J Pharmacol Sci **103**, 207 – 213 (2007)

Journal of Pharmacological Sciences

Full Paper

In Vivo Electropharmacological Effects of Amiodarone and Candesartan on Atria of Chronic Atrioventricular Block Dogs

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Received August 17, 2006; Accepted December 11, 2006

Abstract. Electropharmacological effects of chronically administered amiodarone and candesartan on atria that had been remodeled against congestive heart failure were assessed using dogs (about 10 kg in weight) with chronic atrioventricular block. Amiodarone was administered orally in a dose of 200 mg/body per day for the initial 7 days followed by 100 mg for the following 21 days (n = 7). Candesartan was administered in a dose of 12 mg/body per day for 28 days (n = 7). All animals survived the 4-week experimental period, indicating the lack of risks for inducing cardiohemodynamic collapse or torsade de pointes by these drugs. The plasma amiodarone concentration was 353 ng/ml at 4 weeks of treatment. Before candesartan treatment (control), intravenous administration of 30 ng/kg of angiotensin II increased the mean blood pressure by 18 mmHg, which was significantly decreased to 1 mmHg by 4 weeks of treatment. Amiodarone prolonged the atrial effective refractory period without affecting inter-atrial conduction time and decreased the duration of the burst pacing-induced atrial fibrillation, whereas candesartan hardly affected these variables. These results indicate that amiodarone should become a pragmatic pharmacological strategy against atrial fibrillation in patients with chronically compensated heart failure and suggest that a much higher dose of candesartan may be needed to exert its efficacy in this model.

Keywords: amiodarone, candesartan, atrial fibrillation, atrioventricular block

Introduction

Atrial fibrillation is the most common cardiac arrhythmia, with age-related prevalence reaching >10% in octogenarians (1). Atrial fibrillation has been treated primarily with antiarrhythmic drugs that alter atrial electrical properties directly, while such drugs may also accompany proarrhythmia risks. So, new pharmacological therapy is being explored to prevent the remodeling processes that promote the occurrence and maintenance of atrial fibrillation at a more fundamental level (2). For example, recent studies using the atrial rapid pacing model of dogs have indicated that the Vaughan-Williams class III antiarrhythmic agent amiodarone and angiotensin II type 1 receptor (AT_1) blocker candesartan are the most promising drugs that can suppress structural and electrophysiological remodelings in the atria after a long-term treatment (3, 4). The results obtained by the atrial rapid pacing model have provided much insight into how atrial fibrillation alters electrophysiology to promote its own maintenance, but do not necessarily reproduce the pathophysiology that induces atrial fibrillation in patients (5). Indeed, congestive heart failure is a particularly common clinical cause of atrial fibrillation (5), which was absent in the standard atrial rapid pacing model.

In this study, we directly compared the electropharmacological effects of chronically administered

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Published online in J-STAGE: February 14, 2007
doi: 10.1254/jphs.FP0060945

amiodarone and candesartan on the atria that had been remodeled against congestive heart failure for the first time. We used the canine chronic atrioventricular block model (6 – 8). Previous studies have indicated that this model complicates the pathophysiology of chronically compensated heart failure together with the increase of sympathetic tone and the stretch activating paradigm of atria (5 – 8). In a limited number of our preliminary experiments (n = 4 – 5), there was no significant difference in the atrial effective refractory period between the normal dogs and the chronic atrioventricular block dogs, which is essentially in accordance with a previous report by others (5). Meanwhile, inter-atrial conduction time was 1.6 times greater in the chronic atrioventricular block dog than in the normal dog. Atrial fibrillation was rarely induced by the burst-pacing protocol in the normal dog, whereas most of the animals experienced short duration (1 – 2 s) of paroxysmal atrial fibrillation attack after atrioventricular block, which increased in number and duration gradually with time. Previous knowledge together with our preliminary findings indirectly suggest that the atrial stretch as well as structural and electrophysiological remodeling in the atria of the chronic atrioventricular block dogs might play an important role in the onset and maintenance of atrial fibrillation.

