Original Article

Protective Effects of an Angiotensin II Receptor Blocker and a Long-Acting Calcium Channel Blocker against Cardiovascular Organ Injuries in Hypertensive Patients

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The purpose of this study is to compare the long-term effects of an angiotensin II receptor blocker (ARB) and a long-acting calcium channel blocker (CCB) on left ventricular geometry, hypertensive renal injury and a circulating marker of collagen synthesis in hypertensive patients. Patients with essential hypertension (24 men and 19 women; age, 37–79 years) were treated with a long-acting CCB, amlodipine (AML; 2.5–7.5 mg once daily) for 6 months. Then, AML was switched to an ARB, candesartan (CS; 4–12 mg once daily), in 22 patients (CS group), while AML was continued in the remaining 21 patients for another 6 months (AML group). At the end of each treatment period, ambulatory blood pressure monitoring (ABPM), echocardiography and sampling of blood and urine were performed. The average office blood pressure during the latter period was comparably controlled in the AML and the CS groups (AML: 130±8/87±7 mmHg; CS: 133±11/88±7 mmHg), while the average systolic blood pressure of 24-h ABPM was significantly lower in the AML than in the CS group (127±9 *vs.* 133±14 mmHg, $p<0.05$). Consequently, the left ventricular mass index was significantly decreased in the AML group (102±18 to 92±12 g/m^2, $p<0.05$), while the change was insignificant in the CS group (103±25 to 98±21 g/m^2). On the other hand, plasma procollagen I C-terminal peptide (PICP), a marker of collagen synthesis, was lowered by CS (86±21 to 70±21 ng/ml, $p<0.01$), but was not significantly affected by AML (80±127 to 74±91 ng/ml). CS reduced urinary albumin excretion (57±123 to 26±33 mg/g creatinine, $p<0.05$), but AML did not bring about significant changes (85±27 to 73±19 mg/g creatinine). The results suggested that long-acting CCBs are effective in improving left ventricular hypertrophy by controlling 24-h blood pressure, while ARBs possess protective effects against cardiovascular fibrosis and renal injury beyond their antihypertensive effects. (*Hypertens Res* 2005; 28: 351–359)

***Key Words*: candesartan, amlodipine, hypertension, left ventricular hypertrophy, urinary albumin excretion**

Introduction

Calcium channel blockers (CCBs) and angiotensin II receptor blockers (ARBs) are now being widely used for the treatment of hypertension. Recent large-scale clinical trials have revealed that CCBs and ARBs do in fact prevent the incidence of cardiovascular diseases in hypertensive patients (*1*–*5*). However, it has been pointed out that short-acting CCBs may not be as effective as other classes of antihypertensive

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Table 1. Background Characteristics of the Study Subjects

	AML group	CS group
Age (years)	57±11	56±7
Sex (men/women)	13/8	11/11
Body mass index (kg/m^2)	25.9±3.7	25.0±4.0
Systolic blood pressure (mmHg)*	161±13	165±11
Diastolic blood pressure (mmHg)*	106±9	104±7
Pulse rate (bpm)*	74±10	75±11
Duration of hypertension (years)	10±9	7±6
WHO stage (I/II)	15/6	15/7
Habitual smoking (yes/no)	3/18	4/18
Habitual alcohol intake (yes/no)	10/11	11/11
Previous antihypertensive drug		
Diuretic	2	1
β-Blocker	1	0
Calcium channel blocker	14	15
ACE inhibitor	2	3
Angiotensin II receptor blocker	2	3

Mean±SD. AML, amlodipine; CS, candesartan; ACE, angiotensin-converting enzyme. *Values when antihypertensive drugs were not given.

agents for reducing the risk of coronary artery disease (*6*, *7*). The reflexive activation of the sympathetic nerve system is thought to contribute to the development of ischemic heart attack in hypertensive patients treated with a short-acting CCB. However, recent clinical trials using long-acting CCBs with slow pharmacokinetics have shown that long-acting CCBs are effective in preventing coronary events (*8*, *9*). On the other hand, ARBs have been shown to exhibit comparable clinical effects with fewer side effects as compared with angiotensin-converting enzyme (ACE) inhibitors (*10*, *11*). Thus, prescriptions of these two classes of antihypertensive drugs, long-acting CCBs and ARBs, are expected to increase in the years ahead.

