Original Article

Impact of the Angiotensin II Receptor Antagonist, Losartan, on Myocardial Fibrosis in Patients with End-Stage Renal Disease: Assessment by Ultrasonic Integrated Backscatter and Biochemical Markers

Yasunobu SHIBASAKI, Takashi NISHIUE, Hiroya MASAKI, Koji TAMURA, Noriko MATSUMOTO, Yasukiyo MORI*, Mitsushige NISHIKAWA, Hiroaki MATSUBARA**, and Toshiji IWASAKA

Myocardial fibrosis commonly occurs in patients with end-stage renal disease (ESRD) and has proven to be an important predictor for cardiovascular events. In experimental settings, angiotensin II type 1 receptor (AT1-R) antagonists have been shown to have anti-fibrotic effects on the myocardium independent of their antihypertensive effects. In this study, to investigate whether the AT1-R antagonist losartan would have such anti-fibrotic effects in patients, we administered losartan or, for purpose of comparison, the angiotensin-converting enzyme enalapril or Ca^{2+}-antagonist amlodipine to patients with ESRD. Thirty-nine ESRD patients with hypertension were randomly assigned to receive losartan (n=13), enalapril (n=13), or amlodipine (n=13). Ultrasonic integrated backscatter (IBS) and serological markers of collagen type I synthesis and degradation were used to assess the degree of myocardial fibrosis just before and after 6 months of treatment. There were no significant differences in antihypertensive effects among the three agents. In the enalapril- and amlodipine-treated groups, the mean calibrated IBS values increased significantly after 6 months of treatment (enalapril: −31.6±1.3 to −29.4±1.2 dB, p=0.011; amlodipine: −30.6±1.4 to −27.2±1.2 dB, p=0.012). However, the mean calibrated IBS values in the losartan-treated group did not increase after 6 months of treatment (−31.2±1.7 to −31.3±1.4 dB, p=0.88). The ratio of the serum concentration of procollagen type I carboxy-terminal peptide to the serum concentration of collagen type I pyridinoline cross-linked carboxy-terminal telopeptide was significantly reduced in the losartan-treated group (42.6±4.6 to 34.4±3.6, p=0.038). The present study indicates that losartan more effectively suppresses myocardial fibrosis in patients with ESRD than does enalapril or amlodipine despite a comparable antihypertensive effect among the three drugs. (*Hypertens Res* 2005; 28: 787–795)

***Key Words*: angiotensin II type 2 receptor, myocardial fibrosis, hemodialysis, ultrasonic integrated backscatter, collagen turnover**

From the Department of Medicine II, Kansai Medical University, Moriguchi, Japan; and *Department of Hypertension and Nephrology and **Department of Cardiovascular Medicine, Kyoto Prefectural University School of Medicine, Kyoto, Japan.

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Address for Reprints: Yasunobu Shibasaki, M.D., Ph.D., Department of Medicine II, Kansai Medical University, Fumizono-cho 10–15, Moriguchi 570–8507, Japan. E-mail: y_shibachan@ybb.ne.jp

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Introduction

Dialysis patients suffer from various complications, and cardiovascular events are the most life-threatening complication in the setting of end-stage renal disease (ESRD) (*1*, *2*). Myocardial fibrosis is commonly detected in uremic patients and has emerged as a strong and independent predictor of cardiovascular morbidity and mortality (*3*). Several factors, including angiotensin (Ang) II, have been implicated in the pathogenesis of uremia-associated myocardial fibrosis. However, there is still controversy regarding the mechanism of myocardial remodeling in hemodialysis.

Ang II type 1 receptor (AT1-R) antagonists have antifibrotic and anti-growth effects on the myocardium in experimental settings (*4*). It has been reported that circulating Ang II plays a central role in the progression of myocardial fibrosis and hypertrophy in hypertensive patients (*5*–*7*). Through their blockade of AT1-R-mediated activities, AT1-R antagonists would be expected to inhibit the development of myocardial fibrosis more strongly than Ang-converting enzyme (ACE) inhibitors. Although AT1-R antagonists have been clinically used as antihypertensive agents and shown to have anti-fibrotic properties, there has been no study on the effect of AT1-R antagonists in ESRD patients with myocardial fibrosis, and there has been no study comparing such effects of AT1-R antagonists, if any, with those of ACE inhibitors.

