Losartan inhibits hyposmotic-induced increase of I_{Ks} current and shortening of action potential duration in guinea pig atrial myocytes

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Abstract

Objective: The present study aims to investigate the effect of losartan, an selective angiotensin II type 1 receptor (AT_1R) blocker, on both the increase of I_{Ks} current and shortening of action potential duration (APD) induced by stretch of atrial myocytes, and to uncover the mechanism underlying the treatment of fibrillation (AF) by AT_1R blockers.

Methods: Hyposmotic solution (Hypo-S) was applied in the guinea pig atrial myocytes to simulate cell stretch, then patch-clamp technique was applied to record the I_{Ks} and APD in atrial myocytes.

Results: Hypo-S increased the I_{Ks} by 105.6%, while Hypo-S+1-20 μM of losartan only increased the I_{Ks} by 70.3-75.5% ($p<0.05$ vs. Hypo-S). Meanwhile, Hypo-S shortened APD_{90} by 20.2%, while Hypo-S+1-20 μM of losartan shortened APD_{90} by 13.03-14.56% ($p<0.05$ vs. Hypo-S).

Conclusion: The above data indicate that the effect of losartan on the electrophysiological changes induced by stretch of atrial myocytes is associated with blocking of AT_1 receptor, and is beneficial for the treatment of AF that is often accompanied by the expansion of atrial myocytes and the increase of effective refractory period. *(Anatol J Cardiol 2020; 23: 35-40)*

Keywords: angiotensin II type 1 receptor, action potential, atrial myocytes, losartan, I_{Ks}

Introduction

Renin–angiotensin system (RAS) is an important humoral regulation system composed of renin, angiotensin, and its receptor that plays a fundamental role in maintaining the cardiovascular normal development, functional homeostasis, balance of electrolyte and body fluid, as well as regulation of blood pressure. Previous reports have shown that experimental atrial arrhythmias were closely involved in RAS abnormalities (1-4). Clinical investigations also found that RAS blockers, including angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor (AT_1R) blockers (ARBs), were effective in the treatment of atrial fibrillation (AF) (5–10). However, the mechanism underlying the treatment of AF by such drugs has not been fully elucidated. Especially, the effect of RAS blockers on cardiac electrophysiological properties during AF is poorly understood.

The shortening of action potential duration (APD) and effective refractory period (ERP) in atrial myocytes is generally regarded as the main factors responsible for the occurrence of reentry-based AF. During AF, the atrial systolic function is impaired, resulting in the swelling or stretch of atrial myocytes (11, 12) and the increase of angiotensin II secretion (13, 14). Many studies have reported that exogenous angiotensin II and hyposmotic-induced myocardial cell membrane expansion can increase the slow delayed outward rectifying potassium channel (I_{Ks}) and shorten the APD in atrial myocytes by the stimulation of

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AT_1R in guinea pig atrial myocytes (15, 16). It suggests that the potentiation of I_{Ks} and resultant shortening of the APD via AT_1R stimulation in atrial myocytes play an important role in both the occurrence and the maintenance of AF. The AT_1R blocker irbesartan is capable of inhibiting the channel currents formed by the heterologous expression of *KCNQ1/KCNE1*, suggesting that the therapeutic action of ARBs for AF may be achieved by blocking of AT_1R (17).

The present study investigated the effect of losartan, an efficient selective AT_1R blocker, on both the increase of I_{Ks} current and shortening of APD induced by hyposmotic extracellular solution (Hypo-S) in guinea pig atrial myocytes. The results indicate that the effect of losartan on the electrophysiological changes by the stretch of atrial myocytes is associated with blocking of the AT_1 receptor, which may be one of the important mechanisms underlying the prevention and treatment of AF by ARBs.

Methods

Isolation of guinea pig atrial myocytes

Adult Hartley guinea pigs of either sex, weighing 300±25 g, were anesthetized by intraperitoneal injection of 40 mg/kg sodium pentobarbital, then Langendorff perfusion devices were used to perfuse the heart of guinea pigs, and single atrial myocytes were enzymatically dissociated (16).