Materials and Methods

All experiments were carried out according to the Guidelines for Animal Experiments, University of Yamanashi, which are equivalent to those of the US National Institute of Health (NIH). Beagle dogs of either sex weighing about 10 kg were obtained through the Animal Laboratory for Research of the University of Yamanashi. All surgical procedures were carried out using the standard percutaneous technique (9) under sterile condition, and each cardiovascular variable was monitored using a polygraph system (RM-6000; Nihon Kohden, Tokyo).

Production of the canine complete atrioventricular block model

The persistent atrioventricular block was induced in the beagle dogs as previously described (6, 10). Briefly, the animals were anesthetized with pentobarbital sodium (30 mg/kg, i.v.) and artificially ventilated with room air (SN-480-3; Shinano, Tokyo). Tidal volume and respiratory rate were set at 20 ml/kg and 15 strokes /min, respectively. A quadripolar electrodes catheter with a large tip of 4 mm (D7-DL-252; Cordis-Webster, Baldwin Park, CA, USA) was inserted into the right femoral vein and positioned around the tricuspid valve, watching the bipolar electrograms from the distal electrodes pair. The optimal site for the atrioventricular node ablation, namely the compact atrioventricular node, was determined on the basis of the intracardiac electrogram, of which a very small His deflection was recorded and atrial/ventricular voltage ratio was >2. The power source for the atrioventricular node ablation was obtained from an electrosurgical generator (MS-1500; Mera, Tokyo) that delivers continuous unmodulated radiofrequency energy (500 kHz). After proper positioning, radiofrequency energy of 20 W was delivered for 10 s from the tip electrode to an indifferent patch electrode positioned on the animal's back, which was followed by additional 30-s ablation if junctional rhythm was induced. The endpoint of this procedure was the development of complete atrioventricular block with an onset of stable idioventricular escaped rhythm.

Preparation of the study

More than 3 months after the induction of the atrioventricular block, the dogs were anesthetized with pentobarbital sodium (30 mg/kg, i.v.). After intubation with a cuffed endotracheal tube, the animals were artificially ventilated with 100% oxygen using an animal respirator (SN-408-3, Shinano). Tidal volume and respiratory rate were set at 20 ml/kg and 15 strokes /min, respectively. The surface lead II ECG was obtained from the limb electrodes. A heparinized catheter was placed in the right femoral artery to continuously monitor the systemic blood pressure. A standard 6-French quadripolar electrodes catheter (Cordis-Webster) was positioned at the top of the right atrium via the right femoral vein to electrically pace the sinus nodal area and record the local electrogram. The spontaneously beating rate of the atrium (=sinoatrial rate) was measured with a heart rate counter (AT-601G, Nihon Kohden) triggered by the right atrial electrogram. A second 6-French quadripolar electrodes catheter (Cordis-Webster) was positioned in the esophagus via os to record the left atrial electrogram. Finally, a third 6-French quadripolar electrodes catheter (Cordis-Webster) was positioned at the inter-atrial septum of the right atrium via the left femoral vein to electrically induce atrial fibrillation. The optimal sites of each catheter were determined by watching the temporal relationship between the bipolar electrograms from the distal electrodes pair and P wave of the ECG.

Examinations through electrical pacing of the heart

Inter-atrial conduction time: The sinus nodal area was electrically driven in a cycle length of 400, 300, or 200 ms using a cardiac stimulator (SEC-3102, Nihon Kohden). The 1 – 2 V stimulation pulses (about twice

the threshold voltage) were rectangular in shape and had a duration of 1 ms. The inter-atrial conduction time was defined as the difference between right and left atrial electrograms (in ms), which was measured using the analytical software AcqKnowlwdge (ver 3.2.6; BIOPAC Systems, Inc., Goleta, CA, USA) with an analog/digital converting system (MP-100A, BIOPAC Systems, Inc.).

