Arterial Hypertension, Atrial Fibrillation, and Hyperaldosteronism

The Triple Trouble

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● Online Data Supplement

Atrial fibrillation (AF) involves 1% to 2% of the adult general population, a rate that increases to 15% in those 80 years and above.[1] Because of the aging of the general population, this epidemic of AF is expected to increase over the next decades[2–4] and to impose an increasing burden on the healthcare system because of the need for life-long care and pharmacological treatment. Identification of the mechanisms underlying AF represents an unmet need and a first step toward developing more effective preventive measures.

Arterial hypertension (HT) is tightly associated with AF, as originally reported in the Framingham Heart Study[5] and thereafter confirmed by several studies.[6–13] HT is a major predictor of AF, and 50% to 90% of AF patients have HT.

Accumulating evidences point to a role for the renin–angiotensin–aldosterone system (RAAS) in the pathophysiology of cardiac inflammation, fibrosis, and hypertrophy.[14–17] Aldosterone not only exerts well-known pressor effects, but also promotes inflammation, myocardial necrosis, cardiac collagen deposition, fibrosis, and left ventricular hypertrophy (LVH).[18,19] Accordingly, there is renewed interest in aldosterone as one of the major culprits leading to chamber remodeling and ultimately creating the stage for AF in hypertensive patients.[15,17,20–25] The evidence supporting a role for aldosterone in AF was, however, derived from observational studies performed in patients with heart diseases that are known to cause AF. This leaves open the question of whether aldosterone triggers AF per se or only in the presence of structural heart disease.

In recent years, 3 reviews examined the relation between aldosterone and AF: one focused on the antiarrhythmic potential of mineralocorticoid receptor (MR) antagonists in AF patients;[26] another on the role of the MR in arrhythmias;[27] and the last one on aldosterone-induced oxidative stress in atrial remodeling in AF.[28] Thus, we thought it interesting to focus on the general role of hyperaldosteronism in AF starting with the epidemiological data and moving on to discuss the molecular mechanisms whereby aldosteronism can induce AF in hypertension and the results of the clinical trials that either reduce aldosterone production or block its actions. To this aim, the literature was searched using the PICO strategy (Table S1 in the online-only Data Supplement).[29]

Relationship Between Hyperaldosteronism and AF

The association of AF with hyperaldosteronism was not recognized for many years. About a decade ago, 2 case reports first described AF as the presenting sign of primary aldosteronism (PA), the most common, albeit often unrecognized, cause of secondary HT.[30,31] In 2006, a 58-year-old man with PA was hospitalized 4× for AF and hypokalemia; correction of the latter coincided with sinus rhythm restoration.[32] In 2009, in another case AF occurred despite optimal blood pressure (BP) and electrolytes control.[33] These cases led to the proposal that hypokalemia and aldosterone can cause paroxysmal AF. The relative importance of hyperaldosteronism and hypokalemia for AF remains unknown because disentangling the role of these 2 factors is challenging; hyperaldosteronism leads to hypokalemia, whereas hemolysis at blood sampling can factitiously mask hypokalemia.

In 2005, a retrospective survey of cardiovascular complications in hypertensive patients with and without PA demonstrated a highly significant 12.1-fold increased risk of AF in patients with PA when compared with essential hypertensive patients.[34] It is noteworthy that, along with age and known duration of hypertension, PA independently predicted AF on multivariate analysis, which strongly implicated hyperaldosteronism in the pathophysiology of AF in hypertensive patients. These results were confirmed in a larger prospective cohort study of systematically screened patients with HT, which found a somewhat lower rate of AF, likely because of the earlier diagnosis of PA; yet AF was significantly increased

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by 7-fold in the PA patients when compared with the essential hypertensive patients. Further, during long-term (median 36 months) follow-up, PA patients with greater increases in LV mass had a shorter AF-free survival.[35]