Solutions and chemicals

Normal Tyrode's solution (pH adjusted to 7.4 with 1 M NaOH) was used as "isosmotic" extracellular solution (Iso-S, average osmotic pressure 285 mosM/kg) that contained 140 mM NaCl, 5.4 mM KCl, 1.8 mM $CaCl_2$, 0.5 mM $MgCl_2$, 0.33 mM NaH_2PO_4, 5.5 mM glucose, and 5.0 mM HEPES. "Hyposmotic" extracellular solution (Hypo-S, average osmotic pressure 210 mosM/kg) was prepared by simply reducing the NaCl concentration of normal Tyrode's solution to 100 mM, and others remained the same (17). Losartan (Sigma-Aldrich, USA) was firstly formulated into 20 mM of stock solution with dimethyl sulfoxide (DMSO, Sigma, USA), and Iso-S or Hypo-S was used to dilute it to experimental concentrations before use. The final concentration of DMSO in the perfusion bath was <0.1% (V/V), which had no effect on the I_{Ks} current. The pipette solution (pH adjusted to 7.2 with 1 M KOH) contained 70 mM potassium aspartate, 50 mM KCl, 10 mM KH_2PO_4, 1 mM $MgSO_4$, 3 mM Na_2-ATP (Sigma, USA), 0.1 mM Li_2-GTP (Roche Diagnostics GmbH, Mannheim, Germany), 5 mM EGTA, and 5 mM HEPES.

Electrophysiological records and data analysis

The isolated atrial myocytes were placed in a 5 mL perfusion bath mounted on an inverted microscope and were perfused with extracellular solution in a rate of 1–2 ml/min at 36±1°C. Axopath 200B amplifier (Axon Instruments, Sunnyvale, CA, USA) was used to record currents and voltages of atrial myocytes by whole-cell patch-clamp technique. Tip resistances of borosilicate glass electrodes were 2.5–4.0 MΩ when filled with the pipette solution. I_{Ks} was elicited by depolarizing voltage-clamp steps given from a holding potential of −50 mV to various test potentials under conditions in which the Na^+ current was inactivated by setting the holding potential to −50 mV. Then, 0.4 μM nisoldipine (Bayer AG, Germany) and 0.5 μM dofetilide (Sigma, USA) were added into the extracellular solution to block L-type Ca^{2+} channels ($I_{Ca,L}$) and rapidly delayed outward rectifying potassium channel (I_{Kr}).

Variations of I_{Ks} amplitude were determined by measuring the amplitude of tail currents elicited upon repolarization to a holding potential of −50 mV following 2 s depolarization to +30 mV every 10 s. Voltage dependence of I_{Ks} activation was evaluated by fitting the normalized I–V relationship of tail currents to a Boltzmann equation: $I_{K,tail}=1/(1+\exp((V_h-V_m)/k))$, where $I_{K,tail}$ is the tail current amplitude normalized with reference to the maximum value measured at +50 mV, V_h is the voltage at half-maximal activation, V_m is the test potential, and k is the slope factor. The deactivation time constant of I_{Ks} channel was evaluated by fitting the tail current curve to a single exponential equation. Action potentials were evoked at a rate of 0.2 Hz with suprathreshold current pulses of 2 ms duration applied via patch electrode in the current-clamp mode. The APD was measured at 90% repolarization (APD_{90}).

Statistical analysis

Data were analyzed using the SPSS software version 24.0 (SPSS Inc., Chicago, IL, USA) for statistical analyses. Kolmogorov–Smirnov test was used to determine variables whether they were normally distributed. All normally distributed data were expressed as mean±standard error of mean, with sample size shown in parentheses. Independent samples t-test or ANOVA was used for statistical comparisons, followed by Dunnett's post hoc, as appropriate. A p value <0.05 was considered statistically significant.

Results

Losartan did not affect the basic I_{Ks} current, but weakened the increase of I_{Ks} induced by Hypo-S

Figure 1 shows that 10 min exposure to 20 μM of losartan did not change I_{Ks} current in atrial myocytes. However, when the perfusion solution was switched to the Hypo-S, I_{Ks} current in atrial myocytes increased significantly. The results showed that losartan did not affect the basal I_{Ks} currents (curves 1 and 2 in Fig. 1), but Hypo-S significantly increased the I_{Ks} steady state and tail current amplitude (current curve 3 shown in Fig. 1).