In this study, we investigated whether the AT1-R antagonist losartan is more effective in reducing myocardial fibrosis in ESRD patients than the ACE inhibitor enalapril or the Ca^{2+}-antagonist amlodipine using ultrasonic integrated backscatter (IBS) to assess myocardial fibrosis non-invasively (*8*) and serologic marker and serologic markers of collagen type I synthesis and degradation (*9*, *10*).

Methods

Patients

The study group consisted of consecutive patients who began hemodialysis treatment at our hemodialysis unit. All uremic patients were dialyzed with bicarbonate 3 times a week, with the duration of treatment (3 to 4 h) and dialyzer surface area (1.0 to 1.5 m^2) prescribed individually based on the ureakinetic model criteria. Patients were enrolled in this study if they met the following criteria: 1) they had been receiving maintenance hemodialysis for at least 1 month; 2) a postdialysis weight at which all or most excess body fluid was removed, without postdialysis hypotension; and 3) they had a systolic blood pressure (SBP) $>$150 mmHg and/or diastolic blood pressure (DBP) $>$90 mmHg just before the initiation of hemodialysis treatment. Patients were excluded if they had any of the following: 1) a history of ischemic heart disease; 2) a history of cerebrovascular accident; 3) an inadequate echocardiographic study for the measurement of IBS values; 4) atrial fibrillation; 5) recurrent congestive heart failure; 6) significant valvular heart disease; 7) nephrotic syndrome; 8) anemia with a hematocrit (Ht) $<$20%; or 9) a history of neoplastic disease.

Study Protocol

The study was a double-blind, randomized controlled clinical trial with three treatment arms. Informed consent was obtained from all participants before the start of the study. After a 2-week run-in phase, the patients underwent echocardiographic study before the initiation of antihypertensive treatment. Patients were subsequently treated with either losartan (50 mg/day), enalapril (5 mg/day) or amlodipine (5 mg/day) in a randomized double-blind manner. After 6 months of treatment, the echocardiographic study and blood examinations were repeated. There were no changes in the dosages or types of antihypertensive drugs used during the course of the study. Patients who required a change of medication or the addition of other antihypertensive drugs were excluded from this study. The majority of patients were receiving treatment with oral phosphate binders and vitamin D analogues, and these drugs were continued during the study. None of the patients had undergone parathyroidectomy. Blood pressure was measured just before dialysis with the patients in the supine position using a mercury sphygmomanometer. These measurements were repeated every day before dialysis until the end of study. Arterial blood samples were collected before the midweek hemodialysis session. The serum concentrations of procollagen type I carboxy-terminal peptide (PIP), collagen type I pyridinoline cross-linked carboxy-terminal telopeptide (CITP), and parathyroid hormone (i-PTH) were measured by radioimmunoassay. Ang II (Ang1–8) concentrations were measured by separating the compound from its metabolites using reversed-phase high-performance liquid chromatography (HPLC) as previously reported (*11*). Determinations of complete blood counts, blood urea nitrogen (BUN), creatinine (CRTN) and uric acid (UA) were performed using a conventional automated technique.

Recordings and Analysis of Echocardiographic Data

Echocardiographic studies were performed on an interdialytic day in the midweek hemodialysis session using a Sonos-5500 model ultrasound system (Phillips Medical Systems, Andover, USA) equipped with an ultraband S4 (2 to 4 MHz) sector transducer according to the criteria of the American Society of Echocardiography (*12*–*14*). Two independent examiners performed the echocardiography; one (Y.S.) performed and recorded the study, and the other (T.N.) analyzed the data while blinded to all patient information. Conventional two-dimensional images (short axis left ventricular [LV] images at the mid-papillary muscle level, and apical