The ultimate aim of antihypertensive therapy is to inhibit cardiovascular organ injuries such as cardiac hypertrophy and renal dysfunction and to prevent the incidence of cardiovascular diseases such as stroke and myocardial infarction. Regarding the process of these hypertensive cardiovascular complications, much attention is being paid to the involvement of the renin-angiotensin-aldosterone system (RAAS) in the remodeling of cardiovascular tissues and organs (*12*, *13*). In the present study, we compared the chronic effects of amlodipine, a long-acting CCB, and candesartan, an ARB on the cardiovascular endocrine system and the indices of cardiovascular organ injuries in outpatients with essential hypertension.

Methods

We enrolled a total of 43 outpatients with essential hypertension who were receiving monotherapy and classified as stage I or II according to the World Health Organization (WHO) criteria for organ damage. Secondary causes of hypertension and complications of cancer, bone diseases or inflammatory disorders were ruled out through a comprehensive checkup. The study protocol was in accordance with the recommendations of the World Medical Association for biomedical research involving human subjects (Edinburgh version, 2000), and informed consent was obtained from all subjects. The study protocol was approved by the institutional review board. At the beginning of the study period, antihypertensive medication was directly switched to the long-acting CCB, amlodipine (AML), without inserting a wash-out period, and all the patients were treated with AML monotherapy for 6 months. Then, AML was switched to an ARB, candesartan (CS), in 22 patients (CS group), while AML was continued in the remaining 21 patients for another 6 months (AML group). The assignment of AML or CS was performed in a random manner. Each drug was given once daily after breakfast. All the patients were treated with the study drug alone. In each treatment period, the dose of study drug was titrated during 2- to 4-week interval visits within the range of 2.5–7.5 mg/day for AML and 4–12 mg/day for CS so that the blood pressure was maintained below 140/90 mmHg. If the target blood pressure was not achieved by the maximum dose of each drug, 1–2 mg of trichlormethiazide, a thiazide diuretic, was added.

At the end of each treatment period, we performed ambulatory blood pressure monitoring, ultrasound cardiography, blood sampling and urine collection. Ambulatory blood pressure and pulse rate were monitored at 30-min intervals for 24 h using a portable and noninvasive cuff-oscillometric device (TM-2421; A & D Co., Ltd., Tokyo, Japan). The device satisfies the criteria of the Association for the Advancement of Medical Instrumentation (AAMI) and British Hypertension Society (BHS) (*14*). To minimize the effect of the patient's physical activities on blood pressure and pulse rate, the ambulatory monitoring was performed on the same day of the week in each patient. Recorded blood pressure and pulse rate data were analyzed for four segments of the day: morning (5:30–9:00), daytime (9:30–18:00), evening (18:30–23:00) and night (23:30–5:00). A diagnosis of white-coat hypertension was made when the office blood pressure was ≥140 mmHg in systole and/or ≥90 mmHg in diastole, while the averaged 24-h ambulatory blood pressure was <135 mmHg in systole and <85 mmHg in diastole (*15*). On the other hand, a diagnosis of masked hypertension was made when the office blood pressure was <140 mmHg in systole and <90 mmHg in diastole and the averaged 24-h ambulatory blood pressure was ≥135 mmHg in systole and/or ≥85 mmHg in diastole (*15*). The morning blood pressure surge was calculated as the mean systolic blood pressure during the 2 h after waking minus the mean systolic blood pressure during the 1-h period that included the lowest value during sleep (*16*). Standard M-mode and two-dimensional echocardiography were performed using a Toshiba SSH-380A unit with a 2.5 MHz transducer. The ejection fraction (EF), which was used as an index of left ventricular systolic function, was calculated using

Table 2. Physical Findings during the Study Periods

Parameter	AML group		CS group	
	AML period	AML period	AML period	CS period
Systolic blood pressure (mmHg)	131±7	132±7	130±8	133±11
Diastolic blood pressure (mmHg)	88±7	88±7	87±7	88±7
Pulse rate (bpm)	71±7	70±7	71±8	70±6
Body weight (kg)	64.9±12.2	65.2±12.0	61.4±12.7	61.4±12.9

Mean±SD of the averaged values measured during each 6-month treatment period except for body weight where the values at the end of treatment periods are shown. AML, amlodipine; CS, candesartan.