Given the lack of prospective studies, the on-going PAPPHY study (Prospective Appraisal of the Prevalence of Primary Aldosteronism in Hypertensive Patients) was undertaken to assess prospectively the prevalence of PA and its subtypes, that is, aldosterone-producing adenoma and idiopathic hyperplasia, in consecutive hypertensive patients referred for evaluation of AF.[36] The hypothesis that AF is a common clinical presentation of PA is important from the practical standpoint; if verified, it would provide compelling evidence for a role for HT and hyperaldosteronism in the multitude of patients with AF. These patients may have underlying heart disease, but no other obvious cause for the arrhythmia. Currently, they only receive antihypertensive treatment and, if they have a CHA_2DS_2VASc (congestive heart failure, hypertension, age ≥75 [doubled], diabetes mellitus, stroke [doubled], vascular disease, age 65–74, and female sex) score of ≥2 or ≥3 in males and females, respectively, life-long anticoagulation along with drugs aimed at achieving rate control or restoring and maintaining sinus rhythm.[1] All these measures impose a burden on the healthcare systems and on the patients' quality of life.

The demonstration that PA is a cause of AF in hypertensive patients might eventually change clinical practice in this field in that it may lead to systematic screening for PA. This is important because PA involves >11% of the hypertensive patients referred to specialized centers, and surgical cure can be achieved in over 50% of PA patients.[30] Moreover, cure of PA by surgery or treatment with MR blockade not only regresses LVH[35] but can even restore sinus rhythm as suggested in a long-term study.[35]

Vicious Circle of Aldosteronism and AF: Does AF Raise Aldosterone?

Plasma aldosterone concentrations were found to be elevated during AF and to fall with restoration of sinus rhythm in patients with persistent AF.[37] Furthermore, plasma aldosterone concentrations were described to be higher in patients with long-standing persistent AF than in patients with restored sinus rhythm.[38] A decrease in plasma aldosterone concentrations after successful DC cardioversion with maintenance of sinus rhythm was also reported in patients with normal LV function.[39] One probable mechanism for the increase in aldosterone with AF is that AF decreases BP, which will activate the RAAS. During AF, the release of atrial natriuretic peptide,[40] which potently inhibits aldosterone secretion,[41] will serve to blunt the effects of AF on RAAS activation.

As mentioned above, the aldosterone-induced cardiac remodeling can create the substrate for AF, thus facilitating the persistence of the arrhythmia. Investigation of the role of aldosterone in AF seems, therefore, a chicken-egg puzzle, which needs well-planned studies in different models to be solved. Moreover, we will examine below the possibility that AF alters sensitivity of the heart to the action of aldosterone.

Atrial MR in AF

In 2010, the expression of the MR was reported to be higher in the right atrial appendages obtained from AF patients than from patients in sinus rhythm, thus implicating the upregulation of this receptor in AF.[42] It remained, however, unknown whether the onset of AF by itself was responsible for the enhanced MR expression, or if the latter facilitates the development of AF. Moreover, these data were generated using specimens from patients undergoing mitral or aortic valve replacement, in which the atrium could be remodeled, stretched, and affected by the underlying disease. Hence, it remained altogether unclear whether the MR expression was increased just because of the concomitance of valvular diseases that are known to be associated with AF.

Because the MR not only binds aldosterone, but also cortisol, that circulates at much higher (100- to 1000-fold) levels, it might be argued that some detrimental effects attributed to aldosterone were in fact driven by cortisol. However, the cortisol-inactivating enzyme 11βHSD2 has been reported to be more expressed in the atria of AF patients, which suggests that under physiological conditions, MR activation in the atria of AF patients is mainly because of aldosterone, rather than to endogenous glucocorticoids.[43] Given the difficulty of obtaining tissue, information on MR expression in the atria from hypertensive patients with or without AF is unavailable. Hence, the role of MR in the atria in mediating the onset or perpetuation of AF remains to be established.