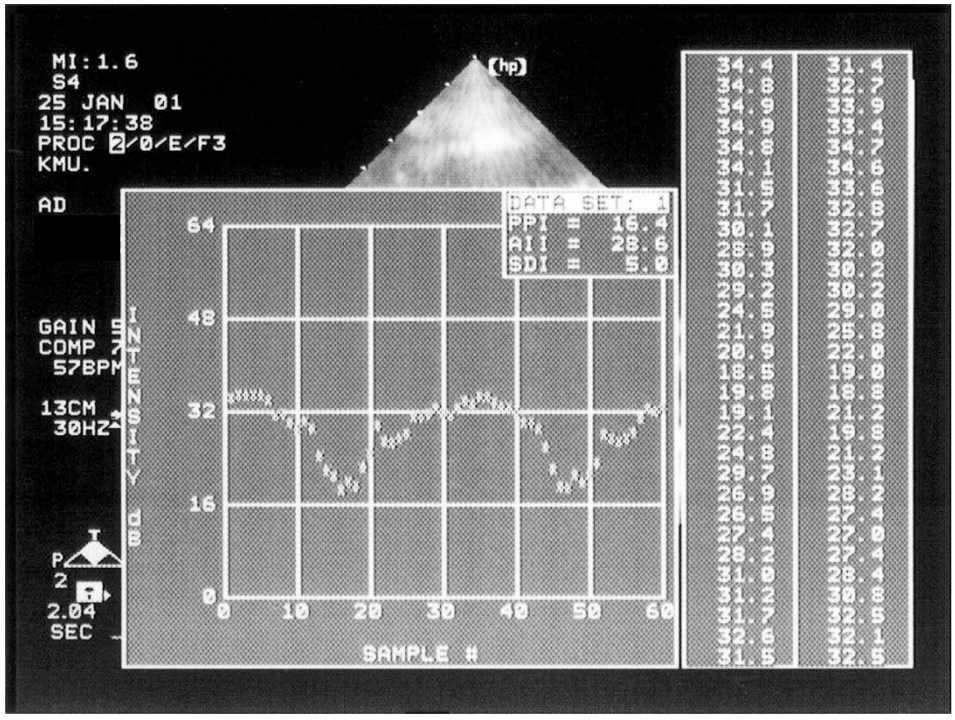

Fig. 1. *To reconstruct the curve representing the relationship of ultrasonic integrated backscatter (IBS)* vs. *time, we retrieved digitally stored backscatter images from optical magnetic disks. Then, the region of interest was adjusted to fit the mid-portion of the LV posterior wall in the parasternal long-axis view spanning two cardiac cycles by an examiner in a blinded manner. After reconstruction of the curve representing the relationship of IBS (a vertical axis)* vs. *time (a horizontal axis), we measured and calculated valuables including the mean calibrated IBS values and cyclic variation of IBS. The list on the right side of the figure indicates the absolute IBS values at each point of measurement.*

four- and two-chamber LV images) were recorded and stored digitally on an optical magnetic disk for later analyses. LV mass was measured according to the area-length method and the left ventricular mass index (LVMI, g/m^2) was calculated by dividing the LV mass by the body surface area. The modified Simpson's rule was used to determine LV volume, and the ejection fraction was derived from the standard equation. LV volumes were corrected for body surface area to obtain a volume index. Relative wall thickness (RWT) was calculated as 2 × LV posterior wall (PW)/LV end-diastolic dimension. For quantitative analysis of IBS, we used a commercially available software package (acoustic densitometry) developed by Phillips Medical Systems and incorporated into the echo machine. The IBS images in the parasternal long-axis view also were recorded and stored digitally on an optical disk. The transmit power, compression setting, and individual values of time gain compensation were kept constant for each patient. We analyzed the digitally acquired images to generate time waveforms of IBS spanning two cardiac cycles in both studies for each patient. The largest possible region of interest, which did not include the endocardium, epicardium, or bright specular spots or streaks, was adjusted to fit the mid-portion of the LV posterior wall. An experienced echocardiographer manually adjusted the location of the site on a frame-by-frame basis to keep the site within the myocardium throughout the cardiac cycle, and thereby reconstruct the curve representing the relationship of integrated backscatter *vs.* time (Fig. 1). To assess quantitatively the reflectivity of the LV wall, myocardial IBS was compared to that for the pericardial surface, expressed as myocardial IBS – pericardial IBS (calibrated IBS), and the mean calibrated IBS values were calculated for two consecutive beats. Cyclic variation of integrated backscatter (CVIBS) was determined as the differences between the minimum and maximum values of IBS spanning a cardiac cycle averaged over two consecutive beats.