Table 3. Ambulatory 24-h Monitoring of Blood Pressure and Pulse Rate at the End of Each Treatment Period

Parameter	AML group		CS group	
	AML period	AML period	AML period	CS period
Systolic blood pressure (mmHg)	130±9	127±9*	131±10	133±14
Diastolic blood pressure (mmHg)	85±8	83±8	84±7	85±9
Pulse rate (bpm)	72±9	70±8	70±8	69±7

Mean±SD. AML, amlodipine; CS, candesartan. *$p<0.05$ *vs.* CS.

Teichholz's method. Left ventricular mass (LVM) was calculated according to Devereux's formula: $LVM = 0.8 \times [1.04 \times \{(IVST + LVDd + PWT)^3 - (LVDd)^3\}] + 0.6$ g, where IVST, LVDd and PWT are interventricular septal thickness, left ventricular end-diastolic diameter and left ventricular posterior wall thickness, respectively (*17*). LVM was divided by body surface area in m^2 to obtain the left ventricular mass index (LVMI). Pulsed Doppler recordings of transmitral flow were taken from the apical long axis view. The sample volume was placed at the tips of the mitral leaflets. The peak early velocity (*E*) and peak late velocity (*A*) of ventricular filling were measured, and their ratio (*E*/*A*) was used as an index of left ventricular diastolic function.

A blood sample was taken after an overnight fast and 30 min of supine rest from the antecubital vein and was transferred into two chilled tubes, one containing EDTA (1 mg/ml) and the other containing EDTA (1 mg/ml) plus aprotinin (500 U/ml). Plasma was separated by centrifugation at 4°C, and stored at −80°C until assayed. Plasma levels of adrenaline (PA) and noradrenaline (PNA) were determined by high-performance liquid chromatography. Plasma renin activity (PRA) and aldosterone concentration (PAC) were determined by radioimmunoassay. Plasma angiotensin II was directly radioimmunoassayed using an Angiotensin II RIA kit (SRL Inc., Tokyo, Japan). Plasma procollagen type I carboxy-terminal peptide (PICP) was also directly radioimmunoassayed using a Procollagen PICP RIA kit (Orion Diagnostica, Espoo, Finland) (*18*).

The first urine in the morning was collected and centrifuged at 4°C to remove sediments. The supernatant was stored at −20°C until the assays. In women who had not reached menopause, the menstrual period was avoided when obtaining blood and urine samples. The urinary concentration of albumin was measured using a commercial kit (Microalbumin HA Test Wako; Wako Pure Chemical Industries, Osaka, Japan) based on the immunoturbidimetric method (*19*), and the value was expressed as a ratio to the urinary creatinine concentration measured by colorimetry.

Values are expressed as the means±SD. Clinical data between the two groups were compared by unpaired Student's *t*-test for parametric data, by Mann-Whitney's *U*-test for nonparametric data and by χ^2 test for categoric data. The effects of drug treatments in the two groups were analyzed using two-way ANOVA followed by Tukey's method for post-hoc multiple comparisons. A p value less than 0.05 was considered to indicate statistical significance.

Results

Table 1 shows the background characteristics of the study subjects. The AML and CS groups were not significantly different in age and sex ratio. The numbers of patients at the ages of 30–39, 40–49, 50–59, 60–69, and 70–79 years were 3, 3, 7, 6, and 2 in the AML group and 1, 3, 11, 6, and 1 in the CS group, and the distribution was not significantly different between the two groups ($\chi^2=2.20$, $p=0.699$). Physical findings such as body mass index, blood pressure and pulse rate were comparable between the two groups. In addition to the averaged blood pressure values, such parameters as known history of hypertension and WHO criteria for organ damage were also comparable between the two groups. The two groups had similar frequencies of habitual smoking and alcohol consumption. The antihypertensive drugs previously given to the patients are also listed in Table 1. CCBs were the drugs most frequently used before entry into the study. There was no significant difference between the two groups with