This issue was addressed by an elegant experiment where rapid electric field stimulation was used to induce depolarization of HL-1 atrial cardiomyocytes. This led to unambiguous increases in MR protein expression,[44] via mechanisms involving intracellular Ca^{2+}, because the MR increase was abrogated by chelating intracellular Ca^{2+} with BAPTA-AM (bis-ethane-*N*,*N*,*N*',*N*'-tetra acetic acid acetoxymethyl-ester) and also by verapamil, a L-type Ca^{2+} channel blocker.[43] Thus, it can be concluded that electric remodeling by itself increases the expression of the MR via Ca^{2+}-dependent pathways (Figure S1).[44]

In turn, increased MR expression can amplify the effects of aldosterone, and possibly cortisol, on the cardiomyocytes. Of note, aldosterone increases T-type Ca^{2+} currents and induces sarcoplasmic reticulum Ca^{2+} overload in HL-1 cells, most likely by acting through the MR as these effects are blunted by the MR antagonist spironolactone.[44] Because neither HL-1 nor human atrial cells can produce aldosterone,[44] blood-borne aldosterone is the likely driver of these effects (Figure S1).

The following can, therefore, be a likely sequence of events: aldosterone enhances T-type Ca^{2+} currents and Ca^{2+} influx, thus increasing MR expression and reinforcing aldosterone's effects on the heart. Moreover, it favors reentry mechanisms by inducing LVH and fibrosis, leading to stiffening of the LV, impaired LV filling, with ensuing atrial stretching and increasing left atrial size.[45] Noteworthy, the hyperaldosteronism-associated hypokalemia prolongs the PQ interval (atrioventricular conduction time) and favors atrioventricular reentry mechanisms. By rendering the LV more dependent on the atrial kick for its filling, this can explain why PA patients can be more prone to pulmonary edema when they develop AF (Figure).[21,46]

Aldosterone Favors Inducible Atrial Arrhythmias

In 2012, a well-designed experimental study provided a direct demonstration that aldosterone induces AF. Rats received an

