Angiotensin II Antagonist Prevents Electrical Remodeling in Atrial Fibrillation

Hideko Nakashima, MD; Koichiro Kumagai, MD; Hidenori Urata, MD; Naoki Gondo, MD; Munehito Ideishi, MD; Kikuo Arakawa, MD

Background—The blockade of angiotensin II (Ang II) formation has protective effects on cardiovascular tissue; however, the role of Ang II in atrial electrical remodeling is unknown. The purpose of this study was to investigate the effects of candesartan and captopril on atrial electrical remodeling.

Methods and Results—In 24 dogs, the atrial effective refractory period (AERP) was measured before, during, and after rapid atrial pacing. Rapid atrial pacing at 800 bpm was maintained for 180 minutes. The infusion of saline (n=8), candesartan (n=5), captopril (n=6), or Ang II (n=5) was initiated 30 minutes before rapid pacing and continued throughout the study. In the saline group, AERP was significantly shortened during rapid atrial pacing (from 149±11 to 132±16 ms, P<0.01). There was no significant difference in AERP shortening between the saline group and the Ang II group. However, in the candesartan and captopril groups, shortening of the AERP after rapid pacing was completely inhibited (from 142±9 to 147±12 ms with candesartan, from 153±15 to 153±14 ms with captopril, P=NS). Although rate adaptation of the AERP was lost in the saline group, this phenomenon was preserved in the candesartan and captopril groups.

Conclusions—The inhibition of endogenous Ang II prevented AERP shortening during rapid atrial pacing. These results indicate for the first time that Ang II may be involved in the mechanism of atrial electrical remodeling and that the blockade of Ang II may lead to the better therapeutic management of human atrial fibrillation. (Circulation. 2000;101:2612-2617.)

Key Words: angiotensin II fibrillation remodeling

It has been shown that angiotensin-converting enzyme inhibitor (ACEI) and the angiotensin II (Ang II) type 1 (AT1) receptor antagonist have beneficial effects on ventricular function and ventricular arrhythmias; however, little is known about how they affect atrial pathophysiology or electrophysiology.

Pedersen et al observed that ACEI reduced the incidence of atrial fibrillation in patients with left ventricular dysfunction after acute myocardial infarction, but they did not show the underlying mechanism of their finding.

Recent studies in animal models and humans have shown that atrial fibrillation induced by rapid atrial pacing itself produces shortening of the atrial effective refractory period (AERP) and reverses the normal physiological rate adaptation of refractoriness. This phenomenon of electrical remodeling increases the inducibility and stability of atrial fibrillation. However, the pathophysiological role of tissue Ang II in atrial electrical remodeling has not been investigated. In addition, our recent study performed with human heart indicated that non-ACE-dependent Ang II–forming activity caused by chymase was higher in the left atrium than in other chambers (M. Ihara, MD, et al, unpublished observations, 1999). It is important to determine which Ang II formation pathway (ACE or chymase) is more closely related to atrial electrophysiology. Therefore, in the present study, we examined the inhibitory effects of an AT1 receptor antagonist, candesartan, or an ACEI, captopril, on the atrial electrical remodeling induced by rapid pacing in a dog model.

Animal Preparation

All experiments were performed in accordance with the guidelines specified by the Institutional Animal Care and Use Committee, the American Heart Association Policy on Research Animal Use, and the Public Health Service Policy on Use of Laboratory Animals.

For this study, 24 adult mongrel dogs of either sex, weighing 12 to 25 kg, were used. The dogs were initially anesthetized with pentobarbital (25 mg/kg), and, after intubation and mechanical ventilation, anesthesia was maintained with halothane. Tidal volume was adjusted to maintain arterial pH between 7.35 and 7.45. The surface ECG lead II, intracardiac electrograms, right atrial pressure, and blood pressure were continuously monitored and recorded at a paper speed of 100 mm/s (San Ei 8 MI4). Four 7F sheaths were placed in the left femoral vein and artery and bilateral internal jugular veins. A quadripolar electrode pacing catheter was introduced into an internal jugular vein and positioned in the high lateral...
right atrium for high-frequency pacing. A pacing lead introduced into the femoral vein was placed in the right atrial appendage to measure the AERP. To minimize confounding effects caused by electrode polarization, all refractory period measurements were made with the pacing lead, which was not used for high-frequency pacing and was positively affixed to the right atrial appendage. Blood pressure was monitored from a femoral artery, and right atrial pressure was measured by a Swan-Ganz catheter introduced into an internal jugular vein. Pharmacological autonomic blockade was achieved by an initial bolus of atropine (0.04 mg/kg) and propranolol (0.2 mg/kg) followed by maintenance infusion during the experiment (0.007 and 0.04 mg·kg\(^{-1}\)·h\(^{-1}\), respectively).