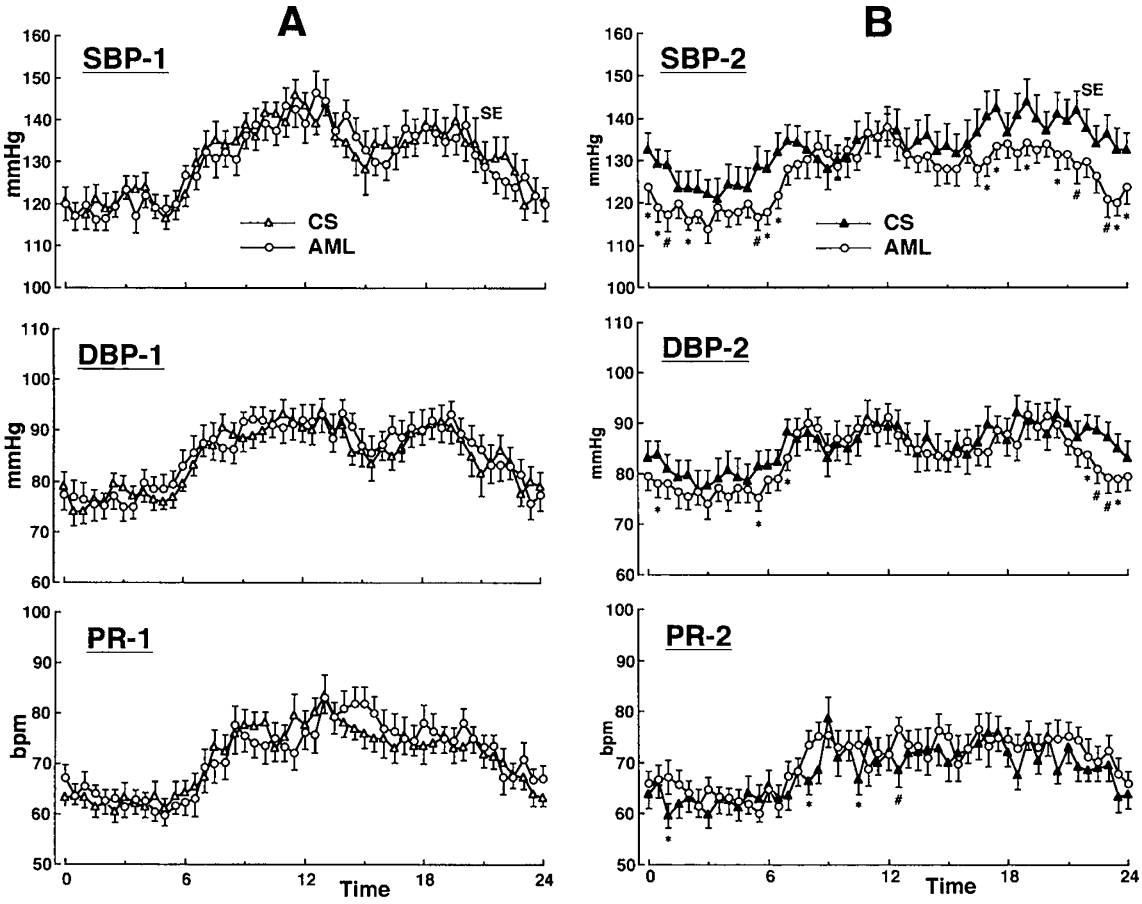

Fig. 1. *Line graphs showing the 24-h ambulatory blood pressure monitoring at the ends of the first (A) and second (B) treatment periods. SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; AML, amlodipine; CS, candesartan.* $^{*}p < 0.05$, $^{\#}p < 0.01$.

respect to the classes of antihypertensive drugs used previously.

No patient experienced adverse side effects and all of the 43 subjects completed the study protocol. Addition of trichlormethiazide was required in two patients of the AML group and four patients of the CS group. Table 2 shows the blood pressure, pulse rate and body weight measured at the outpatient clinic in each treatment period. The averaged values of systolic and diastolic blood pressure (SBP and DBP) during the 6-month periods were comparable between the two groups. The averaged pulse pressure did not differ significantly between the first and the second treatment periods in either the AML or CS group. The body weight measured at the end of each treatment period did not show significant changes in either group.

Table 3 shows the data of 24-h blood pressure monitoring performed at the end of each treatment period. In the first treatment period, neither the 24-h average of SBP nor that of DBP differed significantly between the two groups. However, in the second treatment period, the 24-h SBP was significantly higher in the group assigned CS than in the group assigned AML, while the difference in 24-h DBP was not significant. The pulse rate values monitored for 24 h were not significantly different between the first and the second treatment periods in either group. Figure 1 shows line graphs of ambulatory blood pressure and pulse rate monitoring. The blood pressure and pulse rate profiles were not significantly different between the AML and the CS groups in the first period. In the second period, the CS group, as compared with the AML group, had significantly higher SBP at 5:30–6:30, 17:00–17:30, 19:00, 20:30, 21:30, and 23:00–1:00; higher DBP at 5:30, 7:00, 19:00–20:30, and 0:30; and lower pulse rate at 8:00, 10:30, 12:30, and 1:00. Figure 2 compares the averaged blood pressure and pulse rate values in the morning, daytime, evening and night hours between the AML and the CS groups. Although the values were not significantly different between the two groups in the first period, the averaged SBP in the evening and night segments was significantly higher in the CS group than in the AML group. In the first period, the white-coat phenomenon was observed in 2 patients of the AML group (9.5%) and 2 patients of the CS group (9.1%), while masked hypertension was observed in 5