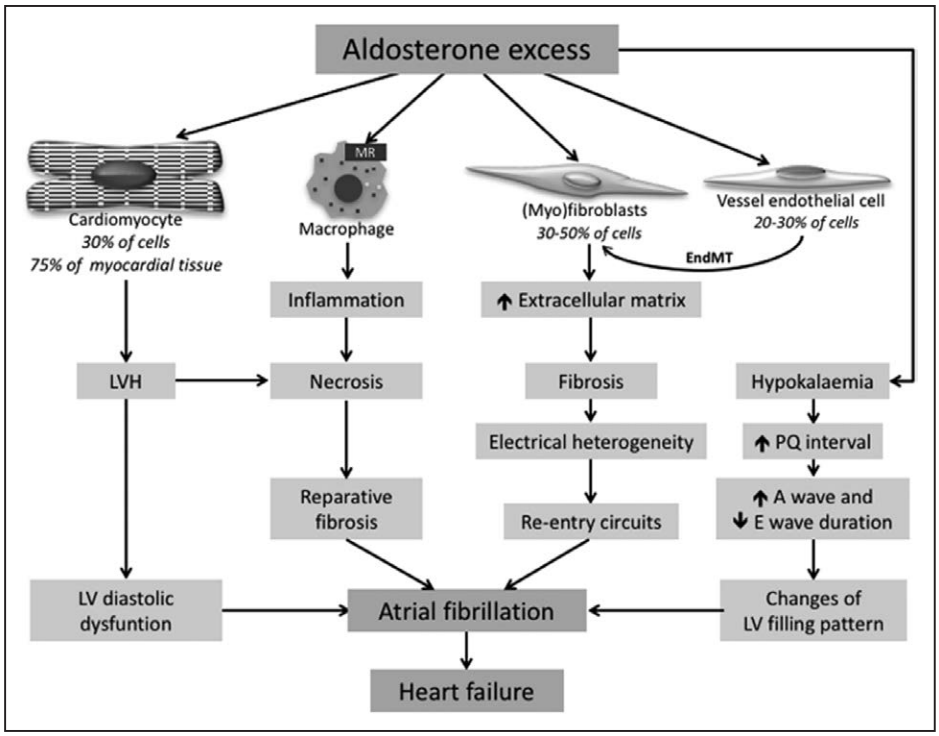

Figure. Mechanisms by which aldosterone excess favors onset of atrial fibrillation. Aldosterone affects all cell types that are the primary constituents of cardiac tissue: (1) cardiomyocytes, which constitute 30% of myocardial cells, but 75% of myocardial tissue volume, (2) fibroblasts (30%–50% of myocardial cells), (3) endothelial cells (20%–30% of myocardial cells), and also activates macrophages. Aldosterone excess induces enlargement of cardiomyocytes and remodeling leading to left ventricular hypertrophy (LVH) that predisposes to diastolic dysfunction. Aldosterone excess also activates the transition of fibroblasts into myofibroblasts, which produce collagen and other extracellular matrix proteins, favoring fibrosis. Fibrotic tissue induces electric heterogeneity of the myocardium that causes reentry circuits, thereby leading to onset of atrial fibrillation. Endothelial cells exposed to aldosterone excess undergo transition into myofibroblasts (endothelial-to-mesenchymal transition, EMT), which contribute to the development of fibrosis. The activation of the mineralocorticoid receptor (MR) on the monocytes/macrophages favors inflammation, necrosis and reparative fibrosis, and eventually atrial fibrillation.[47] Aldosterone excess induces hypokalemia, which causes prolongation of the atrioventricular conduction time (PQ interval) and changes in the duration of A and E waves, leading to abnormal left ventricular (LV) filling that promotes AF, which in turn favors heart failure.

infusion of aldosterone for 8 weeks at a dose (0.5 µg/h) that does not affect ventricular function or atrial pressures but lengthens the P-wave duration of and the total right atrial activation time. The rats developed AF after transesophageal atrial burst stimulation.[48] In the same year, it was shown that aldosterone, even when infused for a shorter time (4 weeks) at a dose (0.5 µg/h) that did not increase BP, induced shortening of the left atria action potential and doubling of the mean time until spontaneous conversion into sinus rhythm.[49] In both studies, the minimal changes in BP (systolic BP 134±10 versus 129±5 mm Hg, aldosterone versus control) suggested that aldosterone per se can create a substrate for atrial arrhythmias without markedly affecting LV afterload.[48]

Besides its electrophysiological effects, aldosterone can promote arrhythmia by causing inflammation, vascular remodeling, and possibly microcirculatory dysfunction.[19,50] Aldosterone has been shown to increase the levels of proinflammatory genes (including cyclooxygenase-2, osteopontin, tumor necrosis factor-α, monocyte chemotactic protein-1, and NADPH oxidase [nicotinamide adenine dinucleotide phosphate, reduced form])[51,52] with ensuing fibrosis and to induce electrophysiological alterations that lead to early and delayed afterdepolarization of the cardiomyocytes.[53] The deposition of fibrotic tissue, by decreasing gap junctions coupling and creating muscle bundle discontinuities, alters the spatial location and propagation of depolarization waves, thereby reducing conduction velocity and promoting reentry circuits.[53,54] Because of the relatively low membrane potential of fibroblasts (−30 mV), fibroblast–cardiomyocyte coupling promotes delayed afterdepolarization of the cardiomyocytes and ectopic firing.[53] It also increases transient Ca^{2+} amplitude, leading to increased intracellular Ca^{2+} concentrations and spontaneous sarcoplasmic reticulum Ca^{2+} release, finally favoring AF maintenance (Figure S1).[53]

Electrophysiological changes were also documented with aldosterone in neonatal rat cardiomyocytes and atrial mouse cells. Aldosterone increased the expression of T-type channels in cardiomyocytes and L-type Ca^{2+} channels in atrial cells and decreased the activity of the rapidly activating delayed rectifier potassium current Ikr and transient outward K^+ currents Ito1.[55] It also promoted the prolonged release of Ca^{2+} from the sarcoplasmic reticulum because of the opening of ryanodine receptors,[56,57] finally leading to Ca^{2+} overload and thereby promoting AF (Figure S1).

