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Effects of Angiotensin II Type 1 Receptor Antagonist on Electrical and Structural Remodeling in Atrial Fibrillation

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OBJECTIVES The purpose of the present study was to evaluate the effect of angiotensin II type 1 receptor (AT1R) antagonist on chronic structural remodeling in atrial fibrillation (AF).

BACKGROUND We previously reported that an AT1R antagonist, candesartan, prevents acute electrical remodeling in a rapid pacing model. However, the effect of candesartan on chronic structural remodeling in AF is unclear.

METHODS Sustained AF was induced in 20 dogs (10 in a control group and 10 in a candesartan group) by rapid pacing of the right atrium (RA) at 400 beats/min for five weeks. Candesartan was administered orally (10 mg/kg/day) for one week before rapid pacing and was continued for five weeks. The AF duration, atrial effective refractory period (AERP) at four sites in the RA, and intra-atrial conduction time (CT) from the RA appendage to the other three sites were measured every week.

RESULTS The mean AF duration in the control group after five weeks was significantly longer than that with candesartan (1,333 ± 725 vs. 411 ± 301 s, $p < 0.01$). The degree of AERP shortening after five weeks was not significantly different between the two groups. The CT from the RA appendage to the low RA after five weeks with candesartan was significantly shorter than that in the control (43 ± 14 vs. 68 ± 10 ms, $p < 0.05$). The candesartan group had a significantly lower percentage of interstitial fibrosis than the control group (7 ± 2% vs. 16 ± 1% at the RA appendage, $p < 0.001$).

CONCLUSIONS Candesartan can prevent the promotion of AF by suppressing the development of structural remodeling. (J Am Coll Cardiol 2003;41:2197–204) © 2003 by the American College of Cardiology Foundation

Several studies have shown that activation of the renin-angiotensin system is associated with the mechanism of atrial fibrillation (AF) (1–3). We previously reported that the blockade of angiotensin II (Ang II) prevented the electrical remodeling induced by short-term rapid atrial pacing (4). However, the effects of these drugs on long-term atrial electrophysiologic and structural remodeling are still unclear. Goette et al. (1) observed that the activation of angiotensin-converting enzyme (ACE)-dependent extracellular signal-regulated kinases (Erk1/Erk2) was involved in the mechanism of the development of atrial fibrosis in patients with AF. They also showed the down-regulation of atrial angiotensin II type 1 receptor (AT1R) and the up-regulation of AT2R in AF patients (2). It is well known that architectural alterations of the atria, including atrial dilation and tissue fibrosis, are associated with atrial dysfunction (5,6). Li et al. (6) reported that electrical heterogeneity probably due to atrial fibrosis might play a critical role in the induction and promotion of AF in an arrhythmogenic substrate in the canine heart failure model. Considering previous observations, we hypothesized that structural abnormalities caused by an activated renin-angiotensin system during chronic atrial activation might participate in the mechanisms of AF maintenance.

See page 2205

The purpose of this study was to investigate the effects of the blockade of Ang II on long-term atrial remodeling in the canine rapid pacing model.

METHODS

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 the Use of Laboratory Animals.

Twenty mongrel dogs of either gender, weighing 12 to 25 kg, were randomly divided into two groups. In the candesartan group (n = 10), oral administration of candesartan (10 mg/kg/day) was started one week before the baseline study and was continued to the end of the study. The dogs in the control group (n = 10) did not receive candesartan.

All dogs were anesthetized with an intravenous injection of pentobarbital (25 mg/kg), and, after intubation and mechanical ventilation, anesthesia was maintained with halothane. A tachy-pacing generator (Medtronic, Minneapolis, Minnesota) was implanted in a subcutaneous pocket in the neck and attached to a pacing lead in the right atrial

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Abbreviations and Acronyms

ACE = angiotensin-converting enzyme
AERP = atrial effective refractory period
AF = atrial fibrillation
Ang II = angiotensin II
AT1R = angiotensin II type 1 receptor
CT = conduction time
Erk = extracellular signal-regulated kinases

appendage. The chest was opened through the right fourth intercostal space, and four electrodes pair were sutured to four sites in the right atrium (appendage, and high lateral, low lateral, and anterior wall). At the completion of surgery, the dogs were given antibiotics and then allowed to recover. Postoperative care included the administration of antibiotics and analgesics.