Atrial effective refractory period: The effective refractory period of the atrium was assessed by a programmed electrical stimulation of the right atrium using a cardiac stimulator (SEC-3102, Nihon Kohden). The 1 – 2 V stimulation pulses (about twice the threshold voltage) were rectangular in shape and had a duration of 1 ms. The pacing protocol consisted of 5 beats of basal stimuli in a cycle length of 400, 300, or 200 ms followed by an additional stimulus at various coupling intervals. Starting in the late diastole, the coupling interval was shortened by consecutive reductions of 5 ms until the additional stimulus could no longer elicit a response. The atrial effective refractory period was defined as the shortest coupling interval (in ms) that still produced an electrical response.

Induction of atrial fibrillation: A 60-V pacing pulse of 10-ms width and rectangular shape was used for induction of atrial fibrillation (about 1.5 times of the diastolic threshold voltage). The inter-atrial septum was paced at a cycle length of 60 ms (1,000 bpm) for 10 s (=burst pacing) via the distal electrode pair of the catheter using a stimulator (SEN-7203, Nihon Kohden) and the isolation unit (SS-201J, Nihon Kohden). Extensive preliminary studies have confirmed that this burst pacing protocol was optimized for the induction of atrial fibrillation in this canine model. In this study, atrial fibrillation was defined as a period of rapid irregular atrial rhythm resulting in an irregular baseline of the ECG. The duration of atrial fibrillation was measured after its induction, and the cycle length was determined using the left atrial electrograms.

Experimental protocol

Amiodarone was given orally to the animals every day for 4 weeks, in doses of 200 mg/body per day for the 1st week followed by 100 mg/body per day for the following three weeks (n = 7). Candesartan at the dose of 12 mg/body per day (n = 7) was given orally to the animals every day for 4 weeks. The effects of the drugs on the electrophysiological profile and neurohumoral factors were assessed before and 4 weeks after the start of drug administration.

The systemic blood pressure and ECG were analyzed using the real time full automatic data analysis system MP-VAS from Physio-Tech (Tokyo). The cardiovascular variables were assessed in the following order: Initially, sinoatrial rate and mean blood pressure were recorded. Then, inter-atrial conduction time was measured at spontaneous sinus rhythm and at a pacing cycle length of 400, 300, and 200 ms. Next, atrial effective refractory period was measured at a basic pacing cycle length of 400, 300, and 200 ms. Finally, atrial fibrillation was induced by the burst pacing protocol, which was repeated 10 times at each time point. When the atrial fibrillation was maintained for >30 s, it was terminated electrically. In this case, the duration of atrial fibrillation was calculated as 30 s. In the candesartan-treated group, 30 ng/kg of angiotensin II was intravenously administered to the animals to confirm the extent of AT_1-receptor blockade.

Neurohumoral factors were assayed before and 4 weeks after the start of the drug administration, whereas the amiodarone concentration was measured 2 and 4 weeks after the start of the drug administration. A volume of 10 ml of venous blood was drawn from the animals in the conscious state. The blood samples were centrifuged at 1,500 × *g* for 30 min at 4°C. The plasma was stored at −80°C until each concentration was determined at the laboratory of SRL Co., Ltd. (Tokyo).

Drugs

The following drugs were used: amiodarone (Ancaron™; Taisho Toyama Pharmaceutical, Tokyo); candesartan cilexetil (Blopress™; Takeda Chemical Industries, Osaka); angiotensin II (Peptide Institute, Osaka); heparin calcium (Mitsui Pharmaceuticals, Tokyo); and pentobarbital sodium (Tokyo Kasei, Tokyo).

Statistical analyses

All data are presented as the mean ± S.E.M. The statistical differences of paired data within a parameter were evaluated by the paired *t*-test, whereas those of unpaired data between the groups were evaluated by the unpaired *t*-test. A *P*-value of <0.05 representing a 95% confidence level was considered statistically significant.

Results

There was no statistically significant difference in the respective control values between the amiodarone-treated group and candesartan-treated group except for the effective refractory period at a cycle length of 300 ms and angiotensin II level. All animals survived the 4 weeks of pharmacological treatment.

