *vs* placebo. MRI demonstrated significant improvement in left ventricular ejection fraction (35 *vs* 26%, $p < 0.01$) and other parameters evaluated in tissue Doppler in patients treated with two drugs, indicating inhibition of left ventricular remodeling [71].

Recently some papers addressed the issue of aldosterone-receptor antagonism as a potential therapeutic target in prevention and regulation of AF [72, 73].

Conclusions

Aldosterone antagonists treatment may be a simple and valuable additional option in low-risk, hypertensive and HF patients in primary and secondary prevention of refractory paroxysmal and persistent AF. In patients with chronic AF aldosterone antagonists can suppress atrial and ventricular remodeling.

Conflict of interest: none declared

References

1. Wijffels MC, Kirchof CJ, Dortland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation, 1995; 92: 1954–1968.
2. Nattel S. New ideas about atrial fibrillation 50 years on. Nature, 2002; 415: 219–226.
3. Nattel S. Therapeutic implications of atrial fibrillation mechanisms: Can mechanistic insight be used to improve AF management? Cardiovasc Res, 2002; 54: 347–360.
4. Dobrev D, Graf E, Wettwer E et al. Molecular basis of downregulation of G-protein-coupled inward rectifying K(+) current I (K, Ach) in chronic human atrial fibrillation, decrease in G/RK4 mRNA correlates with reduced I(K,Ach)) and muscarinic receptor-mediated shortening of action potentials. Circulation, 2001; 104: 2551–2557.
5. Cha TJ, Ehrlich J, Goette JW. Constitutive acetylocholine-dependent current: a novel ionic target for atrial fibrillation. Circulation, 2004; 558: 338–342.
6. Beck-da-Silva L, de Bold A, Fraser M, Williams K, Haddad H. Brain natriuretic peptide predicts successful cardioversion in patients with atrial fibrillation and maintenance of sinus rhythm. Can J Cardiol, 2004; 20: 1245–1248.
7. Petersen P, Kastrup J, Vilhelmsen R, Schutten HJ. Atrial natriuretic peptide in atrial fibrillation before and after electrical cardioversion therapy. Eur Heart J, 1988; 9: 639–641.
8. Nattel S, Shiroshita-Takeshita A, Cardin S, Pelletier P. Mechanisms of atrial remodeling and clinical relevance. Curr Opinion Cardiol, 2005; 20: 21–25.
9. Ehrlich JR, Hohnloser SH, Nattel S. Role of angiotensin system and effects of its inhibition in atrial fibrillation: clinical and experimental: clinical and experimental evidence. Eur Heart J, 2006; 27: 512–518.
10. Nakashima H, Kumagai K, Utrata H, Gondo N, Ideishi M, Arakawa K. Angiotensin II antagonist prevents electrical remodeling in atrial fibrillation. Circulation, 2000; 101: 2612–2617.
11. Macrez N, Morel JL, Kalkbrenner F, Viard P, Schultz G, Mironneau JA. A beta-gamma dimer derived from G13 transduces the angiotensin AT1 receptor signal stimulation of Ca2+ channels in rat portal vein myocytes. J Biol Chem, 1997; 272: 23180–23185.
12. Clement-Chomiennne O, Walsh MP, Cole WC. Angiotensin II activation of protein kinase C decreases delayed rectifier K+ current in rabbit vascular myocytes. J Physiol (Lond.), 1996; 495: 689–700.
13. De Mello W, Crespo MJ. Correlation between changes in morphology, electrical properties and angiotensin converting enzyme actiity in the failing heart. Eur J Pharmacol, 1999; 378: 178–194.
14. Musgrave F, Majewski H. Evidence that angiotensin II enhances noradrenaline releases from sympathetic nerves in mouse atria by acyivating protein kinase C. J Auton Pharmacol, 1991; 11: 211–221.
15. Asano K, Dutcher DL, Port JD et al. Selective downregulation of the angiotensin II AT-1 receptor subtype in failing human ventricular myocardium. Circulation, 1997; 95: 1193–1200.
16. Goette A, Staack T, Rocken C et al. Increased expression of extracellular signal-regulated kinase and angiotensin-converting enzyme in human atria during atrial fibrillation. J Am Coll Cardiol, 2000; 35: 1669–1677.