Baseline electrophysiologic study. One week after the operation, the dogs were reanesthetized with pentobarbital (25 mg/kg) and ventilated by halothane. The arterial blood gases were adjusted to between pH 7.35 and 7.45 during ventilation. The surface electrocardiogram lead II, intracardiac electrograms, and blood pressure were continuously monitored and recorded during the experiment. The pulmonary capillary wedge pressure, the pulmonary artery pressure, and the right atrial pressure were measured using a Swan-Ganz catheter.

Atrial effective refractory periods (AERPs) at four sites were measured at three basic cycle lengths (200, 300, 400 ms). Five basic drive stimuli were followed by a single premature stimulus, and all stimuli were twice the diastolic threshold. The S1-S2 interval was increased in steps of 2 ms, and AERP was determined to be the shortest S1-S2 interval that resulted in a propagated atrial response. The AERP dispersion was measured as the difference between maximum and minimum AERP among four sites. Intra-atrial conduction times (CT) from the appendage to the other three sites (high lateral, low lateral and anterior wall) were measured during appendage pacing at each basic cycle length.

Atrial fibrillation was defined as a rapid, irregular atrial rhythm with varying atrial electrogram morphology. The inducibility of AF was assessed by premature atrial stimulation during AERP measurement and atrial burst pacing (10 Hz for 1 to 10 s). If induced AF persisted >30 min, electrical cardioversion was performed. To estimate the mean AF duration, AF was induced 30 times if the AF duration was <10 min and 5 times if AF lasted between 10 and 15 min. When electrocardioversion was applied, AF induction was repeated after the 15-min rest period.

Electrophysiologic study after rapid atrial pacing. After the measurement of baseline electrophysiologic and hemodynamic parameters, programmed atrial pacing at 400 beats/min using 2-ms pulses at twice the threshold current was started and continued for five weeks in both the control and candesartan groups. The tachy-pacing generator was turned off every week to allow for repeated assessment by an electrophysiologic study.

Table 1. Characteristics and Hemodynamic Parameters in the Control and Candesartan Groups

	Control	Candesartan
Body weight (kg)	20 ± 5	15 ± 4.3
Heart weight (g)	128 ± 31	107 ± 6
Heart weight/body weight (g/kg)	7.3 ± 0.9	7.0 ± 0.2
Systolic BP (mm Hg)	101 ± 17	90 ± 12
Diastolic BP (mm Hg)	63 ± 6	54 ± 5
PCWP (mm Hg)	10 ± 1	7 ± 1*
Mean PAP (mm Hg)	15 ± 1	11 ± 1*
RAP (mm Hg)	8 ± 2	5 ± 1†

*$p < 0.01$, †$p < 0.05$ compared with the control group.
BP = blood pressure; PAP = pulmonary artery pressure; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure.

Histology. At the end of the experiments, the heart was quickly removed and weighed. To investigate the influence of rapid pacing on pathologic properties, the atrial tissues of five sham dogs without rapid atrial pacing were observed in the same operation. The tissues of the left and right atrial free wall and appendages were cut into small blocks about 10 × 5 mm and immersed in 10% phosphate-buffered formalin for 24 h. After dehydration, each section was cut in 4-μm-thick slices. Deparaffinized sections were stained with hematoxylin-eosin and Masson's trichrome. Microscopic images were scanned into a personal computer with Photoshop. Image files were analyzed with National Institutes of Health software (NIH image 1.61). Connective tissue was differentiated on the basis of its color and expressed as a percentage of the reference tissue area.

Statistical analysis. All values are expressed as mean ± SD. Continuous values were compared with analysis of variance. A paired *t* test was used to evaluate differences between groups of discrete variables. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Hemodynamic changes. The hemodynamic data are provided in Table 1. Although the blood pressure was not significantly different between the control and candesartan groups throughout the experiment, the pulmonary capillary wedge pressure, mean pulmonary artery pressure, and mean right atrial pressure in the candesartan group were significantly less than those in the control group.