Effects on the sinoatrial rate and mean blood pressure

The effects of 4 weeks p.o. administration of amiodarone and candesartan on the sinoatrial rate and mean

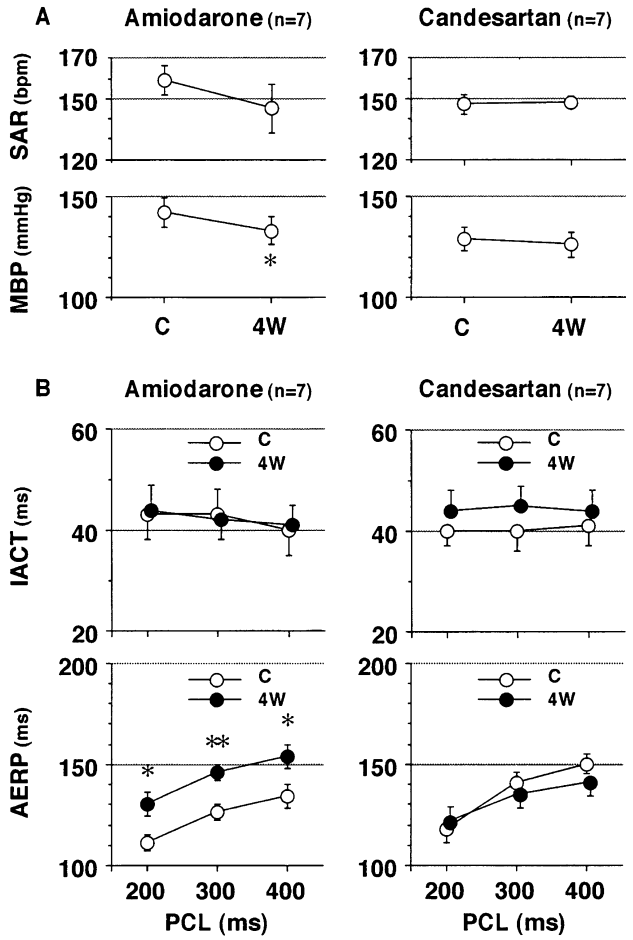

Fig. 1. Electropharmacological effects of amiodarone and candesartan. The effects on the sinoatrial rate (SAR), mean blood pressure (MBP) (A), inter-atrial conduction time (IACT), and atrial effective refractory period (AERP) (B). **P*<0.05, ***P*<0.01 *vs* pre-drug control value (C). PCL: pacing cycle length. 4W: 4 weeks after the start of drug administration.

blood pressure are summarized in Fig. 1A (n = 7 for each group). The pre-drug control values (C) of the sinoatrial rate (beats/min) and mean blood pressure (mmHg) were 159 ± 7 and 142 ± 7 in the amiodarone-treated group, whereas they were 147 ± 5 and 129 ± 6 in the candesartan-treated group, respectively. Amiodarone significantly decreased the mean blood pressure. Also, it tended to decrease the sinoatrial rate; however, the change did not achieve the statistical significance. Candesartan hardly affected the sinoatrial rate or mean blood pressure. Administration of 30 ng/kg of angiotensin II increased the mean blood pressure by 18 ± 2 mmHg before drug treatment (control), which was significantly decreased to 1 ± 1 mmHg after the 4 weeks of the candesartan treatment (n = 7).

Effects on the inter-atrial conduction time and atrial effective refractory period

The effects of the drugs on the inter-atrial conduction time and atrial effective refractory period are summarized in Fig. 1B (n = 7 for each group). The pre-drug control values (C) of the inter-atrial conduction time (ms) were 43 ± 5, 43 ± 5, and 40 ± 5 at a pacing cycle length of 200, 300, and 400 ms in the amiodarone-treated group, respectively; and they were 40 ± 3, 40 ± 4, and 41 ± 4 in the candesartan-treated group, respectively. The pre-drug control values (C) of the atrial effective refractory period (ms) were 111 ± 4, 126 ± 4, and 134 ± 6 at a pacing cycle length of 200, 300 and 400 ms in the amiodarone-treated group, respectively; and they were 118 ± 7, 141 ± 5, and 150 ± 5 in the candesartan-treated group, respectively. Amiodarone prolonged the atrial effective refractory period at each pacing cycle length, whereas no significant change was detected in the inter-atrial conduction time. Candesartan hardly affected the inter-atrial conduction time or atrial effective refractory period.