**Electrophysiological Measurements**

A cardiac stimulator (Fukuda Denshi BC02A) was used to deliver square-wave impulses of 1-ms duration. Thirty minutes after pharmacological autonomic blockade, the AERP of the right atrial appendage was measured at 3 different basic cycle lengths (BCLs) (200, 300, and 400 ms). Five basic drive stimuli were followed by 1 single premature stimulus, and all stimuli were twice the diastolic threshold. The interval between \(S_1\) and \(S_2\) was increased in steps of 2 ms, and AERP was determined to be the shortest \(S_1\)-\(S_2\) interval resulting in a propagated atrial response. After measurement of the baseline AERP, high-frequency atrial pacing of 800 bpm was started (4 times the diastolic threshold) and maintained for 3 hours. Rapid pacing was briefly interrupted every 30 minutes for the first hour and (4 times the diastolic threshold) and maintained for 3 hours. Rapid pacing was briefly interrupted every 30 minutes for the first hour and (4 times the diastolic threshold) and maintained for 3 hours.

**Table 1. Change in Mean AERP Before, During, and After Rapid Atrial Pacing**

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\(R\) indicates time after offset of rapid pacing.  
*\(P<0.01\), †\(P<0.02\), ‡\(P<0.05\) compared with baseline (time 0).

**Infusion of Drugs**

The magnitude and time course of pacing-induced electrical remodeling were assessed in 8 control animals that were subjected to the high-frequency pacing protocol described above. To assess the effects of Ang II blockade on electrical remodeling, the protocol was performed in dogs treated with candesartan (an AT\(_1\) receptor antagonist) or captopril (an ACEI). The infusion of candesartan (1 mg·kg\(^{-1}\)·min\(^{-1}\), n=5) or captopril (15 μg·kg\(^{-1}\)·min\(^{-1}\), n=6) was started 30 minutes before rapid atrial pacing and maintained until the protocol was completed. The effects of Ang II on electrical remodeling were assessed in 5 additional dogs. Ang II (100 mg·kg\(^{-1}\), min\(^{-1}\)) infusion was started 30 minutes before the beginning of pacing and was continued for 1 hour because of its tachyphylactic effect.\(^{11}\) These drug and control saline experiments were performed in random order.

**Statistical Analysis**

All values are expressed as mean±SD. Continuous values were compared with a paired t test. ANOVA was used to evaluate differences between groups of discrete variables. A 2-sided probability level of \(P<0.05\) was considered to be significant.

**Results**

**Time Course and Magnitude of Electrical Remodeling**

In the saline group, the baseline AERP (after autonomic blockade and before the onset of high-frequency pacing) was 136±9, 149±11, and 154±14 ms at BCLs of 200, 300, and 400 ms, respectively (Table 1). AERP shortening began and was most pronounced in the first 30 minutes and continued during pacing (Figure 1A). After 180 minutes of rapid pacing, AERP was significantly shortened at all 3 cycle lengths (-7±14%, -11±9%, and -11±11%, respectively) (Figure 2). Because the degree of AERP shortening induced by high-frequency pacing was greater at longer BCLs than that at shorter BCLs (Figure 2), physiological rate adaptation of the AERP was lost in the remodeled state.

The mean right atrial pressure did not change significantly during the course of the experiment (baseline versus after 180 minutes of pacing: 4.1±1.1 versus 5.1±2.6 mm Hg) (Table 2). Furthermore, mean systolic blood pressure did not show any significant change over the course of the experiment (baseline versus after 180 minutes of pacing: 98±15 versus 113±18 mm Hg) (Table 2).
Effects of Candesartan, Captopril, and Ang II on Electrical Remodeling

During candesartan infusion, the AERP was no longer shortened by rapid pacing (Figure 1A). The AERP at baseline (131 ± 5, 142 ± 9, and 148 ± 10 ms at BCLs of 200, 300, and 400 ms, respectively) was not significantly different from the corresponding AERP after the termination of rapid pacing (136 ± 9, 147 ± 12, and 153 ± 13 ms at BCLs of 200, 300, and 400 ms respectively) (Table 1). The percent change in AERP in the candesartan group was significantly less than that in the saline group (+4.1 ± 7.7% versus −11.3 ± 8.9%, +3.7 ± 8.3% versus −10.6 ± 11.0% at BCLs of 300 and 400 ms, respectively, P<0.01) (Figure 2).