The inferior vena cava (IVC) index was measured by B-mode electron-scan ultrasonography and calculated according to methods described previously (*15*). In short, the probe was placed in the subxyphoid portion, and the sagittal section of the IVC behind the liver was examined. Because the IVC dilates in expiration and collapses in inspiration, the maximal diameter during quiet expiration (IVC_e) and the minimal diameter during quiet inspiration (IVC_i) were measured in a distal portion of the IVC-hepatic vein junction where the anterior and posterior wall of the IVC were parallel. The col-

Table 1. Patient Characteristics and Laboratory Data before and after Antihypertensive Therapy

	Losartan		Enalapril		Amlodipine	
	Baseline	6 months	Baseline	6 months	Baseline	6 months
n	13		13		13	
Women	6		5		7	
DM	5		6		5	
Age (years)	57.5±4.4		56.4±3.4		56.2±3.9	
HR (bpm)	68.8±2.3	65.1±2.3	69.1±2.1	67.2±1.4	68.9±1.4	67.8±1.6
mBp (mmHg)	101.3±3.4	90.8±2.1	101.7±2.6	90.6±0.7	99.5±2.2	88.8±1.4
BUN (mg/dl)	74.4±6.0	63.6±2.9	79.0±6.7	77.3±2.8	78.7±5.7	79.5±2.7
CRTN (mg/dl)	8.9±0.4	9.3±0.4	9.3±0.6	9.8±0.4	8.8±0.4	9.3±0.6
UA (mg/dl)	7.3±0.2	7.2±0.2	7.1±0.3	7.6±0.4	7.3±0.2	7.5±0.2
Hb (g/dl)	7.7±0.3	9.9±0.2*	8.5±0.4	10.2±0.2*	7.4±0.4	10.2±0.2*
i-PTH (pg/ml)	235.8±31.6	214.5±26.6	215.0±36.0	205.2±28.4	210.5±35.2	200.5±27.2
Ang II (pg/ml)	7.9±0.6	31.8±8.2*	7.5±0.5	8.9±1.1	8.4±0.6	14.9±2.1*

Data are shown as means±SEM. DM, diabetes mellitus; HR, heart rate; mBp, mean blood pressure; BUN, blood urea nitrogen; CRTN, serum creatinine; UA, serum uric acid; Hb, concentrations of hemoglobin; i-PTH, plasma parathyroid hormone; Ang II, plasma angiotensin II concentrations. *$p<0.05$ as compared to the baseline.

Table 2. Echocardiographic Findings before and after Antihypertensive Therapy

	Losartan		Enalapril		Amlodipine	
	Baseline	6 months	Baseline	6 months	Baseline	6 months
IVS + PW (mm)	23.9±1.2	20.1±0.8*	25.2±1.2	23.7±1.3	23.3±1.3	22.9±1.1
LVMI (g/m^2)	150.7±8.2	117.4±4.7*	154.5±11.1	131.0±8.9*	155.9±7.2	137.2±4.2*
RWT	0.49±0.03	0.45±0.03*	0.52±0.03	0.52±0.03	0.50±0.03	0.51±0.04
LVEDVI (ml/m^2)	63.3±4.1	47.9±3.0*	58.3±5.6	45.7±4.6*	64.1±7.5	50.3±2.6*
CI	0.48±0.02	0.47±0.05	0.59±0.05	0.54±0.05	0.48±0.05	0.49±0.03
EF (%)	71.7±1.9	73.0±2.7	69.1±2.3	70.4±2.9	71.7±2.7	75.0±2.2

Data are shown as means±SEM. IVS, interventricular septum; PW, left ventricular posterior wall; LVMI, left ventricular mass index; RWT, relative wall thickness; LVEDVI, left ventricular end-diastolic volume index; CI, collapsibility index of inferior vena cava; EF, left ventricular ejection fraction. *$p<0.05$ as compared to the baseline.

lapsibility index (CI) was calculated as $CI = (IVC_e - IVC_i)/IVC_e$.

Statistical Methods

All data are expressed as the mean±SEM. The three groups were compared using one-way analysis of variance with a post hoc Bonferroni test. Paired samples were compared by a paired Student's *t*-test. Two-way repeated analysis of variance with a Bonferroni test was used to evaluate the changes in interventricular septal (IVS) + PW thickness over time among the three groups. Values of $p<0.05$ (two-tailed) were considered statistically significant.