17. Black HR. Evolving role of aldosterone blockers alone and in combination with angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers in hypertension management: A review of mechanistic and clinical data. Am Heart J, 2004; 147: 564–572.
18. Struthers AD. Aldosterone: Cardiovascular assault. Am Heart J, 2002; 144: S2–S7.
19. Mizuno Y, Yoshimura M, Yasue H et al. Aldosterone production is activated in failing ventricle in humans. Circulation, 2001; 103: 72–77.
20. Delcayre C, Swynghe B. Molecular mechanisms of myocardial remodeling. The role of aldosterone. J Moll Cell Cardiol, 2002; 34: 1577–1584.
21. Harada E, Yoshimura M, Yasue H et al. Aldosterone induces angiotensin--converting enzyme gene expression in cultured neonatal rat cardiocytes. Circulation, 2001; 104: 137–139.
22. Schmidt BMW, Schmmieder RE. Aldosterone-induced cardiac damage: focus on blood pressure independent effects. Am J Hypertens, 2003; 16: 80–86.
23. Barr CS, Lang CC, Hanson J et al. Effects of adding spironolactone to an ACE inhibitor in chronic congestive heart failure secondary to coronary artery disease. Am J Cardiol, 1995; 76: 1259—1265.
24. Tsai CT, Chaing FT, Tseng CD et al. Increased expression of mineralocorticoid receptor in human atrial fibrillation and a cellular model of atrial fibrillation. J Am Coll Cardiol, 2010; 55: 758—770.
25. Korantzopoulos P, Goudevenos JA. Aldosterone signaling in atrial fibrillation. Another piece in the puzzle of atrial remodeling. J Am Coll Cardiol, 2010; 55: 771–773.
26. Madrid AH, Bueno MG, Rebollo JMG et al. Use of irbesartan to maintain sinus rhythm in patients with long-standing persistent atrial fibrillation. Circulation, 2002; 106: 331–336.
27. Ueng K-Ch, Tsai T-P, Yu W-C et al. Use of enalapril to facilitate sinus rhythm maintenance after external cardioversion of long-standing persistent atrial fibrillation. Results of a prospective and controlled study. Eur Heart J, 2003; 24: 2090–2098.
28. Yin Y, Dalal D, Liu Z et al. Prospective randomized study comparing amiodarone *vs* amiodarone plus losartan vs. amiodarone plus losartan plus perindopril for the prevention of atrial fibrillation recurrence in patients with lone paroxysmal atrial fibrillation. European Heart J, 2006; 27: 1841–1846.
29. Belluzzi F, Sernesi L, Preti P, Salinaro F, Fonte ML, Perlini S. Prevention of recurrent lone atrial fibrillation by the angiotensin-II converting enzyme inhibitor ramipril in normotensive patients. J Am Coll Cardiol, 2009; 53: 24–29.
30. The GISSI-AF Investigators. Valsartan for prevention of recurrent atrial fibrillation. N Engl J Med, 2009; 360: 1606–1617.
31. Shi Y, Li D, Tardif J-C, Nattel S. Enalapril effects on atrial remodeling and atrial fibrillation in experimental congestive heart failure. Cardiovasc Res, 2002; 54: 456–461.
32. Schaer BA, Schneider C, Jick SS, Conen D, Ossswald S, Meier CR. Risk for incident AF in patients who receive antihypertensive drugs. Ann Intern Med, 2010; 152: 78–84.
33. Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol, 2005; 45: 1243–1248.
34. Goette A, Hoffmanns P, Enayati W, Meltendorf U, Geller JC, Klein HU. Effect of successful electrical cardioversion on serum aldosterone in patients with persistent atrial fibrillation. Am J Cardiol, 2001; 88: 906–909.
35. Pei DA, Li L, Xu ZY et al. Expression of mineralocorticoid receptor and 11-betahydroxysteroid dehydrogenase type 2 in human atria turing chronic atrial fibrillation: study of 25 cases. Zhonghua Yi Xue Za Zhi, 2007; 87: 816–819.
36. Spach MS, Boineau JP. Microfibrosis produces electrical load variations due to loss of side-to-side cell connections: A major mechanism of structural heart disease arrhythmias. Pacing Clin Electrophysiol, 1997; 20: 397–413.