In the captopril-treated group, the time course of electrical remodeling was similar to that in the candesartan-treated group and the AERP was not shortened during rapid pacing (baseline versus after 180 minutes of pacing: from 140 ± 15 to 137 ± 11, from 153 ± 15 to 153 ± 14, and from 166 ± 22 to 174 ± 20 ms at BCLs of 200, 300, and 400 ms, respectively) (Table 1, Figure 1A). In contrast to the saline group, candesartan and captopril maintained physiological rate adaptivity and completely prevented electrical remodeling (Figure 2).

As the result of a tachyphylactic phenomenon, the effect of Ang II on atrial electrical remodeling did not last >60 minutes. AERP after 60 minutes of pacing was significantly shorter than the baseline value (from 135 ± 4 to 119 ± 5, P<0.01, from 149 ± 4 to 133 ± 5, P<0.01, and from 159 ± 6 to 143 ± 9 ms, P<0.02, at BCLs of 200, 300, and 400 ms respectively). Thus, in contrast to the results in the candesartan and captopril groups, Ang II infusion induced marked electrical remodeling (Figure 1B).

In candesartan- and captopril-treated groups, although the mean systolic blood pressure after infusion of these drugs was significantly decreased compared with the baseline value, the mean systolic blood pressure during 180 minutes of rapid pacing was comparable to the baseline value (before drug versus baseline versus after 180 minutes of pacing: 125 ± 18 versus 104 ± 22 versus 110 ± 19 mm Hg in the candesartan group, 107 ± 12 versus 83 ± 7 versus 89 ± 16 mm Hg in the captopril group) (Table 2). Ang II infusion significantly increased the mean systolic blood pressure at baseline, but there were no differences in systolic blood pressure during rapid pacing (before drug versus baseline versus after 60 minutes of pacing: 106 ± 17 versus 140 ± 10 versus 107 ± 31 mm Hg).

As in the control group, right atrial pressure in the candesartan- and captopril-treated groups did not show any significant change during this study (baseline versus after 180 minutes of pacing: 4.4 ± 1.7 versus 4.8 ± 0.8 mm Hg in the candesartan group, 4.2 ± 0.6 versus 4.7 ± 0.8 mm Hg in the captopril group, respectively). In contrast, Ang II infusion increased right atrial pressure during rapid atrial pacing.
The major findings of this study are as follows: (1) AERP was significantly shortened during rapid atrial pacing in closed-chest dog models, and the physiological rate adaptation of the AERP was lost in the remodeled state, (2) this shortening of the AERP during rapid pacing was prevented by treatment with candesartan or captopril but increased by Ang II, and physiological rate adaptation of AERP was maintained in candesartan and captopril groups, (3) AERP after the termination of rapid pacing recovered to almost the baseline value within 10 minutes in the control group, and (4) Ang II infusion markedly delayed the recovery of refractory periods after the cessation of rapid pacing. Thus, these findings are the first to indicate that Ang II contributes to atrial electrical remodeling.

**Ang II Inhibition and Atrial Fibrillation**

Previous studies have shown that AT1 receptor antagonists and ACEI significantly reduced ventricular arrhythmias after ischemic injury, suggesting that these drugs have beneficial effects on reperfusion arrhythmias.1–5 However, the effect of these drugs on atrial fibrillation has not been thoroughly examined.

Recently, Pedersen et al6 demonstrated that ACEI treatment with trandolapril reduced the risk of developing atrial fibrillation by 55% during a 2- to 4-year follow-up period in patients with left ventricular dysfunction after acute myocardial infarction. In that study, the difference in the incidence of atrial fibrillation with or without ACEI could not be explained by differences in the serum potassium concentration or left ventricular systolic function. Therefore, the detailed mechanism of the role of ACEI in preventing atrial fibrillation has not yet been clarified. Our results may provide insight into the mechanism by which AT1 receptor antagonist or ACEI can prevent the risk of developing atrial fibrillation.

