Atrial fibrillation (AF) is a rapidly evolving epidemic representing a multifactorial, dynamic disorder with different underlying substrates and serious health consequences (1). A growing body of evidence indicates that, apart from the triggers, AF development and perpetuation depends on the electrical and structural remodeling of the atria (2,3). Currently, the role of the renin-angiotensin-aldosterone system in AF is under intensive investigation (4), whereas much of the current interest regarding pharmacologic therapy has shifted to nonchannel-blocking drugs with pleiotropic properties including agents interfering in the renin-angiotensin-aldosterone system (2,4,5).

Specifically, the role of aldosterone in AF has not been well studied. Indirect evidence from hypertensive patients with primary aldosteronism indicates increased prevalence of AF (6). Three previously published laboratory studies, which examined the role of aldosterone and its blockade on atrial remodeling, focused on heart failure experimental models (7–9). They showed that aldosterone blockade reduces atrial fibrosis (7,9) and suppresses AF (8,9). On the clinical level, the existent data is sparse and conflicting. Goette et al. (10) reported that aldosterone levels are elevated in patients with persistent AF, whereas restoration of sinus rhythm lowers serum aldosterone. However, another study showed no significant association between AF and aldosterone levels when use of diuretics was included in the multivariate model, suggesting that the excessive activation of the renin-angiotensin–aldosterone axis by volume depletion may be the primary mechanism of aldosterone increase (11). Moreover, a recent genetic analysis showed that a specific polymorphism related to increased aldosterone synthase activity pre-disposes to AF in patients with heart failure (12). Interestingly, a small randomized controlled study in heart failure patients has demonstrated that spironolactone treatment reduces the risk for AF/atrial flutter (13).

In this issue of the Journal, Tsai et al. (14), using state-of-the-art methodology, provide important new information on this subject combining clinical and experimental data. The investigators showed that aldosterone is not synthesized locally in the atrial tissue and its principal effects in the atria depend on the expression of mineralocorticoid receptors (MRs), which mediate its genomic effects. Although there was no difference in the atrial aldosterone level, the patients with AF, compared with sinus rhythm patients, had increased MR expression. In a second set of experiments using an atrial cell line it was shown that rapid depolarization induces increased MR expression through calcium-dependent mechanisms enhancing aldosterone responsiveness. Of note, aldosterone increased intracellular calcium load and induced electrical remodeling through a genomic (MR-dependent) pathway without the contribution of oxidative stress. Specifically, aldosterone increased T-type calcium current, decreased rapidly activating delayed rectifier potassium current, and had no effect on L-type calcium current. These changes were attenuated by the coadministration of spironolactone. It should also be noted that aldosterone increased intracellular oxidative stress by a nongenomic pathway (nicotinamide adenine dinucleotide phosphate oxidase-dependent). As the investigators correctly point out, the aforementioned pathways indicate a positive feedback vicious cycle (14).

Undoubtedly, these results represent a step forward to the understanding of signaling pathways in atrial remodeling and further reinforce the potential value of MR antagonists in AF. They also provide evidence for effective modulation of calcium overload by MR blockers, given that calcium-channel blockers have failed to control AF and atrial electrical remodeling in the clinical setting. However, it should be acknowledged that the remodeling process is very complex and several aspects remain obscure. As with any good study, the questions and the unclear points outnumber the answers.

First, the present results cannot be easily extrapolated in other populations despite the fact that an additional small group of patients without significant valvular disease was
examined. The main population of the study consisted of subjects with severe mitral or aortic regurgitation subjected to cardiac surgery. Even though the ejection fraction does not reliably reflect the systolic function especially in the case of severe mitral regurgitation, the patients of both groups had normal left ventricular ejection fractions. Unfortunately, other indexes of systolic and diastolic function were not reported. In fact, it is not known whether aldosterone signaling is different in subjects with underlying substrates such as ischemic cardiomyopathy, dilated cardiomyopathy, hypertension, and so on. It is also unclear whether aldosterone signaling changes according to the extent of atrial remodeling. Although the AF patients of the study had permanent AF with a mean duration of 8.3 years and larger atria than sinus rhythm patients did, the investigators did not find any important differences in indexes of fibrosis and extracellular matrix, and the in vitro experiments showed no significant effect of aldosterone. Despite some inconsistent results regarding atrial fibrosis, aldosterone is considered a key component of structural remodeling especially at the ventricular level (15). Taking into account that aldosterone is implicated in the ventricular remodeling, it is reasonable to assume that the resulting ventricular systolic and diastolic dysfunction and the associated elevation of diastolic pressures promote AF due to increased atrial stretch. Atrial stretch can induce both structural and electrical remodeling (mechanoelectrical phenomenon). These latter mechanisms may be operative in the population of the present study because valvular regurgitations cause a volume overload.