37. Verheule S, Sato T, Everett TT et al. Increased vulnerability to atrial fibrillation in transgenic mice with selective atrial fibrosis caused by overexpression of TGF-beta1. Circ Res, 2004; 94: 1458–1465.
38. Kostin S, Klein G, Szalay Z, Hein S, Bauer EP, Schaper J. Structural correlate of atrial fibrillation in human patients. Cardiovasc Res, 2002; 54: 361–379.
39. Burstein B, Qi XY, Yeh YH, Calderone A, Nattel S. Atrial cardiomyocyte tachycardia alters cardiac fibroblast function: A novel consideration in atrial remodeling. Cardiovasc Res, 2007; 76: 442–452.
40. Tanaka K, Zlochiver S, Vikstrom KL et al. Spatial distribution of fibrosis governs fibrillation wave dynamics in the posterior left atrium during heart failure. Circ Res, 2007; 101: 839–847.
41. Oakes RS, Badger TJ, Kholmovski EG et al. Detection and quantification of left atrial structural remodeling using delayed enhancement MRI in patients with atrial fibrillation. Circulation, 2009; 119: 1758–1767.
42. Morillo CA, Klein GJ, Jones DL, Guiraudon CM. Chronic rapid atrial pacing: Structural, functional, and electrophysiological characteristics of a new model of sustained atrial fibrillation. Circulation, 1995; 91: 1588–1595.
43. Jenkins J, Noh KH, Guezennec A, Bump T, Arzbaecher R. Diagnosis of atrial fibrillation using electrograms from chronic leads: evaluation of computer algorithms. Pacing Clin Electrophysiol, 1988; 11: 622–631.
44. Boldt A, Wetzel U, Lauschke J et al. Fibrosis in left atrial tissue of patients with atrial fibrillation with and without underlying mitral valve disease. Heart, 2004; 90: 400–405.
45. Akoum N, Daccarett M, McGann C et al. Atrial fibrosis helps select the appropriate patient and strategy in catheter ablation of atrial fibrillation: A DE-MRI Guided Approach. J Cardiovasc Electrophysiol, 2011; 22:16–22.
46. Casaclang-Verzosa G, Gersh BJ, Tsang TSM. Structural and functional remodeling of the left atrium: clinical and therapeutic implication for atrial fibrillation. J Am Coll Cardiol, 2008; 51: 1–11.
47. Milliez P, DeAngelis N, Rucker-Martin C et al. Spironolactone reduces fibrosis of dilated atria during heart failure in rats with myocardial infarction. Eur Heart J, 2005; 26: 2193–2199.
48. Zannad F McMurray J, Krum H et al. EMPHASIS-HF Study Group. Eplerenone in patients with systolic heart failure and mild symptoms. N Engl J Med, 2011; 364: 11–21.
49. Swedberg K. European Society of Cardiology Heart Failure Association Congress, Gothenburg, Sweden 21–24 May, 2011.
50. Dąbrowski R, Borowiec B, Smolis-Bąk E et al. Effect of combined spironolactone: beta-blocker ± enalapril treatment on the occurrence of Symptomatic Atrial Fibrillation Episodes in Patients with a History of Paroxysmal Atrial Fibrillation (SPIR-AF Study). Am J Cardiol, 2010; 106: 1609–1614.
51. Goette A, Lendeckel U, Klein HU. Signal transduction systems and atrial fibrillation. Cardiovasc Res, 2002; 54: 247–258.
52. Schmidt BMW, Schmmieder RE. Aldosterone-induced cardiac damage: focus on blood pressure independent effects. Am J Hypertens, 2003; 16: 80–86.
53. Sanfilippo AJ, Abascal VM, Sheehan M et al. Atrial elargement as a consequence of atrial fibrillation: a prospective echocardiographic study. Circulation, 1990; 82:792–797.
54. Suarez GS, Lampert S, Ravid S, Lown B. Changes in left atrial size in patients with lone atrial fibrillation. Clin Cardiol, 1991; 14: 652–656.
55. Li D, Shinagawa K, Pang L et al. Effects of angiotensin-converting enzyme inhibition on the development of the atrial fibrillation substrate in dogs with ventricular tachypacing-induced congestive heart failure. Circulation, 2001; 104: 2608–2614.