Results

From September 2000 through November 2002, 89 patients with ESRD were started on hemodialysis in our unit. Although 61 of the 89 patients (36 males and 25 females) met the criteria for entry and were enrolled in this study, 22 patients were withdrawn from the study because of acute myocardial infarction ($n=3$), switching from hemodialysis to peritoneal dialysis ($n=3$), myocarditis ($n=2$), death from pulmonary bleeding ($n=1$), or transfer to an other hospital ($n=13$). Thus the final study group consisted of 39 patients (losartan, $n=13$; amlodipine, $n=13$; enalapril, $n=13$). The mean age was 56.7±2.2 years. The baseline clinical characteristics are shown in Table 1. Age, gender, and cause of ESRD were similar among the three groups. There were no significant differences in heart rate or mean blood pressure among the three groups. BUN, CRTN, UA, and i-PTH concentrations did not change significantly during the study. The baseline hemoglobin concentration also was similar and increased to a similar extent after 6 months with erythropoietin treatment in all three groups. There were no significant differences in antihypertensive effects among losartan, enalapril, and amlodipine.

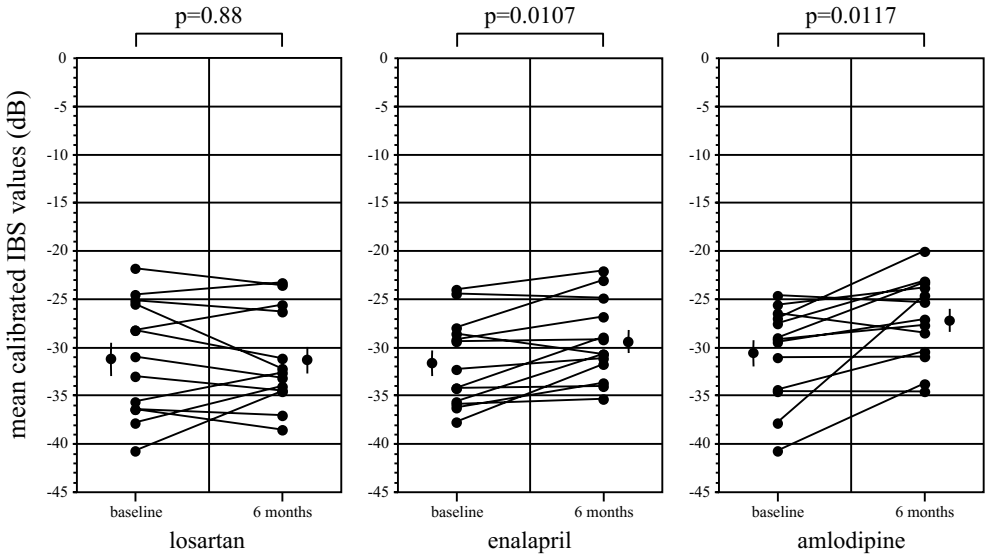

Fig. 2. *Changes in the mean calibrated ultrasonic integrated backscatter (IBS) value before and after 6 months of treatment with losartan (−31.2±1.7 to −31.3±1.4 dB, NS), enalapril (−31.6±1.3 to −29.4±1.2 dB,* p< *0.05), or amlodipine (−30.6±1.4 to −27.2±1.2 dB,* p< *0.05).*

Echocardiography

Table 2 summarizes the echocardiographic data before and 6 months after treatment in the three groups. There were no significant differences in baseline echocardiographic parameters such as LVMI, IVS + PW thickness of the LV, RWT, LV end-diastolic volume index, ejection fraction and IVC CI among the three groups. There were no significant differences in the mean calibrated IBS values among the three groups in the baseline echocardiographic examination. After 6 months of treatment, LVMI significantly regressed in all three groups (Table 2). RWT decreased significantly only in the losartan-treated group (0.49±0.03 to 0.45±0.03, $p=0.039$), but did not change significantly in the enalapril- (0.52±0.03 to 0.52±0.03, $p=0.98$) or the amlodipine-treated (0.50±0.03 to 0.51±0.04, $p=0.79$) groups (Table 2).

In the enalapril- and amlodipine-treated groups, the mean calibrated IBS value increased significantly after 6 months of treatment (enalapril: −31.6±1.3 to −29.4±1.2 dB, $p=0.011$; amlodipine: −30.6±1.4 to −27.2±1.2 dB, $p=0.012$; Fig. 2). However, the mean calibrated IBS value of the losartan-treated group did not change significantly after 6 months of treatment (−31.2±1.7 to −31.3±1.4 dB, $p=0.88$; Fig. 2). CVIBS was not significantly changed by drug treatment in any of the groups.