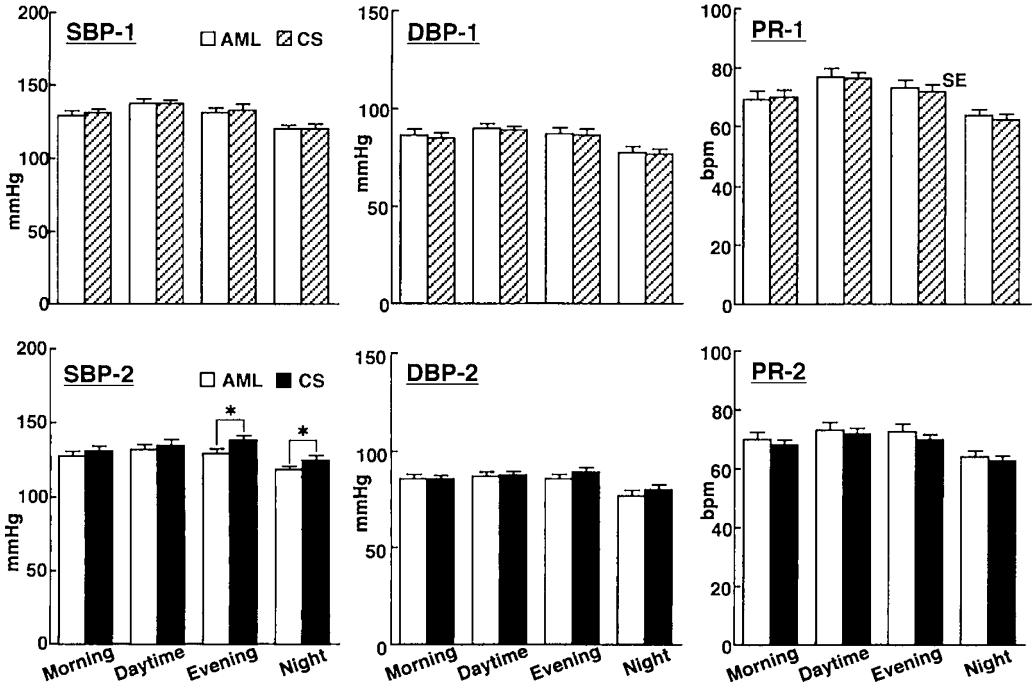

Fig. 2. *Bar graphs comparing the averaged blood pressure and pulse rate values in the morning (5:30–9:00), daytime (9:30–18:00), evening (18:30–23:00) and night (23:30–5:00) hours between the amlodipine (AML) and the candesartan (CS) groups at the ends of the first (upper) and second (lower) treatment periods. SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate.* $^{*}p < 0.05$.

(23.8%) and 4 (18.2%) patients in the AML and CS groups, respectively. In the second period, 3 patients in the AML group (14.3%) and 1 in the CS group (4.5%) showed white-coat hypertension, and 4 in the AML group (19.0%) and 4 in the CS group (18.2%) showed masked hypertension. Thus, the frequency of white-coat hypertension or masked hypertension was not significantly different between the two drug groups or the two treatment periods.

The laboratory data on blood cell counts and routine blood chemistry are listed in Table 4. There were no significant changes in any of these parameters. The levels of serum alkaline phosphatase, an enzyme derived from the bones as well as the liver, were within the normal range (82–232 U/l) in all patients in both study periods. Serum levels of C-reactive protein, a marker of inflammation, as determined by conventional immunoturbidimetry were below the lower limit of the assay range (3 mg/l) in all patients in both periods. In the CS group, serum K was not significantly changed at the end of the 6-month period of CS administration. Even after excluding the four patients given trichlormethiazide, the change in serum K was not significant between the two treatment periods in the CS group. Table 5 lists the changes in circulating cardiovascular hormones such as renin, angiotensin, aldosterone, and catecholamines. In the CS group, plasma renin activity and plasma angiotensin II concentration were significantly increased at the end of the period of CS administration, while the plasma aldosterone concentration was not significantly affected. These parameters of RAAS were not significantly changed in the AML group. Three women, one in the AML group and two in the CS group, had not reached menopause. However, the exclusion of these three patients did not substantially affect the results of the statistical analysis of RAAS parameters. With regard to catecholamines, plasma concentrations of adrenaline and noradrenaline were not significantly changed between the two treatment periods in either the AML or the CS group.