Changes of electrophysiologic properties. In both the control and candesartan groups, AERP shortening was most pronounced after one week of rapid pacing and continued during pacing (Table 2, Fig. 1). The degree of AERP shortening after rapid pacing was not significantly different between the two groups (Table 2, Fig. 1). Furthermore, the physiologic rate adaptation of the AERP, which was observed before the rapid pacing, was attenuated after five weeks of pacing in both groups (Table 2). There was no significant difference in the dispersion of AERP after five weeks between the two groups (control group vs. candesar-

Table 2. Change in Mean AERP Before and During Rapid Atrial Pacing

	Baseline	1 Week	2 Weeks	3 Weeks	4 Weeks	5 Weeks
Control group						
RAA						
200 ms	133 ± 14	97 ± 19†	89 ± 13†	90 ± 16‡	86 ± 17	89 ± 22†
300 ms	137 ± 13	102 ± 21‡	92 ± 12†	92 ± 13†	87 ± 12‡	88 ± 14†
400 ms	142 ± 14	102 ± 22‡	99 ± 19†	100 ± 30‡	98 ± 38	94 ± 21‡
LRA						
200 ms	120 ± 14	90 ± 20†	85 ± 17†	81 ± 11†	79 ± 7‡	76 ± 9†
300 ms	131 ± 8	108 ± 16‡	100 ± 24‡	94 ± 23‡	89 ± 4†	88 ± 8†
400 ms	137 ± 6	108 ± 23‡	103 ± 26‡	94 ± 24‡	90 ± 3‡	84 ± 7†
HRA						
200 ms	126 ± 13	94 ± 11	89 ± 3‡	77 ± 18‡	77 ± 10‡	78 ± 7†
300 ms	132 ± 13	104 ± 15‡	90 ± 6	79 ± 19‡	81 ± 16†	80 ± 16†
400 ms	134 ± 12	106 ± 17‡	89 ± 4‡	80 ± 16‡	81 ± 15‡	83 ± 13‡
ARA						
200 ms	128 ± 15	89 ± 22	86 ± 20‡	87 ± 18‡	82 ± 4‡	83 ± 3‡
300 ms	137 ± 14	96 ± 15‡	88 ± 19	85 ± 14‡	81 ± 11‡	85 ± 3‡
400 ms	143 ± 17	102 ± 16‡	93 ± 13	89 ± 18‡	87 ± 5‡	87 ± 4‡
Candesartan group						
RAA						
200 ms	130 ± 18	105 ± 33	102 ± 27‡	97 ± 18‡	99 ± 30†	93 ± 10*
300 ms	139 ± 16	111 ± 31	109 ± 29‡	104 ± 18†	100 ± 28†	98 ± 13*
400 ms	149 ± 19	109 ± 25‡	107 ± 30‡	108 ± 23†	107 ± 30‡	99 ± 12*
LRA						
200 ms	123 ± 15	104 ± 11	96 ± 9†	92 ± 5†	90 ± 13*	87 ± 12‡
300 ms	136 ± 16	116 ± 16	102 ± 12†	97 ± 12‡	98 ± 19†	94 ± 17‡
400 ms	143 ± 17	115 ± 7	105 ± 12‡	113 ± 34‡	109 ± 7*	96 ± 7‡
HRA						
200 ms	118 ± 20	99 ± 10	89 ± 9	89 ± 2	85 ± 4	82 ± 11‡
300 ms	130 ± 26	106 ± 8	101 ± 15	99 ± 10	99 ± 13	92 ± 7‡
400 ms	133 ± 23	105 ± 3	107 ± 16	102 ± 10	97 ± 13	95 ± 5‡
ARA						
200 ms	113 ± 12	95 ± 10	86 ± 12	82 ± 1‡	82 ± 10‡	80 ± 3‡
300 ms	124 ± 18	102 ± 9	94 ± 10	93 ± 5‡	94 ± 7‡	93 ± 8‡
400 ms	131 ± 21	102 ± 9	95 ± 9‡	93 ± 10	94 ± 11‡	95 ± 12‡

*$p < 0.001$, †$p < 0.01$, ‡$p < 0.05$, compared with baseline.
AERP = atrial effective refractory period; ARA = anterior right atrium; HRA = high lateral right atrium; LRA = low lateral right atrium; RAA = right atrial appendage.

tan group: 14 ± 12 vs. 13 ± 13 ms, 9 ± 10 vs. 8 ± 8 ms, and 10 ± 9 vs. 8 ± 10 ms at the basic cycle length of 200, 300, and 400 ms, respectively).

Although the baseline intra-atrial CT was not different between the control and candesartan groups (Table 3), in the control group, the CT from the right atrial appendage to the other three sites gradually prolonged and the value after five weeks of pacing was significantly longer than that in the candesartan group (Table 3, Fig. 1). On the other hand, CT in the candesartan group was not significantly prolonged throughout the study (Table 3, Fig. 1).