Hypo-S-induced stretch of atrial myocytes fits the stretch of myocardial cell membrane, generally causing the various transport changes of related ion channels (including the increase of I_{Ks} in atrial myocytes) in the early stage of AF (11, 16, 18-20). Figure

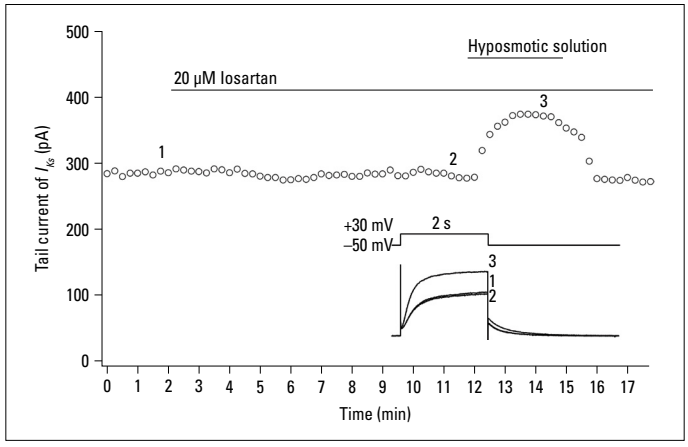

Figure 1. Losartan did not affect the basal I_{Ks} current in guinea pig atrial myocytes. The time course of I_{Ks} current during the perfusion of 20 μM losartan and Hypo-S. The inset shows the superimposed I_{Ks} currents at different points indicated in this figure: (1) before perfusion of 20 μM losartan, (2) perfusion of 20 μM losartan for 10 min, and (3) plus Hypo-S perfusion

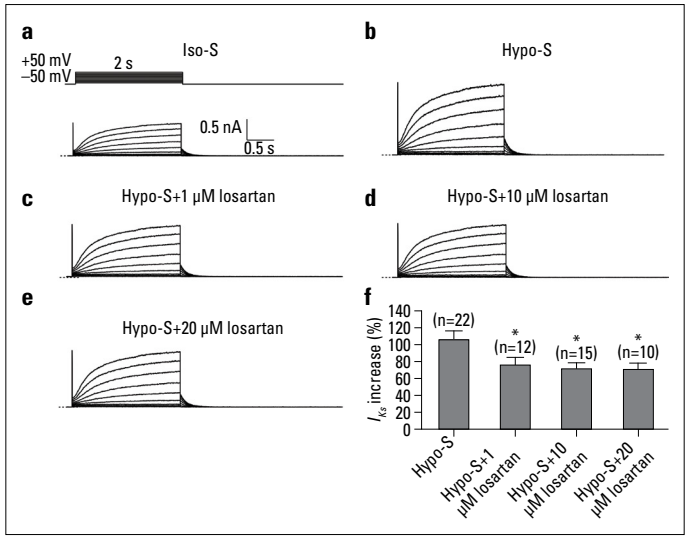

Figure 2. Losartan attenuated the Hypo-S-induced increase of I_{Ks} current in guinea pig atrial myocytes. The atrial myocytes were initially perfused with Iso-S (a). The Iso-S was switched to Hypo-S (b), Hypo-S+1 μM losartan (c), Hypo-S+10 μM losartan (d), and Hypo-S+20 μM losartan (e), respectively. I_{Ks} was activated by depolarizing voltage-clamp steps given from a holding potential of –50 mV to potentials listed as inset in (a). Dashed line indicates zero current level. (f) The percentage increase of I_{Ks} currents in atrial myocytes after perfusion of Hypo-S and Hypo-S plus different concentrations of losartan at +30 mV. **P*<0.05 versus Hypo-S

2a-2e shows the typical I_{Ks} current curves elicited by depolarizing voltage-clamp steps given from a –50 mV holding potential to various test potentials in the presence of Iso-S (panel A), Hypo-S (panel B), Hypo-S+1 μM losartan (panel C), Hypo-S+10 μM losartan (panel D), and Hypo-S+20 μM losartan (panel E). Figure 2f and Table 1 show the percentage increase of I_{Ks} currents in atrial myocytes after perfusion of Hypo-S, Hypo-S+1 μM losartan, Hypo-S+10 μM losartan, and Hypo-S+20 μM losartan, respectively. The percentage increase of I_{Ks} current after perfusion of Hypo-S, Hypo-S+1 μM losartan, Hypo-S+10 μM losartan, and Hypo-S+20 μM losartan was 105.60±10.25%, 75.52±8.65% (Hypo-S, p=0.032), 70.80±6.77% (Hypo-S, p=0.023), and 70.3%±7.18% (Hypo-S, p=0.028), respectively. The results indicated that the percentage increases of I_{Ks} currents after perfusion of Hypo-S+losartan were significantly lower than those of Hypo-S alone (Fig. 2f).