Upstream Therapy of AF and Randomized Clinical Trials

The term upstream therapy refers to non-antiarrhythmic therapy that modifies the atrial substrate and can thereby prevent AF. Upstream therapy was encouraged in the treatment of AF in hypertensive patients because theoretically it could prevent new-onset and recurrent AF.[14] The randomized clinical trials

in arterial hypertension with agents that blunt aldosterone secretion or aldosterone effects[7,58,59] can therefore be regarded as upstream therapy. Unfortunately, none of the randomized clinical trials performed thus far was specifically designed to look at incident AF as a primary end point.

In the LIFE study (Losartan Intervention for End-Point Reduction), which recruited hypertensive patients with LVH, the type 1 angiotensin receptor antagonist losartan was found to be superior to atenolol in regressing LVH and in reducing new-onset AF.[7] In the VALUE study (Valsartan Antihypertensive Long-Term Use Evaluation), which recruited hypertensive patients at high cardiovascular risk, valsartan was more effective than amlodipine in preventing/regressing AF.[58] Moreover, a meta-analysis of 11 studies with a total of 56 308 patients showed that ACE inhibitors and angiotensin receptor antagonists reduced the overall relative risk of AF by 28%, thus confirming the beneficial effects of RAAS blockade in preventing AF.[59,60] Needless to say, these results can be interpreted in 2 ways: either in terms of reducing AT1 receptor signaling or in terms of blunting aldosterone secretion.[31]

Studies with MR antagonists provided further evidence to sort out this issue. As already mentioned, the rationale for using these agents relies in the fact that plasma aldosterone concentrations is increased in AF, and MR is upregulated in the atria of AF patients, which led to consider MR antagonists as promising upstream drugs.

In 1999, the RALES (Randomized Aldactone Evaluation Study), the first large randomized clinical trial evaluating the MR antagonist spironolactone on top of standard care in New York Heart Association classes III and IV heart failure patients, was prematurely stopped on the steering committee's recommendation because the primary end point, that is, the decrease in mortality, was reached.[61] Although data on incident AF were not collected, the authors speculated that a lower risk of sudden death in the spironolactone arm could be related to the prevention of cardiac fibrosis with ensuing decreased susceptibility to arrhythmias. In 2003, the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) also found a decreased incidence of sudden death, thus supporting this hypothesis.

A decade later, the multicenter EMPHASIS-HF study (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) randomized patients with an ejection fraction <35%, but only mild symptoms (New York Heart Association II) of heart failure; over 66% of the patients had hypertension. A post hoc analysis of the study provided evidence that the MR antagonist is more effective than placebo in preventing AF. During the treatment period (median 21 months), newly detected AF occurred in significantly fewer patients in the eplerenone group than in the placebo group (2.7% versus 4.5% hazard ratio, 0.58; 95 confidence interval, 0.35–0.96).[62]

More recently, the TOPCAT study (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) recruited patients with heart failure and preserved LV ejection fraction in North/South America and Eastern Europe. The patients were randomized to receiving spironolactone or placebo on top of other treatment. The study failed on its primary composite end point (that included time to cardiovascular death, aborted cardiac arrest, or hospitalization for heart failure). However, a post hoc analysis showed marked regional heterogeneity in the recruited patients, with American patients demonstrating a significant reduction in the primary outcome with spironolactone, a result not seen in the patients recruited in Russia or Georgia.[63] As in RALES and EPHESUS, data on incident AF in TOPCAT have yet to be given and, unfortunately, to the best of our knowledge, no studies on these databases have been planned to look specifically at AF.