Biochemical Assessment of Myocardial Fibrosis

Although the pretreatment plasma Ang II concentrations did not differ significantly among the three groups, the concentrations increased four-fold over the baseline values in the losartan-treated group (7.9±0.6 to 31.8±8.2 pg/ml, $p=0.018$). In the enalapril-treated group (7.5±0.5 to 8.9±1.1 pg/ml, $p=0.67$), the plasma Ang II concentrations did not change significantly, and in the amlodipine-treated group (8.4±0.6 to 14.9±2.1 pg/ml, $p=0.036$), the values increased modestly after 6 months of treatment (Table 1).

The concentration of PIP was significantly suppressed by losartan (150.1±11.3 to 126.6±10.2 μg/l, $p=0.030$) and enalapril (155.9±12.4 to 119.2±7.1 μg/l, $p=0.019$), and tended to decrease with amlodipine (156.1±9.8 to 124.9±9.5 μg/l, $p=0.067$) (Fig. 3). The concentration of CITP did not change significantly in the losartan-treated (3.9±0.5 to 3.9±0.4 μg/l, $p=0.89$) and amlodipine-treated group (4.0±0.5 to 3.5±0.3 μg/l, $p=0.20$), although it decreased significantly in the enalapril-treated group (4.2±0.4 to 3.3±0.3 μg/l, $p=0.017$) (Fig. 4).

Although the PIP-to-CITP ratio decreased significantly in the losartan-treated group (42.6±4.6 to 34.4±3.6, $p=0.038$), it did not change significantly in the enalapril- (40.6±3.4 to 38.4±2.5, $p=0.16$) or the amlodipine-treated (42.0±3.4 to 38.5±2.6, $p=0.42$) groups (Fig. 5).

Discussion

Interstitial myocardial fibrosis has long been known to be associated with uremia (*16*), and has also been found to be an adverse prognostic factor in patients with ESRD (*17*). The progressive myocardial interstitial fibrosis and perivascular fibrosis contribute to an increase in myocardial stiffness and development of diastolic LV dysfunction. Therefore, ameliorating and preventing myocardial fibrosis are very important

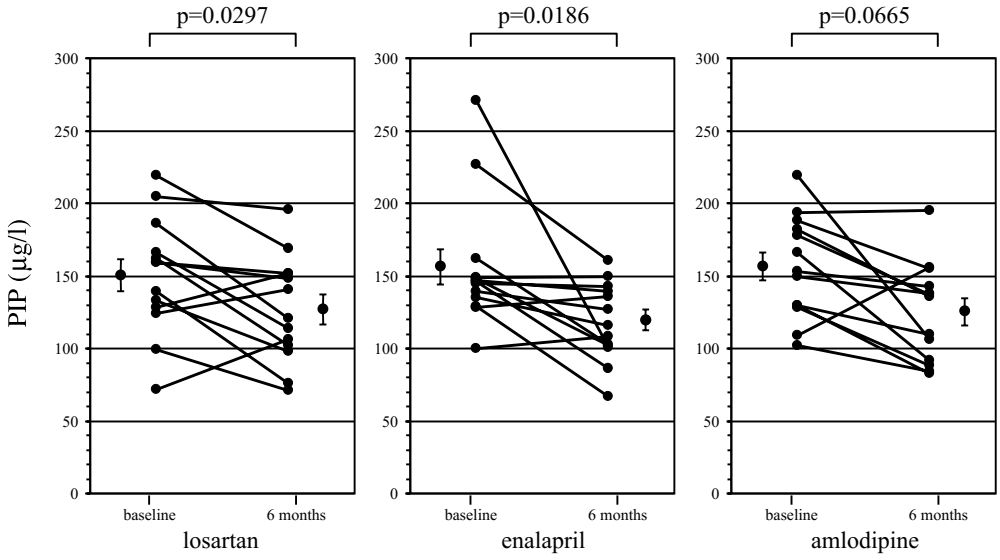

Fig. 3. *Serum concentration of procollagen type I carboxy-terminal peptide (PIP) before and after 6 months of treatment with losartan (150.1±11.3 to 126.6±10.2 μg/l,* $p<0.05$*), enalapril (155.9±12.4 to 119.2±7.1 μg/l,* $p<0.05$*), or amlodipine (156.1±9.8 to 124.9±9.5 μg/l, NS).*