The experiments also investigated the *I–V* relationship of I_{Ks} after perfusion of Iso-S, Hypo-S, Hypo-S+1 μM losartan, Hypo-S+10 μM losartan, and Hypo-S+20 μM losartan, which were fitted to the Boltzmann equation. Table 1 also shows the voltage at half-maximal activation (V_h) of the I_{Ks} channel after perfusion of Iso-S, Hypo-S, Hypo-S+1 μM losartan, Hypo-S+10 μM losartan, and Hypo-S+20 μM losartan, respectively. Similar to the effect of Hypo-S, Hypo-S plus three different concentrations of losartan can also make the channel more easily open up (p<0.001 vs. Iso-S); but compared with Hypo-S, Hypo-S plus three different concentrations of losartan showed no significant difference, indicating that losartan did not change the effect of hyposmotic environment on the I_{Ks} channel activation curves in atrial myocytes.

In addition, the effect of losartan on deactivation time (τ) of I_{Ks} channel during perfusion of Hypo-S was observed at –50 mV (Table 1). The results show that Hypo-S significantly increased the τ value of I_{Ks} channel (Hypo-S: 386.8±27.5 ms vs. Iso-S: 295.5±19.2 ms, p<0.001) and slowed the channel closing process, but there was no significant change between Hypo-S and Hypo-S+1, 10, or 20 μM losartan (Table 1). These results suggested that losartan had no significant effect on the I_{Ks} channel gating kinetics induced by the hyposmotic environment.

Losartan attenuated the Hypo-S-induced shortening of APD_{90}

Figure 3a shows the action potentials in guinea pig atrial myocytes after perfusion of Iso-S, Hypo-S, Hypo-S+1 μM losartan, Hypo-S+10 μM losartan, and Hypo-S+20 μM losartan, respectively. Table 1 and bar graphs in Figure 3b show that Hypo-S

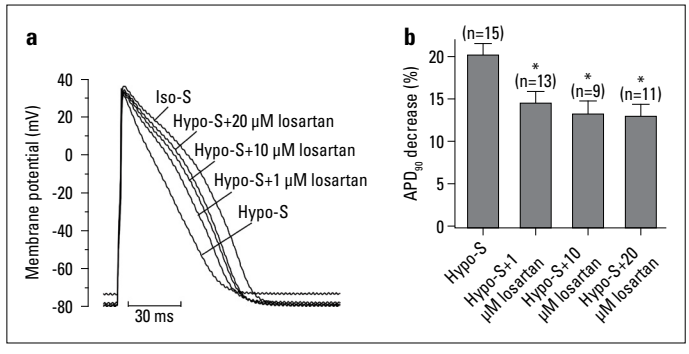

Figure 3. Losartan reduces the Hypo-S-induced shortening of APD_{90} in guinea pig atrial myocytes. (a) Superimposed action potentials in guinea pig atrial myocytes when firstly perfusion of Iso-S and then switched to Hypo-S, Hypo-S+1 μM losartan, Hypo-S+10 μM losartan, and Hypo-S+20 μM losartan. (b) Percentage decrease of APD_{90} in guinea pig atrial myocytes when perfusion solution was switched to Hypo-S, Hypo-S+1 μM losartan, Hypo-S+10 μM losartan, and Hypo-S+20 μM losartan. **P*<0.05 and ***P*<0.001 versus Hypo-S

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Table 1. Effect of losartan on biophysical parameters of I_{Ks} and AP in Iso-S and Hypo-S in guinea pig myocytes