Effects on the burst pacing-induced atrial fibrillation

Typical tracings of intracardiac electrograms from the right and left atria, ECG and blood pressure during the burst pacing-induced atrial fibrillation are depicted in Fig. 2A, and the effects of the drugs on the duration and cycle length of atrial fibrillation are summarized in Fig. 2B (n = 7 for each group). The pre-drug control values (C) of the duration (s) and cycle length (ms) of atrial fibrillation were 5.94 ± 1.30 and 119 ± 4 in the amiodarone-treated group, whereas those were 5.27 ± 1.21 and 123 ± 3 in the candesartan-treated group, respectively. Amiodarone shortened the duration of atrial fibrillation to 12% of the control value, whereas no significant change was detected in the cycle length of atrial fibrillation. Candesartan hardly affected the duration of atrial fibrillation or its cycle length.

Effects on the neurohumoral factors and plasma amiodarone concentration

The effects of the drugs on the neurohumoral factors are summarized in Table 1 (n = 5 for each group). Amiodarone tended to decrease norepinephrine, epinephrine, dopamine, angiotensin II, aldosterone, and atrial natriuretic peptide; however, these effects did not achieve the statistical significance. On the other hand, candesartan decreased norepinephrine level but increased angiotensin II level, whereas no significant change was detected in the other neurohumoral factors. The effects of amiodarone on the T_3, T_4, and TSH levels are summarized in Table 2 (n = 5). No significant change was detected in T_3, T_4, or TSH level in the amiodarone-