Figure 3 shows the measurements of urinary albumin excretion and plasma PICP at the end of each treatment period. These parameters of renal injury and collagen synthesis were significantly reduced at the end of the second treatment period in the CS group, while the AML group showed no significant changes in either parameter. Figure 4 depicts the changes in echocardiographic measurements in the study subjects. LVMI was significantly reduced at the end of the second treatment period in the AML group; however, such reduction was not significant in the CS group. Neither EF, an index of left ventricular systolic function, nor *E*/*A*, an index of left ventricular diastolic function, was significantly changed throughout the study in either the AML or the CS group. Table 6 shows the correlations of the office blood pressure, pulse pressure, 24-h ambulatory blood pressure, ambulatory blood pressure for daytime and nighttime segments, coefficient of variation in ambulatory blood pressure, and morning surge of SBP with changes in LVMI, urinary albumin excre-

Table 4. Blood Cell Counts and Blood Chemistry Data at the End of Each Treatment Period

Parameter	AML group		CS group	
	AML period	AML period	AML period	CS period
White blood cell count ($\times10^3/\mu l$)	5.23±1.18	5.45±0.90	5.36±1.19	5.05±1.22
Blood hemoglobin (g/dl)	14.0±1.4	14.0±1.4	13.9±1.0	14.0±1.0
Hematocrit (%)	41.3±4.2	41.8±4.3	41.2±3.1	41.8±3.1
Platelet count ($\times10^3/\mu l$)	225±47	222±37	238±48	238±57
Serum AST (U/l)	28±13	27±11	29±21	33±21
Serum ALT (U/l)	32±22	33±24	35±40	36±33
Serum Na (mEq/l)	140±2	141±1	141±1	141±1
Serum K (mEq/l)	4.1±0.2	4.0±0.2	4.1±0.3	4.1±0.3
Serum total protein (g/dl)	7.3±0.1	7.1±0.2	7.3±0.1	7.1±0.2
Serum albumin (g/dl)	4.2±0.2	4.1±0.2	4.2±0.2	4.2±0.2
Serum creatinine (mg/dl)	0.71±0.15	0.69±0.14	0.71±0.22	0.69±0.19
Serum uric acid (mg/dl)	5.5±1.1	5.4±1.0	5.6±1.4	5.7±1.7
Serum total cholesterol (mg/dl)	193±37	187±29	183±21	187±30
Serum triglycerides (mg/dl)	122±81	110±53	118±89	127±104
Plasma glucose (mg/dl)	107±19	103±9	100±11	105±13

Data are mean±SD. AML, amlodipine; CS, candesartan; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 5. Measurements of Cardiovascular Hormones at the End of Each Treatment Period

Parameter	AML group		CS group	
	AML period	AML period	AML period	CS period
Plasma renin activity (ng/ml/h)	1.0±0.6	0.9±0.7	0.7±0.3	1.4±1.2*
Plasma angiotensin II (pg/ml)	5.5±4.0	6.1±3.7	3.7±1.8	5.7±3.4*
Plasma aldosterone (pg/ml)	76±32	69±30	64±24	59±23
Plasma adrenaline (pg/ml)	19±10	20±8	24±14	27±14
Plasma noradrenaline (pg/ml)	266±98	267±86	256±80	274±102

Data are mean±SD. AML, amlodipine; CS, candesartan. *$p<0.05$ *vs.* the AML period.