Parameters	Iso-S	Hypo-S	Hypo-S+losartan		
			1 μM	10 μM	20 μM
I_{Ks}					
Peak tail current of I_{Ks} at 30	3.90±0.57 (n=25)	8.01±1.05 (n=22)	6.85±0.87 (n=12)	6.66±0.66 (n=15)	6.64±0.72 (n=10)
mV (pA/pF) (Δ%)		(105.60±10.25%)	(75.52±8.65%, ***P*=0.008***)	(70.80±6.77%, ***P*=0.003**)	(70.3±7.18%, ***P*=0.005**)
Activation: V_h (ms) (Δ%)	9.06±1.28 (n=22)	2.08±1.09 (n=13)	2.10±0.96 (n=8)	2.16±1.12 (n=8)	2.22±0.83 (n=9)
		(-77.04±18.85%)	(-76.82±21.22%, *P*=0.57)	(-76.16±17.50%, *P*=0.67)	(-75.50±26.42%, *P*=0.45)
τ of deactivation at –50 mV (ms) (Δ%)	295.5±19.2 (n=25)	386.8±27.5 (n=10)	380.1±33.6 (n=10)	376.4±31.2 (n=9)	374.6±37.2 (n=11)
		(30.90±5.06%)	(28.63±4.11%, *P*=0.38)	(27.38±4.85%, *P*=0.17)	(26.77±6.62%, *P*=0.14)
AP					
APA (Δ%)	125.0±8.55 (n=16)	122.1±7.05 (n=14)	122.8±8.82 (n=12)	123.2±9.43 (n=12)	123.7±8.81 (n=11)
		(-1.16±0.85%)	(-1.76±0.62%, *P*=0.08)	(1.44±0.36%, *P*=0.39)	(1.04±0.28%, *P*=0.68)
RMP (Δ%)	-80.7±0.75 (n=16)	-75.8±0.85 (n=13)	-76.1±0.88 (n=10)	-76.4±1.02 (n=9)	-75.4±0.93 (n=10)
		(6.07±0.76%)	(5.70±0.66%, *P*=0.17)	(5.33±0.95%, *P*=0.09)	(6.56±0.87%, *P*=0.38)
APD_{90} (Δ%)	117.0±9.52 (n=16)	93.3±6.85 (n=15)	100.00±6.36 (n=13)	101.5±8.12 (n=9)	101.7±6.64 (n=11)
		(-20.22±1.28%)	(-14.56±1.33%, ***P*=0.006**)	(-13.28±1.45%, ***P*=0.003**)	(-13.03±1.28%, ***P*<0.001**)

Δ% - the percentage increase of parameters over Hypo-S or Hypo-S+losartan. V_h - the voltages for half-activation of tail I_{Ks}; AP - action potential; APA - action potential amplitude; Iso-S - isosmotic extracellular solution; Hypo-S - hyposmotic extracellular solution; RMP - resting membrane potential; APD_{90} - action potential duration measured at 90% repolarization. Bold values indicate statistical significance at $P<0.05$ (vs. Hypo-S)

shortened APD_{90} in atrial myocytes to 20.22±1.28%, whereas Hypo-S+1 μM losartan, Hypo-S+10 μM losartan, and Hypo-S+20 μM losartan, respectively, shortened the APD_{90} to 14.56±1.33% (Hypo-S, p=0.006), 13.28±1.45% (Hypo-S, p=0.003), and 13.03±1.28% (Hypo-S, p<0.001). The results suggested that 1–20 μM losartan attenuated the Hypo-S-induced APD_{90} shortening in guinea pig atrial myocytes. The effects of losartan on the action potential amplitude and resting membrane potential in hyposmotic solution (Hypo-S) are also shown in Table 1. However, there was no significant difference between Hypo-S and Hypo-S+losartan in the two parameters.

Discussion

Electrophysiological studies have shown that the main effect of AF on cardiac ion channels is the reduction of $I_{Ca,L}$ inward current and calcium overload in atrial myocytes (11), resulting in atrial systolic and diastolic dysfunction. The resultant stretch of atrial myocyte plasma membrane can increase the outward I_{Ks} currents in the cells (16, 19). Changes in $I_{Ca,L}$ and I_{Ks} channel currents cause shortening of APD in atrial myocytes and physiological atrial dysrhythmia, thus contributing to the occurrence of electrophysiological and structural remodeling in the atria, which are the forming basis of persistent AF (11, 20). Hypo-S-induced stretch of atrial myocytes fits the stretch of myocardial cell membrane and various transport changes of related ion channels (11, 16, 20, 21). Therefore, it appears logical to suggest that the treatment of losartan on AF is associated with its reversibility of the electrophysiological remodeling in the atria since this drug attenuated both the I_{Ks} increase and the APD shortening induced by the stretch of guinea pig atrial myocytes.