56. Nakano S, Kobayashi N, Yoshida K, Ohno T, Matsuoka H. Cardioprotective mechanisms of spironolactone associated with the angiotensin-converting enzyme/epidermal growth factor receptor/extracellular signal-regulated kinases, NAD(P)H oxidase/lectin-like oxidized low-density lipoprotein receptor-1, and Rho-kinase pathways in aldosterone/salt-induced hypertensive rats. Hypertens Res, 2005; 28: 925–936.
57. Sonder SU, Mikkelsen M, Rieneck K, Hedegaard CJ, Bendtzen K. Effects of spironolactone on human blood mononuclear cells: mineralocorticoid receptor independent effects on gene expression and late apoptosis induction. Br J Pharmacol, 2006; 148: 46–53.
58. Williams TA, Verhovez A, Milan A, Veglio F, Mulatero P. Protective effect of spironolactone on endothelial cell apoptosis. Endocrinology, 2006; 147: 2496–2505.
59. Grandi AM, Imperiale D, Santilo R et al. Aldosterone antagonist Improves Diastolic Function in Essential Hypertension. Hypertension, 2002; 40: 647–652.
60. Brilla CHG, Matsubara LS, Weber KT. Antifibrotic effects of spironolactone in preventing myocardial fibrosis in systemic arterial hypertension. Am J Cardiol, 1993; 71: 12A–16A.
61. Pitt B, Zannad F, Remme WJ et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. J Am Coll Cardiol, 2003; 41: 211–214.
62. Modena MG, Aveta P, Menozzi A, Rossi R. Aldosterone inhibition limits collagen synthesis and progressive left ventricular enlargement after anterior myocardial infarction. Am Heart J, 2001; 141: 41–46.
63. Zannad F, Alla F, Dousset B, Perez A, Pitt B. Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironoalctone therapy in patients with congestive heart failure: Insights from the Randomized Aldactone Evaluation Study (RALES). Circulation, 2000;102: 2700–2706.
64. Korantzopoulos P, Kolettis T, Kountouris E, Siogas K. Atrial remodeling in persistent atrial fibrillation: the potential role of aldosterone. Eur Heart J, 2004; 25: 1086.
65. Casaclang-Verzosa G, Gersh BJ, Tsang TSM. Structural and functional remodeling of the left atrium: clinical and therapeutic implication for atrial fibrillation. J Am Coll Cardiol, 2008; 51: 1–11.
66. Zhao J, Li J, Li W et al. Effects of spironolactone on atrial structural remodelling in a canine model of atrial fibrillation produced by prolonged atrial pacing. Br J Pharmacol, 2010; 159: 1584–1594.
67. Viridis A, Neves MF, Amiri F at al. Spironolactone improves angiotensin-induced vascular changes and oxidative stress. Hypertension, 2002; 40: 504–510.
68. Fejes-Tóth Géza, Náray-Fejes-Tóth Anikó. Early aldosterone-regulated genes in cardiomyocytes: clues to cardiac remodeling? Endocrinology, 2007; 148: 1502–1510.
69. Ezekowitz JA, McAlister FA. Aldosterone blockade and left ventricular dysfunction: a systematic review of randomized clinical trials. Eur Heart J, 2009; 30: 469–477.
70. Fraccarollo D, Galuppo P, Schmidt I, Ertl G, Bauersachs J. Additive amelioration of left ventricular remodeling and molecular alterations by combined aldosterone and angiotensin receptor blockade after myocardial infarction. Cardiovasc Res, 2005; 67: 97–105.
71. Chan AKY, Sanderson JE, Wang T et al. Aldosterone receptor antagonism induces reverse remodeling when added to angiotensin receptor blockade in chronic heart failure. J Am Coll Cardiol, 2007; 50: 591–596.
72. Lendeckel U, Dobrev D, Goette A. Aldosterone-receptor antagonism as a potential therapeutic option for atrial fibrillation. Br J Pharmacol, 2010; 159: 1581–1583.
73. Laszlo R, Bentz K, Schreieck J. Effects of aldosterone and mineralocorticoid receptor antagonism on cardiac ion channels in the view of upstream therapy of atrial fibrillation. Gen Physiol Biophys, 2011; 30: 11–19.