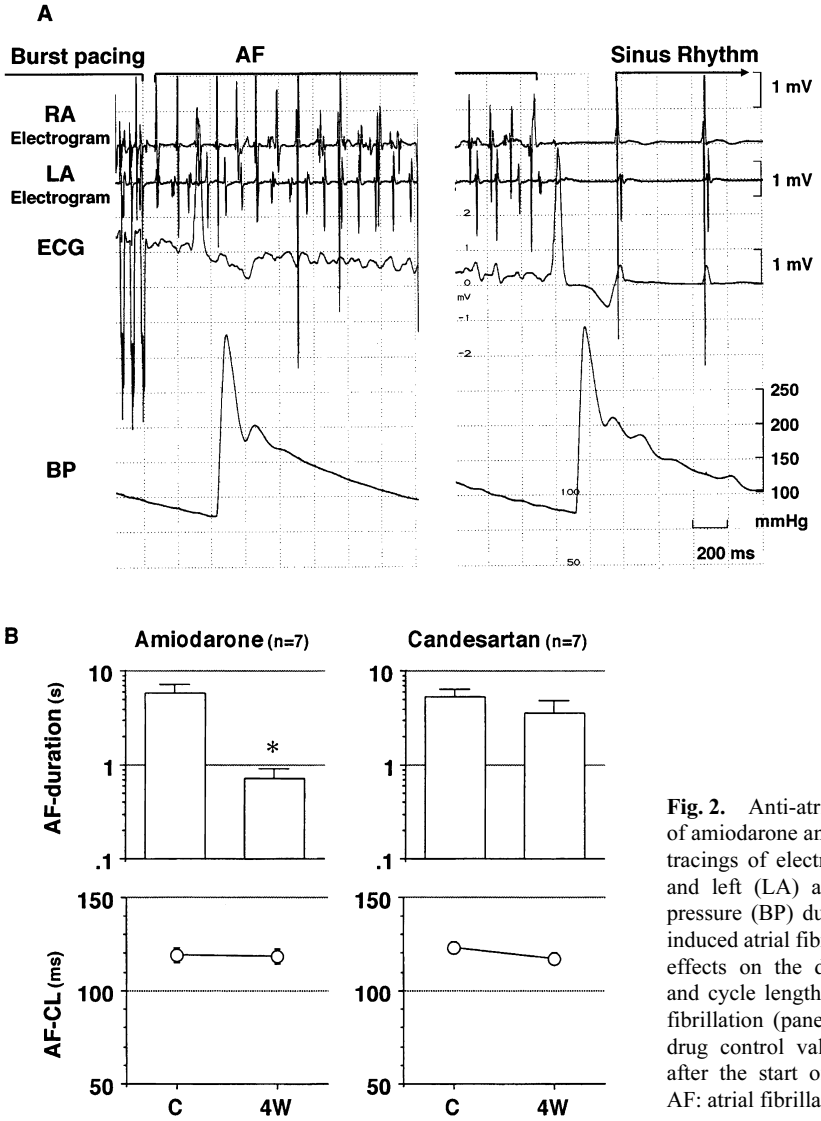

Fig. 2. Anti-atrial fibrillatory effects of amiodarone and candesartan. Typical tracings of electrograms of right (RA) and left (LA) atria, ECG, and blood pressure (BP) during the burst pacing-induced atrial fibrillation (panel A). The effects on the duration (AF-duration) and cycle length (AF-CL) of the atrial fibrillation (panel B). **P*<0.05 *vs* pre-drug control value (C). 4W: 4 weeks after the start of drug administration, AF: atrial fibrillation.

Table 1. Time courses of neurohumoral factors

	Normal range (pg/ml)	Amiodarone		Candesartan	
		Control	4W	Control	4W
Norepinephrine	100 – 450	604 ± 101	479 ± 66	536 ± 122	426 ± 55*
Epinephrine	<100	363 ± 82	315 ± 74	224 ± 71	156 ± 42
Dopamine	<20	32 ± 7	21 ± 1	23 ± 2	19 ± 2
Angiotensin II	<22	68 ± 11	40 ± 4	9 ± 3	187 ± 132*
Aldosterone	36 – 240	81 ± 25	70 ± 16	76 ± 4	101 ± 14
ANP	<40	129 ± 41	86 ± 12	134 ± 41	105 ± 18

Data are presented as the mean ± S.E.M. (n = 5). **P*<0.05 compared with the data at pre-drug control (Control). ANP: atrial natriuretic peptide, 4W: 4 weeks after the start of drug administration.

treated animals. The plasma amiodarone concentrations were 312 ± 23 ng/ml and 353 ± 33 ng/ml at 2 and 4 weeks after the start of administration, respectively (n = 5), and there was no significant difference in the concentrations between these two time points.

Table 2. Time courses of T3, T4, and TSH

		Control	4W
T3	ng/ml	0.92 ± 0.13	0.95 ± 0.05
T4	μg/dl	3.08 ± 0.46	3.02 ± 0.6
TSH	μIU/ml	0 ± 0	0 ± 0

Data are presented as the mean ± S.E.M. (n = 5). Pre-drug control (Control). 4W: 4 weeks after the start of drug administration.

Discussion

Electropharmacological effects of chronically administered amiodarone and candesartan were directly compared using the canine chronic atrioventricular block model. All animals survived the 4 weeks of the experimental period, which indicates the lack of risks for inducing cardiohemodynamic collapse or torsade de pointes by these drugs, since the model has been shown to be highly sensitive in detecting the drug-induced lethal ventricular arrhythmias (6, 10).

Drug doses in the present study

The dose of each drug was determined according to clinically recommended doses in Japan and previous experimental reports (3, 4, 11 – 14). In a previous study on amiodarone (12), a maintenance dose of 600 mg for patients with heart disease provided a mean drug plasma level of 1.6 μg/ml after one-month treatment, indicating that the concentration of amiodarone in this study may be relatively low. On the other hand, we confirmed that the angiotensin II-induced pressor response was abolished in the candesartan-treated animals. More importantly, plasma angiotensin II level increased significantly after the administration of candesartan, possibly through a negative feed back mechanism, suggesting that the AT_1 receptor in the model may be effectively blocked by the currently used dose of candesartan. However, one would need to assess the effect of a higher dose of candesartan in order to confirm the effect of complete AT_1-receptor blockade on the in situ heart of this model.