**Previous Studies of Atrial Electrical Remodeling**

Both animal and human studies have demonstrated that prolonged episodes of atrial fibrillation induced shortening of the AERP and a loss of rate-related AERP shortening. This electrical remodeling may increase the stability of atrial fibrillation and may play a role in the transition of paroxysmal atrial fibrillation to chronic atrial fibrillation and in the loss of the efficacy of antiarrhythmic drugs or electrical shock in the cardioversion of atrial fibrillation of longer duration.7–10,12

High-frequency pacing is known to cause an increase in intracellular calcium levels in cardiac myocytes, and intracellular calcium overload is thought to contribute to this phenomenon. Recent data have suggested that calcium channel blockade prevents AERP shortening during rapid atrial pac-

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**TABLE 2. Hemodynamic Parameters in Control and Experimental Groups**

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Mean systolic blood pressure, mm Hg

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R indicates time after offset of rapid pacing.

*P<0.02 compared with baseline (time 0).
†P<0.01, ‡P<0.05 compared with before drug (time −30).
ing, whereas other studies have suggested that sodium channel, potassium channel, and ovarian hormones also may affect atrial electrical remodeling. Therefore, it appears that many factors play synergistic roles in electrical remodeling, and its mechanism is complex.

### Ang II Inhibition and Atrial Electrical Remodeling

There are several possible mechanisms by which the AT₁ receptor antagonist and ACEI prevent atrial electrical remodeling. These include decreasing atrial stretch, modulation of refractoriness, interference with ion currents, modification of sympathetic tone, and stabilization of electrolyte concentrations. It has been reported that human AT₁ receptor mRNA was upregulated in atria of dilated cardiomyopathy but was undetectable in the corresponding ventricular tissue. In addition, the AT₁ receptor antagonist and ACEI have been reported to decrease atrial pressure. Also in the present study, Ang II infusion significantly increased atrial pressure, whereas atrial pressure did not change during rapid pacing after treatment with AT₁ receptor antagonist or ACEI. Atrial stretch induced by increased atrial pressure may precipitate atrial fibrillation through some effect on atrial refractoriness. Thus, it is possible that the elevation of atrial pressure might cause electrical remodeling by the upregulation of atrial AT₁ receptor expression.

It has been demonstrated that Ang II may affect the genesis of reperfusion ventricular arrhythmias by increasing intracellular calcium through the increased intake of extracellular calcium and increased release from sarcoplasmic reticulum in myocytes through the activation of membrane L-type calcium channel or phosphatidylinositol–phospholipase C pathways. Previous studies have reported the reduction of reperfusion ventricular arrhythmias by AT₁ receptor antagonist and ACEI. It has been shown that Ang II increases the intracellular calcium concentration significantly more in atrial myocytes than in ventricular myocytes in the rat heart. Moreover, the density of Ang II receptor in atria is generally higher than that in ventricles. Thus, intracellular calcium overload induced by Ang II might play a role not only in reperfusion ventricular arrhythmias but also in atrial electrical remodeling. Therefore, it is possible that the blockade of local Ang II by AT₁ receptor antagonist and ACEI could attenuate atrial fibrillation–induced electrical remodeling, probably by preventing calcium overload.

There was no significant difference between the AT₁ receptor antagonist and ACEI with regard to elimination of tissue calcium. However, calcium channel blockers could prevent electrical remodeling. In addition, calcium channel blockers are not effective for cardioversion of atrial fibrillation or for preventing the induction of atrial fibrillation by rapid atrial stimulation. In addition, Kumagai et al. observed that verapamil increased atrial vulnerability in an electrophysiological study.

### Clinical Implications

Previous studies have suggested that calcium channel blockers could prevent electrical remodeling, however, calcium channel blockers are not effective for cardioversion of atrial fibrillation or for preventing the induction of atrial fibrillation by rapid atrial stimulation. In addition, Kumagai et al. observed that verapamil increased atrial vulnerability in an electrophysiological study.

The AT₁ receptor antagonist and ACEI are not antiarrhythmic in the conventional sense; however, the results of the present study demonstrated that AT₁ receptor blockade could prevent atrial electrical remodeling in a clinical situation. Thus, AT₁ receptor antagonist or ACEI may constitute a novel pharmacological approach for the treatment of patients with atrial fibrillation.

### References


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