In the baseline, AF lasting more than 30 s was not induced in both the control and candesartan groups (control group: 11 ± 9 s; candesartan group: 12 ± 10 s) (Fig. 1). Rapid pacing caused a significant increase in the AF duration in both groups compared with the baseline (Fig. 1). When the pacemaker was turned off, there were no dogs with AF. Some episodes of AF were induced with a single extra stimulus in two dogs in the control group and one dog in the candesartan group; however, in other dogs AF was induced with burst pacing. Sustained AF (>900 s) was induced in 7 of 10 control dogs and electrical cardioversion was performed in all 7 dogs, whereas it was not induced at all in the candesartan group, and the mean duration of induced AF in the candesartan group was significantly shorter than that in the control group (control group vs. candesartan group: 1,333 ± 725 vs. 411 ± 301 s after 5 weeks, $p < 0.01$) (Fig. 1).

There was no significant difference in the mean AF cycle lengths (control group vs. candesartan group: 89 ± 19 vs. 95 ± 11 ms after 5 weeks) and the mean ventricular rate during rapid atrial pacing (control group vs. candesartan group: 212 ± 13 vs. 209 ± 10 beats/min after 5 weeks) between the two groups.

Pathologic examination. Histologic studies were performed to identify the potential pathologic substrate underlying conduction abnormalities in rapid-pacing dogs. Pericardial inflammation, effusion, and hemorrhage were not observed in any of the dogs. Representative histologic sections from each group are shown in Figure 2. Atrial myocyte from sham dogs showed a normal composition of sarcomeres distributed throughout the cell, and the intra-

JACC Vol. 41, No. 12, 2003
June 18, 2003:2197–204

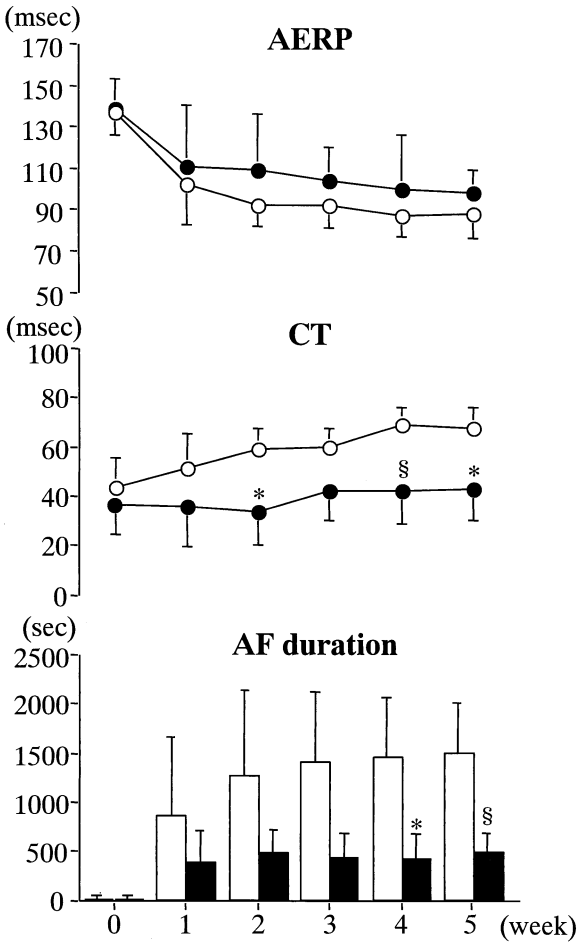

Figure 1. Time course of the percent changes in the atrial effective refractory period (AERP) of the right atrial appendage and intra-atrial conduction time (CT) from the right atrial appendage to the lower right atrial wall at a basic cycle length of 300 ms, and the mean duration of induced atrial fibrillation (AF) in the control **(white circles, white bars)** and candesartan **(black circles, black bars)** groups. The degree of AERP shortening was similar between the two groups, the intra-atrial CT in the candesartan group was significantly shorter than that in the control group, and the mean AF duration in the candesartan group was significantly shorter than that in the control group. §$p < 0.01$, *$p < 0.05$ compared with the control group.

cellular space also appeared normal. In contrast, atrial myocytes of control dogs showed a loss of some contractile materials and abnormal sarcomeres. In addition, extensive interstitial fibrosis, evidenced by Masson trichrome stain was found in these tissues. Thick layers of fibrous tissue were observed in the endocardium and epicardium. Furthermore, the amount of connective tissue was increased, and this extended around parenchymal cells. In contrast, these pathologic abnormalities of atrial tissues were attenuated in the candesartan group.