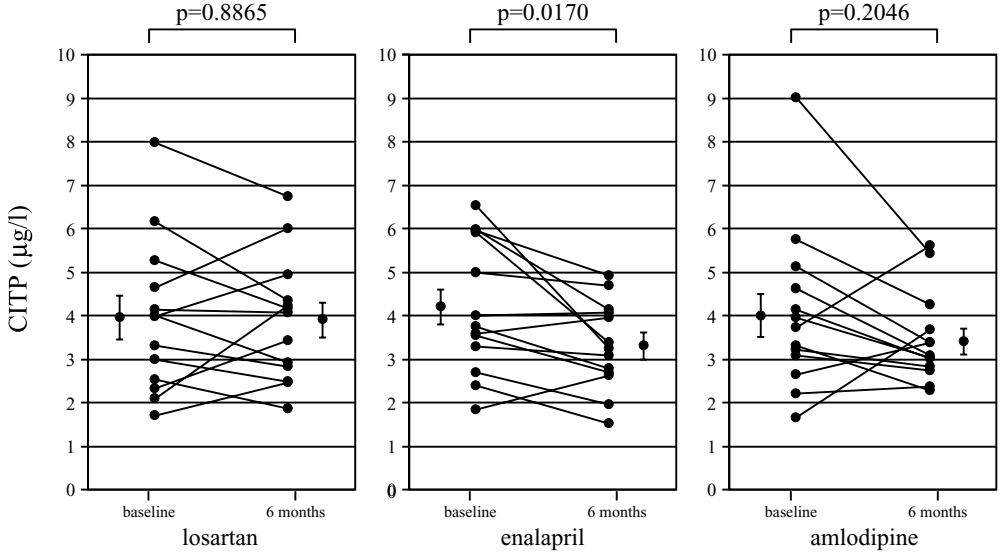

Fig. 4. *Serum concentration of collagen type I pyridinoline cross-linked carboxy-terminal telopeptide (CITP) before and after 6 months of treatment with losartan (3.9±0.5 to 3.9±0.4 μg/l, NS), enalapril (4.2±0.4 to 3.3±0.3 μg/l,* $p<0.05$*), or amlodipine (4.0±0.5 to 3.5±0.3 μg/l, NS).*

in the management of patients with ESRD. Although microscopic examination of endomyocardial biopsies is the most reliable method for documenting and measuring myocardial fibrosis, non-invasive methods have also been developed to assess the degree of the disease. Myocardial tissue characterization with IBS delineates physiologic and pathologic changes in the myocardium, and is directly related to myocardial collagen content (*8*). In this study, we clearly demonstrated that losartan could suppress the increase in the IBS value seen in the enalapril- and amlodipine-treated groups. However, drug treatment induced no significant changes in CVIBS in any of the groups. The mechanisms that contribute to CVIBS include sarcomere length, change in fiber orientation during the cardiac cycle, and the deposition of cross-

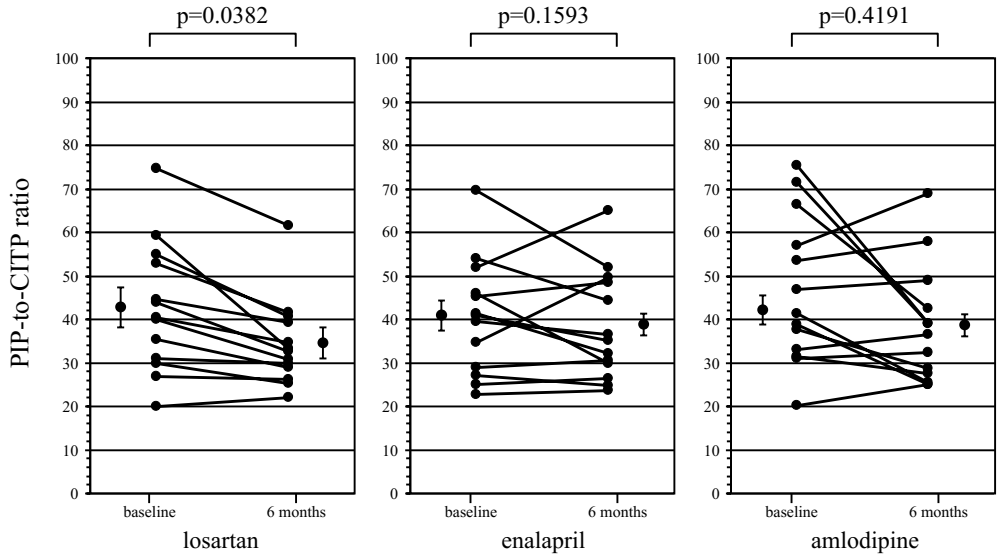

Fig. 5. *The ratio of the serum concentrations of procollagen type I carboxy-terminal peptide (PIP) to collagen type I pyridinoline cross-linked carboxy-terminal telopeptide (CITP) before and after 6 months of treatments with losartan (42.6±4.6 to 34.4±3.6,* $p < 0.05$*), enalapril (40.6±3.4 to 38.4±2.5, NS), or amlodipine (42.0±3.4 to 38.5±2.6, NS).*