Of note, the randomized, placebo-controlled trial Atrial Fibrillation and Renin Angiotensin Aldosterone System study (URL: http://www.clinicaltrials.gov. Unique identifier: NCT00141778) designed to investigate whether the antagonism of the RAAS reduces the risk of postoperative AF in patients undergoing surgery for coronary artery or valvular heart disease failed to show a beneficial effect of either ramipril or spironolactone over placebo.[64] The duration of treatment before surgery (from 4 days to 1 week) could, however, have been too short to evidence such effect.

In a recent study involving patients with primary and secondary hyperaldosteronism, an association of excess aldosterone with changes of LV remodeling and function was documented.[65] The PA patients had increased LV mass, high prevalence of LVH, inappropriate LV mass, and subclinical LV systolic and diastolic dysfunction. The patients with secondary hyperaldosteronism (because of liver cirrhosis) also show increased LV mass, high prevalence of LVH, and diastolic dysfunction, but not subclinical systolic dysfunction. The work overload caused by a hyperdynamic circulatory state and the high renin with ensuing hyperaldosteronism could be driving these changes in patients with liver cirrhosis.[65] Thus, in both PA and secondary hyperaldosteronism, aldosterone contributes to LVH and also cardiac fibrosis, causing LV diastolic dysfunction, increased atrial afterload, with ensuing atrial stretching, and wall stress, favoring AF onset.[65,66]

CYP11B2 Polymorphisms and AF in HT

Variations in the aldosterone synthase (CYP11B2) gene has been linked to cardiac remodeling,[67–69] hypertension, albeit with inconsistent results as discussed in detail in the online-only Data Supplement.

Conclusions

The success of current pharmacological strategies relying on blockade of ion channels that regulate conduction and atrial refractoriness for controlling AF is admittedly limited; AF recurs in most patients. The burden posed on the healthcare system and on patients' quality of life by AF requires swift actions to improve knowledge of the mechanisms underlying AF. This is particularly important given the expected rise in the prevalence of AF in the next decades. Improving our understanding of the mechanisms underlying AF is a key step toward developing more effective strategies for the prevention of AF. Experimental and observational studies have provided compelling evidence for a direct role of aldosterone and the MR in promoting cardiac fibrosis and disrupting the conduction system, thus favoring the onset of AF. As Paul Dudley White, the Father of US Cardiology, used to say "Heart disease's death, before 80, is our fault, not God's or Nature's

will". This could not apply better to a condition like AF that can effectively be prevented by proper managing.

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Disclosures

None.

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Arterial Hypertension, Atrial Fibrillation And Hyperaldosteronism: The Triple Trouble

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Online Supplemental Data

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CYP11B2 Polymorphisms and AF in HT

There is a common T-344C polymorphism (a thymidine [T]-to-cytosine[C] substitution) in the promoter region (rs1799998) of the aldosterone synthase (CYP11B2) gene (GenBank accession no. AC073385). The C allele promoter was associated with increased binding to the steroidogenic transcription factor (SF)-1, resulting in increased aldosterone synthase gene transcription and thus augmented aldosterone synthesis. In a few small studies, this polymorphism has been linked to cardiac remodeling, [1-3] hypertension, [4-6] and incident AF in heart failure patients, as well as with decreased LV systolic function. [7,8] However, these findings were not confirmed in the only study that examined a sizable cohort (n =310) of patients with HT and AF. [9] Hence, further large studies are needed to ascertain if the CYP11B2 T-344C polymorphism can predispose hypertensive patients, without heart failure, to AF.

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Table S1. PICO strategy used for searching literature.