A quantitative analysis of fibrosis is shown in Figure 3. The percentage of fibrosis in all atrial regions in the candesartan group was markedly lower than that in the control group (7 ± 2% vs. 16 ± 1% at the right atrial appendage, $p < 0.001$), although greater than that in the sham group (7 ± 2% vs. 4 ± 1% at the right atrial appendage, $p < 0.05$). Because the rapid pacing lead was fixed to the right atrial appendage, these histologic changes seemed to be slightly greater in the right atria than in the left atria. However, this difference was not significant.

DISCUSSION

Main findings. This study has demonstrated for the first time that Ang II contributes to the development of AF in a long-term rapid pacing model. The major findings of this study are as follows: 1) the degree of AERP shortening and the dispersion of AERP after five weeks were similar between the control group and the candesartan group; 2) the intra-atrial CT in the candesartan group was significantly shorter than that in the control group; 3) candesartan significantly reduced the percentage of interstitial fibrosis compared with that in the control group; and 4) the mean AF duration in the candesartan group was significantly shorter than that in the control group. These findings indicate that Ang II may be involved in structural remodeling in the mechanism of chronic AF.

Possible mechanisms of AF promotion. Previous studies have shown that shortened AERP and loss of its adaptation to rate, which have been referred to as electrical remodeling, are observed in the pacing-induced AF model (7–9). Wijffels et al. (10) reported AERP shortening and increased vulnerability to AF in the instrumented goat model. However, there was a discrepancy in the time course between these two changes. The AERP shortening began within 24 h, whereas AF started to get stable only after more than a week, and this lasted for a long time. These results indicated that a decreased wavelength, which is caused by a shortened AERP and decreased conduction velocity, might play a critical role in the development of chronic AF. Furthermore, Everett et al. (11) demonstrated that a shortened AERP returned to the baseline level in 7 to 14 days after six weeks of rapid atrial pacing. Despite the complete normalization of AERP, the structural abnormalities of the atria persisted. Based on these results, not only AERP shortening but also other additional factors, including functional and structural abnormalities of the atria, may be involved in the promotion of AF.

In the present study, AERP was significantly shortened in the first week, and there was no further shortening of the AERP with pacing. On the other hand, the intra-atrial CT was gradually prolonged, and after five weeks of rapid pacing it was significantly longer than the baseline value. Furthermore, the inducibility of AF and its mean duration tended to increase and run parallel to the intra-atrial conduction slowing, and significant differences were seen after the fourth and fifth weeks compared with that after the first week. These findings indicate that conduction slowing may be related to heterogeneous conduction abnormalities, which may contribute to the initiation and maintenance of AF.

Table 3. Change in Mean Intra-Atrial Conduction Time Before and During Rapid Atrial Pacing

	Baseline	1 Week	2 Weeks	3 Weeks	4 Weeks	5 Weeks
Control group						
RAA-LRA						
200 ms	44 ± 13	52 ± 14	60 ± 9	61 ± 8	69 ± 9†	69 ± 9†
300 ms	43 ± 14	51 ± 16	59 ± 10	60 ± 9	69 ± 9†	68 ± 10*
400 ms	43 ± 15	51 ± 16	58 ± 12	60 ± 17†	70 ± 7*	70 ± 7*
RAA-HRA						
200 ms	34 ± 9	42 ± 15	44 ± 17	44 ± 15	45 ± 4	53 ± 10†
300 ms	34 ± 9	42 ± 15	44 ± 17	44 ± 15	45 ± 4	53 ± 10†
400 ms	34 ± 9	42 ± 15	44 ± 17	44 ± 15	46 ± 5	53 ± 10†
RAA-ARA						
200 ms	26 ± 10	35 ± 9	34 ± 8	35 ± 13	37 ± 12†	41 ± 9
300 ms	26 ± 10	35 ± 9	34 ± 8	35 ± 13	37 ± 12†	41 ± 9
400 ms	26 ± 10	36 ± 10	35 ± 9	35 ± 13	37 ± 12†	41 ± 9†
Candesartan group						
RAA-LRA						
200 ms	38 ± 15	37 ± 16	34 ± 15§	41 ± 13§	43 ± 14‡	42 ± 13‡
300 ms	37 ± 13	36 ± 18	34 ± 15§	42 ± 13	42 ± 14‡	43 ± 14§
400 ms	37 ± 14	39 ± 15	34 ± 15§	42 ± 13	44 ± 13‡	44 ± 13‡
RAA-HRA						
200 ms	26 ± 8	27 ± 13	28 ± 10	34 ± 3	31 ± 3‡	33 ± 3‡
300 ms	26 ± 8	30 ± 10	29 ± 9	35 ± 4	33 ± 3§	34 ± 3‡
400 ms	26 ± 8	28 ± 10	29 ± 9	34 ± 3	33 ± 3§	34 ± 3‡
RAA-ARA						
200 ms	20 ± 4	25 ± 6	24 ± 3§	22 ± 3	22 ± 3	23 ± 3§
300 ms	21 ± 3	23 ± 5§	21 ± 5§	22 ± 3	23 ± 3	24 ± 3‡
400 ms	21 ± 3	23 ± 3§	23 ± 3§	22 ± 3	23 ± 3	24 ± 3‡