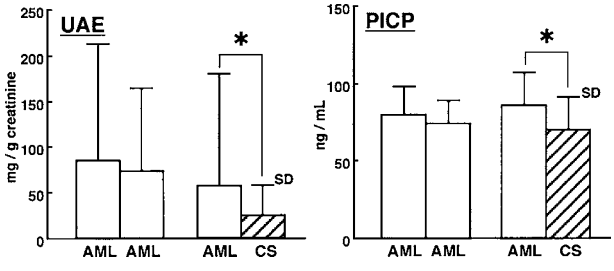

Fig. 3. *Urinary albumin excretion and levels of a circulating marker of collagen synthesis at the end of each treatment period. UAE, urinary albumin excretion; PICP, procollagen I C-terminal peptide; AML, amlodipine; CS, candesartan.* *p < *0.05.*

tion and plasma PICP between the ends of the first and second treatment periods. No significant correlations were observed between these parameters of blood pressure and the changes in LVMI, urinary albumin or plasma PICP.

Discussion

In the present study, AML, a long-acting CCB, was more effective in reducing LVMI than CS, an ARB, when given chronically to hypertensive patients. The office blood pressure was comparably lowered between the AML and the CS groups, but the 24-h SBP was lower in the AML group than in the CS group. Hypertensive injuries in target organs such as the heart, kidney and optic fundi have been shown to correlate with 24-h ambulatory blood pressure more closely than with office blood pressure readings (*20–23*). Therefore, the significant decrease in LVMI in the AML group is likely to be attributable to the fact that the 24-h blood pressure level was lower in this group than in the CS group. AML has a very long pharmacokinetic half-life of 36 h with a slow onset of action, which is thought to confer an advantage in terms of controlling 24-h blood pressure (*24*).

As mentioned earlier, the reflexive sympathetic nerve activation induced by the rapid hypotensive effect of short-acting

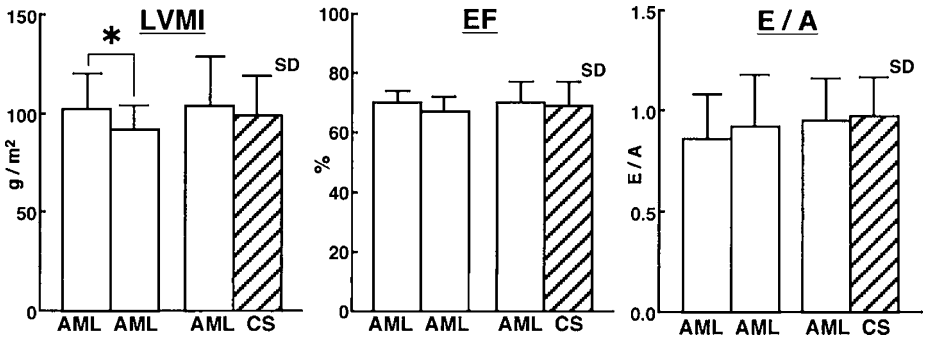

Fig. 4. *Echocardiographic findings at the end of each treatment period. LVMI, left ventricular mass index; EF, ejection fraction;* E/A*, early to atrial transmitral flow velocity ratio; AML, amlodipine; CS, candesartan.* *p<*0.05.*

Table 6. Correlations of Blood Pressure Values in the Second Period with Changes in Left Ventricular Mass Index (LVMI), Urinary Albumin Excretion (UAE) and Plasma Procollagen Type I Carboxy-Terminal Peptide (PICP)

	ΔLVMI		ΔUAE		ΔPICP	
	r	*p* value	*r*	*p* value	*r*	*p* value
Office SBP	−0.047	0.777	−0.071	0.672	−0.034	0.836
DBP	0.026	0.871	0.254	0.108	−0.169	0.304
PP	−0.007	0.963	−0.065	0.685	0.103	0.531
24-h SBP	0.041	0.806	−0.013	0.937	0.004	0.980
DBP	0.165	0.314	0.136	0.414	0.178	0.299
Daytime SBP	−0.015	0.930	−0.115	0.504	0.036	0.839
DBP	0.093	0.582	0.061	0.724	0.161	0.362
Night SBP	0.120	0.486	0.081	0.644	0.009	0.961
DBP	0.205	0.230	0.190	0.273	0.181	0.312
CV of SBP	−0.211	0.210	−0.224	0.189	−0.218	0.216
DBP	−0.084	0.621	−0.050	0.772	−0.220	0.210
Morning surge	−0.255	0.134	−0.123	0.483	−0.109	0.544

ΔLVMI, changes in LVMI; ΔUAE, changes in UAE; ΔPICP, changes in plasma PICP; *r*, correlation coefficient; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; CV, coefficient of variation.