P	Population	Hypertensive patients with hyperaldosteronism
I	Intervention	None
C	Comparison	Normotensive subjects with normoaldosteronism
O	Outcome	Atrial fibrillation

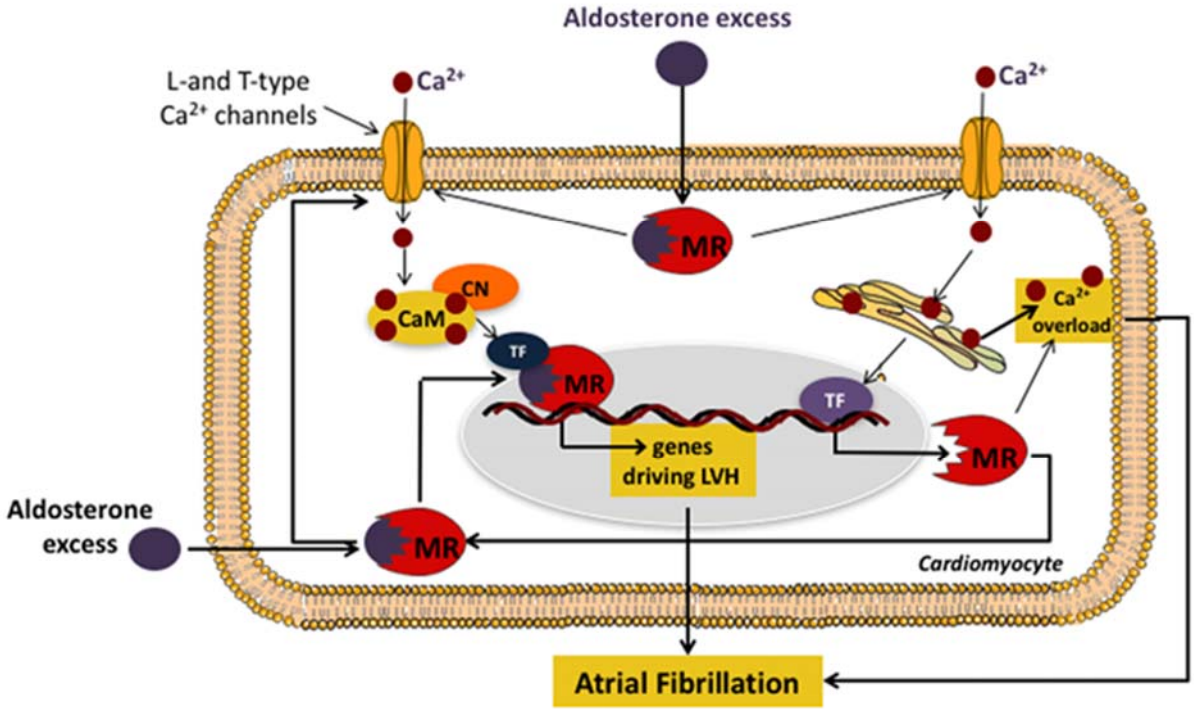

Figure S1. Effects of aldosterone excess in the cardiomyocyte. *After binding to the mineralocorticoid receptor (MR) in the cytoplasm, aldosterone promotes opening of the L- and T-type Ca^{2+} channels. Ca^{2+} binds to calmodulin (CaM), which in turn binds calcineurin (CN) to activate transcription factors (TF) that translocate to the nucleus allowing MR-dependent transcription of genes driving left ventricular hypertrophy (LVH). Hyperaldosteronism also promotes Ca^{2+} efflux from the sarcoplasmic reticulum, which translates into cytoplasmic Ca^{2+} overload, which in turn favors ectopic firing and AF. Cytoplasmic Ca^{2+} acts as second messenger stimulating MR gene transcription and, thereby, generating a vicious circle that amplifies MR-mediated effects.*