*$p < 0.01$, †$p < 0.05$ compared with baseline, ‡$p < 0.01$, §$p < 0.05$ compared with the control group.
Abbreviations as in Table 2.

Electrical remodeling and the renin-angiotensin system. Previous studies have shown that atrial tachycardia–induced electrical remodeling, which consisted of AERP shortening and loss of physiologic rate adaptation, increased the inducibility and stability of AF (7–10). The intracellular calcium overload during high-frequency atrial activation is thought to contribute to this phenomenon of electrical remodeling (8,9,12,13). Accordingly, an L-type calcium channel blocker, verapamil, has been suggested to prevent short-term electrical remodeling in animal and human studies (8,9,12,13). However, several studies have demonstrated that verapamil could not prevent long-term tachycardia-induced AERP shortening and maladaptation of AERP, and rather than reducing the inducibility of AF, it increased the duration of induced AF (14–17). In addition, we have previously reported that verapamil increased intra-atrial conduction delay and fragmented activity in patients with paroxysmal AF (18). These results suggested that intracellular calcium overload might contribute to a mechanism of electrical remodeling only in the short term, but not in the long term.

We previously reported that ACE inhibitor and AT1R antagonist prevented AERP shortening in a canine short-term rapid pacing model (4). The beneficial effects of these drugs may be due to, besides the prevention of intracellular calcium overload, decreased atrial stretching during rapid atrial activation. In the present study, we examined the effects of an AT1R antagonist, candesartan, on long-term atrial electrophysiologic and structural remodeling. Candesartan did not prevent AERP shortening after one week of rapid pacing, suggesting that only prevention of calcium overload cannot prevent long-term electrical remodeling. Shinagawa et al. (19) also reported that the ACE inhibitor enalapril did not prevent AERP shortening after seven days of rapid pacing, suggesting apparent mechanical differences between short-term remodeling and long-term remodeling. They described that short-term remodeling is primarily caused by functional changes such as Ca_i^{2+}- and voltage-dependent L-type Ca current inactivation, whereas long-term remodeling is caused by changes in ion channel expression due to reduced levels of messenger ribonucleic acid encoding ion channel subunits and possibly post-transcriptional mechanisms as well. This may explain why candesartan inhibited short-term electrical remodeling but not long-term electrical remodeling. However, candesartan significantly decreased the inducibility and the duration of AF after five weeks of rapid atrial pacing, probably by preventing the development of conduction slowing. Therefore, the blockade of Ang II may attenuate the arrhythmogenic substrate, which may promote the transition to chronic AF.

Structural remodeling and the renin-angiotensin system. Atrial fibrillation is associated with progressive structural changes of the atria, resulting in atrial dilation and increased interstitial fibrosis (5,11). Li et al. (6) reported that decreased AERP and increased AERP heterogeneity were not