CCBs is unfavorable for inhibiting the onset of cardiovascular events such as ischemic heart disease (*6*, *7*). We have previously shown that AML causes less sympathetic nerve activation than CCBs with shorter pharmacokinetic half-lives (*25*, *26*). In this respect, because angiotensin II facilitates the release of catecholamines from sympathetic nerve (*27*, *28*), inhibitors of the renin-angiotensin system, such as ACE inhibitors and ARBs, are unlikely to cause sympathetic nerve activation in spite of their hypotensive effects (*29*, *30*). In the present study, judging from the monitoring of pulse rate and the measurements of plasma catecholamines, the effects of AML and CS on sympathetic nerve activity would seem to be on a par in the chronic treatment of hypertension.

With respect to the effects on RAAS, it is generally thought that CCBs do not exert obvious direct effects on the components of RAAS. In the CS group of this study, plasma renin activity and angiotensin II concentration were increased as expected; however, plasma aldosterone was not significantly decreased. It has been reported that ARBs and ACE inhibitors reduce plasma aldosterone levels initially, but aldosterone rebound or escape may occur during long-term therapy (*31*). Although hyperkalemia is one of the few adverse effects of ARBs, the serum K level was not significantly affected in the CS group in the present study. Therefore, hyperkalemia is unlikely to be a major problem in the long-term treatment of hypertensive patients with ARBs, unless renal function is impaired.

Recent research has revealed that RAAS is involved in the process of remodeling and injuries of cardiovascular organs and tissues (*12*, *13*). In particular, angiotensin II promotes hypertrophy of cardiovascular cells and aldosterone causes fibrosis of the cardiovascular tissues (*12*, *13*). Therefore, antihypertensive drugs that suppress RAAS, such as ARBs and ACE inhibitors, are expected to confer protection against hypertensive injuries in cardiovascular organs that goes beyond their hypotensive effects (*32*). Fibrosis and deposition of intercellular matrices such as collagen in the cardiac tissue cause reduction in left ventricular distensibility (*33*). Plasma

PICP is thought to be a circulating marker of collagen synthesis and is known to be increased in bone diseases such as cancer metastasis and hyperparathyroidism. However, it has been reported that variation of plasma PICP within the normal range is correlated with histological fibrosis of the cardiac tissue (*34*, *35*). In the present study, plasma PICP was reduced by CS, which suggests that long-term ARB therapy has the advantage of preventing fibrosis of cardiovascular tissues. However, the reduction in plasma PICP was not accompanied by changes in the *E*/*A* of Doppler echocardiography, an index of left ventricular diastolic function. In the VALUE study (*9*), in which hypertensive patients were treated with valsartan or AML, the incidence of heart failure was ultimately lower in the valsartan group than in the AML group, but not until 3 years after starting the treatments. ARBs would thus seem to require years to accomplish their cardiovascular modifications, moving from biochemical alterations, to compositional changes, and finally to the improvement of cardiovascular physiological functions.

A number of studies have indicated that increased urinary excretion of albumin is a predictor of future cardiovascular events not only in hypertensive or diabetic patients but also in the general population (*36–41*). The increased urinary albumin excretion is thought to reflect an elevation of intraglomerular capillary pressure and endothelial dysfunction. Because angiotensin II greatly affects the tonus of efferent glomerular arterioles, ARBs and ACE inhibitors are effective in alleviating glomerular hypertension and reducing urinary excretions of microproteins (*42*, *43*). Also, in the present study, CS was more effective in reducing urinary albumin excretion than AML. Therefore, ARBs may have the advantage of protecting the kidneys from hypertensive injury by lowering intraglomerular pressure and preventing the development of proteinuria.

In the present study, the patients discontinued their previous antihypertensive drugs and were rolled over to the study drug. Because the first AML period ran for 6 months in all patients, it is unlikely that the previous antihypertensive drugs had a substantial influence on the data collected at the ends of the study periods. However, because the present study employed a two-arm design, the comparison between the effects of AML and CS may have been less direct than it would have been if we had used a cross-over design in which the effects are compared in the same subjects.

In summary, the present study showed that AML was effective in controlling blood pressure for 24 h and preventing the LVM increase in patients with essential hypertension. On the other hand, CS lowered the circulating marker of collagen synthesis and reduced urinary albumin excretion. These results suggest that long-acting CCBs and ARBs have different mechanisms for protecting cardiovascular organs and tissues from hypertensive injuries.

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