The investigators showed that aldosterone increases intracellular oxidative stress by a nongenomic pathway and, therefore, this cannot be attenuated by MR blocking. They also reported that oxidative stress does not mediate aldosterone-induced electrical remodeling in the cellular model. However, a growing body of evidence suggests that oxidative stress is implicated in both electrical and structural atrial remodeling (16–18). In a recent review, Gao and Dudley (18) illuminate the central role of redox-sensitive nuclear factor kappa-B in the regulation of ion channels, transcription factors, or splicing factors implicated in atrial remodeling. Although Tsai et al. (14) showed in their cellular model that MR blockade is not able to modulate intracellular oxidative stress, one cannot ignore that a complex interplay exists among angiotensin, aldosterone, and oxidative signaling pathways. In this context, Johar et al. (19) demonstrated that aldosterone mediates angiotensin II-induced cardiac fibrosis via nicotinamide adenine dinucleotide phosphate oxidase whereas spironolactone inhibits oxidative stress as well as the profibrotic effect of angiotensin II. Also, current data from human atrial tissues supports the notion that oxidative stress is implicated in electrical remodeling and is associated with the attenuation of L-type calcium current (20). It is therefore tempting to speculate that a combined intervention targeting the nuclear factor kappa-B signaling, oxidative and inflammatory pathways, and the renin-angiotensin-aldosterone axis would be of special merit in this setting. It has also been suggested that the aldosterone-induced oxidative damage depends on the pre-existing redox status (21), whereas MR activation caused by change in the redox status is accompanied by inflammation (22). Notably, the present study does not provide data on serum or atrial tissue markers of oxidative stress and inflammation.

Calcium overload and calcium-handling abnormalities seem to have an important role in AF pathophysiology (23). The aldosterone-dependent electrical remodeling mediated by calcium overload is a novel, worthwhile finding. However, the investigators studied the effect of rapid electrical stimulation only in the cellular model. In the clinical setting, patients with permanent AF such as those included in the first part of the study have prominent structural remodeling. Also, it is known that the rapid calcium influx after the initiation of rapid atrial depolarization is attenuated over time due to adaptive mechanisms (2,23). The intracellular calcium handling over long periods of sustained AF probably is different and abnormalities in calcium release and reuptake from the sarcoplasmic reticulum may have the primary role (23). Bukowska et al. (24) recently demonstrated that tachycardia-induced calcium overload of human atrial tissue slices induces oxidative stress, mitochondrial dysfunction, and activation of the nuclear factor kappa-B signaling pathway. Moreover, calcium overload has been implicated in myocyte loss and apoptosis, in the contractile remodeling/systolic dysfunction, and in the genesis of afterdepolarizations and the associated triggered activity. Given that the increased firing activity of ectopic foci, mainly in the pulmonary veins, is critical for the initiation of AF, it would be very interesting to examine the aldosterone signaling in this setting.

In conclusion, the present findings should be further investigated in different settings, including various forms of AF, distinct underlying substrates, and both for primary and secondary prevention of AF (25). Furthermore, the role of MR blockade in different types and stages of atrial remodeling remains to be determined. It would also be interesting to test the effect of eplerenone because it is considered more selective for the MR and appears to have more nongenomic effects than spironolactone does. The journey to identify specific targets and specific time points for implementing novel prevention and management strategies in AF continues.

**REFERENCES**


Key Words: atrial fibrillation, atrial remodeling, aldosterone, spironolactone, fibrosis, oxidative stress, calcium, mineralocorticoid receptor, ionic remodeling.