JACC Vol. 41, No. 12, 2003
June 18, 2003:2197–204

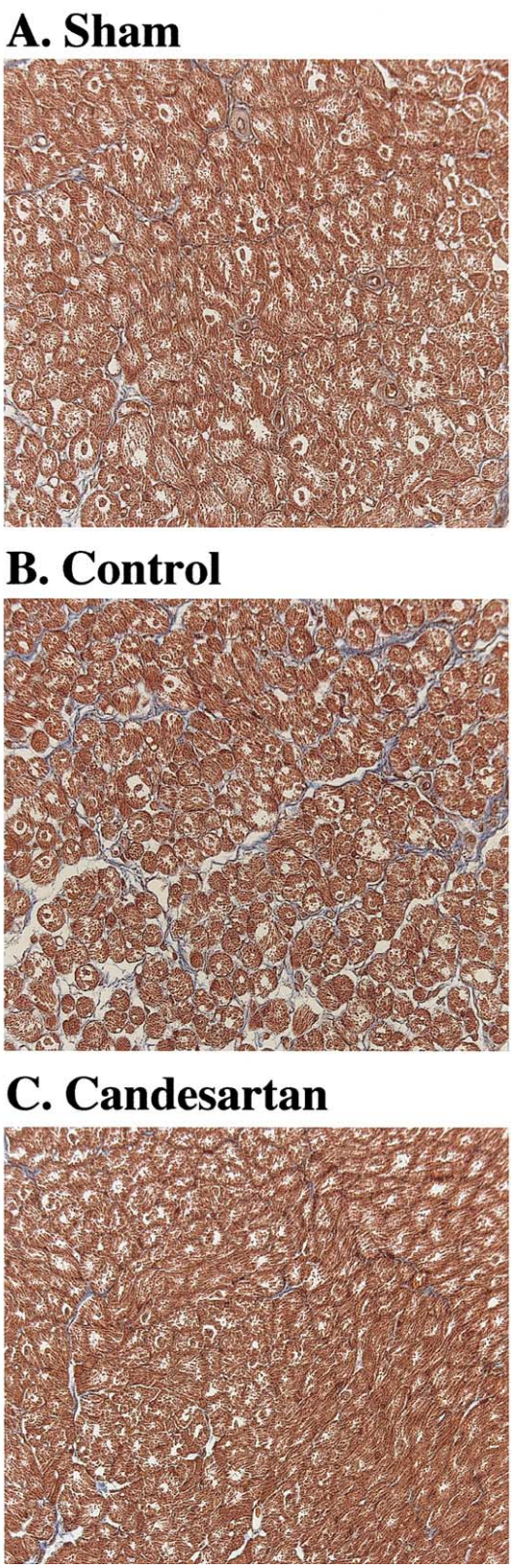

Figure 2. Representative histologic sections of the right atrial free wall from each group (Masson trichrome stain) from a sham dog **(A)**, a fifth week rapid pacing dog **(B)**, and a fifth week rapid pacing with candesartan treated dog **(C)**. In the sham dog, the intracellular space appeared normal. In the control dog, extensive interstitial fibrosis, evidenced by Masson trichrome stain, was found. In the candesartan treated dog, interstitial fibrosis was attenuated. Magnification: ×400.

observed in a heart-failure dog model, whereas AF inducibility and the duration of the induced AF were significantly increased compared with those in control dogs. Local conduction slowing, its heterogeneity, and the percentage of interstitial fibrosis of the atria were prominent in dogs with heart failure. Therefore, the changes in local atrial conduction properties caused by interstitial fibrosis favor the maintenance of AF in dogs with heart failure. Although rapid atrial pacing was performed without creating atrioventricular block, the ventricular rate in the present study was faster than 200 beats/min, which provides similar effects to the previously reported ventricular pacing heart-failure model, as reflected in our data on hemodynamic changes.

Recently, Goette et al. (1) demonstrated that the expression of ACE and Erk1/Erk2 were increased in patients with AF. Willems et al. (20) established that the development of AF by rapid pacing was associated with an increase in plasma level of Ang II in a sheep model. In animal studies, it has been reported that high atrial pressure directly caused AERP shortening and increased AERP dispersion, resulting in increased vulnerability to AF (21–23). In addition to these direct effects on electrophysiologic properties, increased atrial stretching activates the Erk cascade through the AT1R, which may induce interstitial fibrosis of the atria (1,24). More interestingly, treatment with ACE inhibitor decreased the level of an activated Erk1/Erk2. Although we did not measure these intracellular signaling kinases, AT1R antagonist may also have similar inhibitory effects on these kinases, resulting in decreasing atrial fibrosis. The inhibition of local Ang II can prevent the promotion of AF by suppressing the development of arrhythmogenic structural substrate. In addition, AT1R antagonist has been reported to decrease atrial pressure (25). Therefore, it is possible that