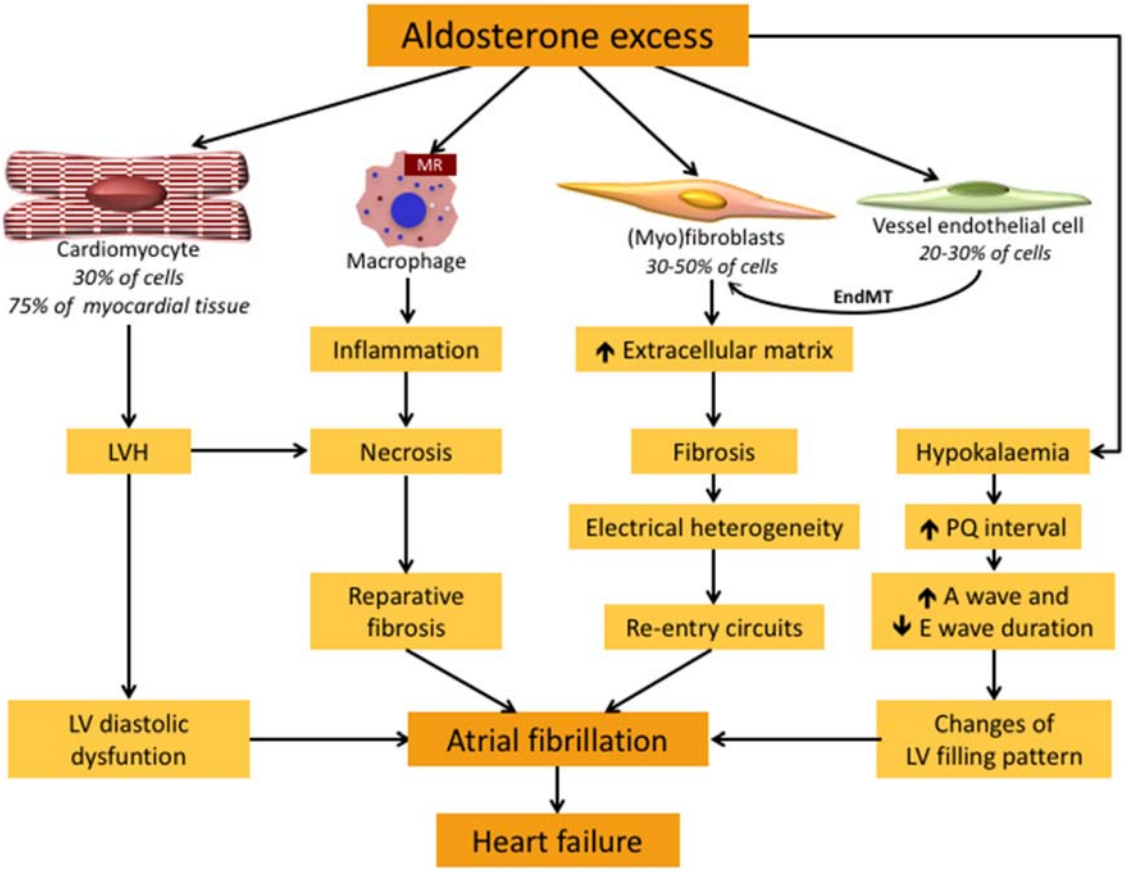

Figure 1. Mechanisms by which aldosterone excess favors onset of atrial fibrillation. *Aldosterone affects all cell types that are the primary constituents of cardiac tissue volume: a) cardiomyocytes, which constitute 30% of myocardial cells, but 75% of myocardial tissue, b) fibroblasts (30-50% of myocardial cells), c) endothelial cells (20-30% of myocardial cells), and also activates macrophages. Aldosterone excess induces enlargement of cardiomyocytes and remodeling leading to left ventricular hypertrophy (LVH) that predisposes to diastolic dysfunction. Aldosterone excess also activates the transition of fibroblasts into myofibroblasts, which produce collagen and other extracellular matrix proteins, favoring fibrosis. Fibrotic tissue induces electrical heterogeneity of the myocardium that causes re-entry circuits, thereby leading to onset of atrial fibrillation. Endothelial cells exposed to aldosterone excess undergo transition into myofibroblasts (endothelial-to-mesenchymal transition, EMT), which contribute to the development of fibrosis.*

The activation of the mineralocorticoid receptor (MR) on the monocytes/macrophages favors inflammation, necrosis and reparative fibrosis, and eventually atrial fibrillation. Aldosterone excess induces hypokalemia, which causes prolongation of PQ interval and changes in the duration of A and E waves, leading to abnormal LV filling that promotes AF, which in turn favors heart failure.