AF is a progressive disease that usually starts as paroxysmal (self-terminating with a few minutes to a few hours) and can evolve relentlessly to persistent and then permanent (duration >1 year) forms. Many lines of evidence suggest that AF progression involves a broad continuum of cumulative electrophysiological and structural remodeling of the atria (22). In both human AF and animal AF models, marked reductions in the densities of L-type voltage-gated Ca^{2+} current $I_{Ca,L}$ and calcium overload have been confirmed in atrial myocytes, which are the primary factors leading to the shortening of the atrial APD and ERP in the fibrillating atria, the characteristic features of AF. In addition to atrial myocytes from patients in AF or animal AF model, it has been also observed in some electrical changes, such as increases in the rectifier background K^+ current I_{K1} and the constitutive acetylcholine-regulated K^+ current I_{KACh}, as well as decreases in the transient outward K^+ current I_{to}, the ultrarapid delayed rectifier K^+ current I_{Kur} and sodium current I_{Na} (22-25). These electrical changes usually occur early in the development of AF, even preceding the onset of arrhythmia. Following the electrophysiological remodeling of the atria, changes in the structure of the atria start to follow. One of the structural changes is the dilatation of atrial myocyte plasma membrane (11, 12), increasing the I_{Ks} currents in the cells and aggravates the atrial remodeling (16, 19). The present study found that losartan attenuated both the I_{Ks} increase and the APD

shortening induced by the stretch of guinea pig atrial myocytes, suggesting that the drug has the effect of improving electrophysiological remodeling and thus the treatment for AF. In addition to the currents attributing to electrophysiological remodeling by previous studies, I_{Ks} change should also be included as one element of the electrophysiological remodeling in AF.

Recent studies reported that R14C and S140G mutations in the *KCNQ1* gene (encoding α subunit of I_{Ks} channel) caused familial AF and increased I_{Ks} current (26, 27), providing clinical support for our experimental speculation. The stretch of atrial myocytes induces the increase of I_{Ks} current and shortening of APD in atrial myocytes and resultantly leads to the occurrence of AF, as well as facilitates its maintenance (16, 28-30). Losartan attenuated the APD shortening induced by the stretch of the cell membrane in guinea pig atrial myocytes, suggesting that the mechanism for treating AF by losartan is related to the inhibition of APD shortening induced by the stretch of atrial myocyte cell membrane.

RAS plays an important role in the occurrence and maintenance of AF. The stretch of atrial myocytes during AF not only activates AT_1R (30, 31) but also induces the secretion of angiotensin II from atrial myocytes (13, 14). Madrid et al. (32) reported that irbesartan in combination with amiodarone is more effective in preventing the recurrence of AF than amiodarone used alone. Lines of recent clinical reports and animal experiments have all confirmed the therapeutic effects of ARBs for the treatment of AF (1, 5-9, 21). In this experiment, losartan attenuated the increase of I_{Ks} induced by the stretch of guinea pig atrial myocytes but did not affect the basal I_{Ks} current, suggesting that the electrophysiological changes caused by the drug in atrial myocytes were related to blocking of the AT_1 receptor. This result is similar to that reported by Von Lewinski et al. (33) who found that irbesartan can prevent angiotensin II-induced arrhythmias by blocking the AT_1 receptor in human atrial myocytes.

Zankov et al. (15, 16) reported that selective ARBs valsartan and candesartan attenuate the increase of I_{Ks} induced by angiotensin II in guinea pig atrial myocytes and shortening of atrial myocyte APD caused by the stretch of guinea pig atrial myocytes, respectively. Together with the result of this experiment on losartan, we conclude that ARBs can improve the electrophysiological changes induced by atrial stretch, the mechanism of which involves the blocking of the AT_1 receptor and be beneficial to preventing the electrophysiological remodeling during AF. Previous studies of the relationship between ARBs and AF were mainly focused on the effect of ARBs on the remodeling of atrial tissues and structures (2, 4, 6). The present study showed that atrial electrophysiological remodeling also occurs under the action of the medicines.

Conclusion

In conclusion, the mechanisms underlying the treatment of AF by ARBs are associated with the melioration of not only atrial structural remodeling but also electrophysiological remodeling.

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