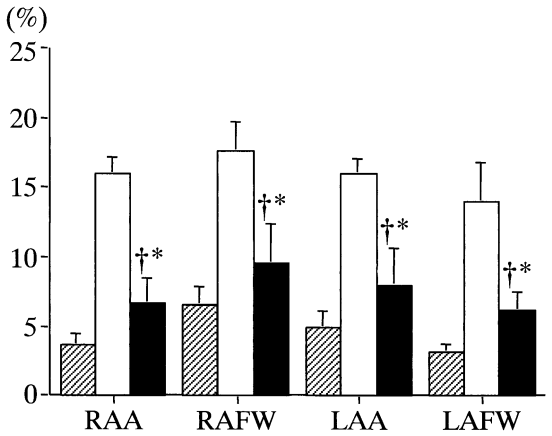

Figure 3. The percentage of fibrosis of the free walls and appendages in both atria after five weeks of pacing. The percentage of fibrosis in all atrial regions in the candesartan group was markedly lower than that in the control, although greater than that in the sham group. **Hatched bars** = sham group; **white bars** = control group; **black bars** = candesartan group. †$p < 0.001$ compared with the control group. *$p < 0.05$ compared with the sham group. RAA = right atrial appendage; RAFW = right atrial free wall; LAA = left atrial appendage; LAFW = left atrial free wall.

a decrease in atrial stretching by candesartan may directly precipitate electrophysiologic changes to prevent AF.

Study limitations. Electrophysiologic measurements were made only in the right atrium, not in the left atrium because to suture electrodes on the left atrial free wall we have to hold up the heart, and this made the heart bent, resulting in dramatically decreased blood pressure and heart rate. Therefore, electrophysiologic characteristics in the left atrium are still unknown.

Angiotensin-converting enzyme inhibitor and AT1R antagonist have each been shown to have beneficial effects on ventricular remodeling after myocardial infarction (26,27). Furthermore, we previously demonstrated that both ACE inhibitor and AT1R antagonist could prevent short-term electrical remodeling in a canine rapid atrial pacing model (4). In the present study, we did not test the effect of ACE inhibitor on long-term remodeling. Therefore, the results of the present study did not provide an answer whether ACE inhibitor was also effective to prevent long-term atrial remodeling. However, our preliminary analysis using dog atrial homogenate suggested that ACE and chymase almost equally contributed to atrial Ang II formation, because approximately 40% of total atrial Ang II formation was due to ACE, whereas the rest was due to chymase (H. Nakashima, MD, et al., unpublished observations, 2002). This fact may indicate that ACE inhibitor is also effective as AT1R antagonist in dog. In fact, the beneficial effect of ACE inhibitor in atrial structural remodeling was shown by Li et al. (28) and Shi et al. (29). Further biochemical analysis is necessary to determine the contribution rate of both enzymes in atrial tissue Ang II formation after long-term pacing.

It is still unclear whether the beneficial effects of AT1R antagonist on long-term remodeling are due to the improvement of systemic conditions or the blockade of local Ang II in the atria. In addition, although it is possible that the density and affinity of Ang II receptor are different in each part of the atria, the density and affinity of AT1R/AT2R and the activities of ACE and Erk1/Erk2 were not measured. Thus, further experiments will be needed to evaluate the detailed mechanisms of preventive effects of AT1R antagonist on AF.

Clinical implications. Previous studies have shown that several antiarrhythmic drugs are effective for preventing short-term electrical remodeling of AF (8,9,12,13,30–32). However, the effects of these drugs on long-term atrial remodeling, including electrophysiologic and structural changes, are still controversial. Atrial fibrillation is a common arrhythmia in patients with heart failure (6,33), and we often experience difficulties in controlling drug-induced negative inotropic and proarrhythmic effects, especially in patients with left ventricular dysfunction. Van Den Berg et al. (34) showed that an ACE inhibitor, lisinopril, decreased the recurrence of AF after cardioversion in patients with congestive heart failure. Recently, Pedersen et al. (3) observed that an ACE inhibitor, trandolapril, reduced the incidence of AF in patients with left ventricular dysfunction after myocardial infarction. In the present study, we showed that an AT1R antagonist could prevent the structural remodeling that promotes AF in a canine pacing model. However, the main Ang II-forming enzyme in the human atria is chymase, but not ACE (chymase:ACE=21:1) (35), suggesting that AT1R antagonist may have more beneficial effects than ACE inhibitor in human atria. Thus, these results suggest that AT1R antagonist may constitute a novel therapeutic approach to preventing AF.

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