Electropharmacological effects of amiodarone

Amiodarone has differential effects on the potassium currents depending on the application period; short-term treatment inhibits primarily rapidly activating component of delayed rectifier potassium current (I_{Kr}), acetylcholine-sensitive potassium current ($I_{K,ACh}$), sodium-activated potassium current ($I_{K,Na}$), and ATP-sensitive potassium current ($I_{K,ATP}$), whereas long-term treatment reduces slowly activating component of delayed rectifier potassium current (I_{Ks}) and transient outward current (I_{to}) (15, 16). Also, amiodarone inhibits sodium and calcium channels, and has a noncompetitive anti-sympathetic effect (12, 15, 17). In addition, amiodarone was reported to reverse the mechanical stretch induced-remodeling process of atria by blocking T-type calcium channels, scavenging oxygen free radicals, and suppressing inflammatory cytokines, including tumor necrosis factor-α and interleukin-6 (3, 12, 17, 18). Long-term effects of amiodarone may be modulated by the direct action of the parent drug and its active metabolite desethylamiodarone in plasma and tissue (16). In our previous acute i.v. study of amiodarone in the same chronic atrioventricular block model (n = 4), administration of 3 mg/kg of amiodarone hardly affected any of the cardiohemodynamic and electrophysiological variables (19). So, the effects of amiodarone observed in this study would largely depend on the long-term effects of amiodarone.

Amiodarone tended to decrease sinoatrial rate and significantly decreased the blood pressure, which may reflect the calcium channel blocking effect and noncompetitive weak β-blocking action (15). Also, reduction of afterload might have suppressed the progression of atrial fibrosis and remodelings. Amiodarone hardly affected the inter-atrial conduction time, indicating lack of sodium channel inhibition in the atria, which supports a previous in vitro report describing that amiodarone is a lidocaine-type fast sodium channels blocker (15). Amiodarone prolonged the effective refractory period of atrium at each pacing rate, which may be most likely explained by a decrease of current density of I_{Ks} and I_{to} (2, 3). Moreover, the β-blocking action of amiodarone may have enhanced the prolongation of the repolarization period since I_{Ks} is regulated by adrenergic tone (20). We found amiodarone to be very effective in terminating the burst pacing-induced atrial fibrillation attack, whereas no prominent change was detected in the cycle-length of atrial fibrillation. These results indicate that chronically administered amiodarone would prolong the atrial effective refractory period without causing significant conduction delay during atrial fibrillation attack.

Electropharmacological effects of candesartan

Candesartan hardly affected the sinoatrial rate, mean blood pressure, inter-atrial conduction time, or effective refractory period of atrium, even though a functionally effective dose of candesartan was administered as confirmed by angiotensin II injection in this study. Moreover, candesartan did not affect the duration or cycle length of atrial fibrillation in this study. These results indicate that blockade of the AT_1 receptor may not significantly modulate the atrial electrophysiological properties of the chronic atrioventricular block model.

These results are partly different from a previous study employing the canine atrial rapid pacing model (4), in which 5 weeks of candesartan treatment hardly affected the time course of the change in the atrial effective refractory period, but suppressed the conduction delay and onset of atrial fibrillation. The difference may be partly explained by the underlying pathophysiology in each model (4, 5). Namely, shortening of the atrial effective refractory periods and the increase of intra-atrial dispersion of refractoriness are the typical predisposing factors for atrial fibrillation in the rapid atrial pacing model, whereas the interstitial fibrosis of atria that interferes with local conduction may play a central role in the congestive heart failure (4, 5). It should be also noted that our dose is considered to be enough to block the AT_1 receptor, whereas about 10 times higher dose of candesartan was used in that study (4), which may related to the difference of the results.

Conclusion

Chronically administered amiodarone will become a pragmatic pharmacological strategy for suppressing the occurrence and maintenance of atrial fibrillation in patients with chronically compensated heart failure. Also, candesartan may have to be used at a higher dose for it to exert its efficacy in the in situ heart of this model.

Acknowledgments

This study was supported in part by Grant-in-aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (#17590216) and The Pharmacological Research Foundation (Tokyo).

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