linked myocardial collagen (*18*–*23*). Several previous studies have demonstrated that CVIBS reflects the intrinsic contractile function of the heart (*18*, *24*, *25*), although other groups have been unable to relate systolic thickening to the amplitude of CVIBS (*26*, *27*). Factors associated with CVIBS may be different for each pathologic condition. Since the loading conditions of the heart changed dramatically after 6 months of treatment in this study, CVIBS may not be directly related to collagen deposition, and the calibrated IBS should be a reliable marker for myocardial fibrosis in this situation.

Recently, a method for biochemical assessment of myocardial fibrosis based on the measurement of serum peptides derived from the synthesis and degradation of fibrillar collagen has been established in experimental and clinical studies (*28*). It has been reported that the serum PIP provides diagnostic information concerning the extent of myocardial fibrosis (*29*). Furthermore, the ratio between PIP and CITP may be an index of the degree of coupling between the synthesis and degradation of collagen type I (*28*). In this study, the concentration of PIP decreased significantly after 6 months of treatment in all three groups (Fig. 3). In the case of the PIP-to-CITP ratio, on the other hand, only the losartan-treated group showed a significant decrease after 6 months of treatment (Fig. 4), suggesting that losartan stimulated a degradation of collagen type I fibers in our patients. Therefore, Ang II-mediated collagen type I accumulation may play a direct role in the development of myocardial fibrosis in patients with ESRD.

Renin-angiotensin system (RAS) activation is an independent predictor of cardiovascular events (*30*). Most of the cardiovascular effects of Ang II function are mediated *via* AT1-R. However, the physiologic function of Ang II type 2 receptor (AT2-R) has been less well defined, but has been reported to be comparable to the effect of AT1-R (*7*). The expression of AT2-R is upregulated in the hypertrophied myocardium (*31*), and mechanical stretch-induced hypertrophy in myocytes causes an increase in AT2-R expression (*32*). In hemodialysis patients, intravascular volume is drastically changed between hemodialysis sessions, which might cause intermittent stretching of the myocardium. Therefore, the number of AT2-R in the myocardium of hemodialysis patients with volume and pressure overload might be increased, suggesting that AT2-R effects predominate in those patients.

Treatment with losartan markedly increased the concentrations of Ang II (Table 1), which could activate cardiac AT2-R. In contrast, enalapril inhibits ACE-dependent production of Ang II and blocks both AT1-R and AT2-R-mediated effects, while Ang II action by non-ACE dependent pathways is not disturbed. The ACE-independent (chymase-dependent) Ang II forming pathway is dominant and only 11% of the formation of Ang II is mediated by ACE in the heart (*33*). Therefore, ACE inhibitors are not able to inhibit Ang II effects sufficiently in the heart. In contrast, AT1-R antagonists could completely inhibit Ang II actions at the level of the receptor; the elevated Ang II might stimulate AT2-R. These different pharmacologic effects might account for the reason why losartan attenuated the development of myocardial fibrosis to a greater extent than enalapril in patients with ESRD.

Other factors have been reported to be responsible for the development of myocardial fibrosis in patients with ESRD, including hypervolemia (*34*), chronic anemia (*35*, *36*), uncontrolled arterial hypertension (*37*), a high i-PTH concentration

(*38*), and hyperuricemia (*39–41*). The patients in our study were dialyzed in keeping with widely accepted criteria. The IVC collapsibility index, i-PTH concentration, and BUN and CRTN concentrations did not change during the study. The hemoglobin concentration was significantly increased in all three groups during the 6 months. Since regression of the myocardial fibrosis was observed only in the losartan-treated group, the anti-fibrotic effect of improving anemia might not be significant over 6 months. A feature of losartan that differentiates it from other AT1-R antagonists is its lowering of serum UA (*42*), but this effect is due to the ability of the losartan molecule (not its active metabolite) to interfere with urate reabsorption in the renal proximal tubules (*43*). Thus its effects are closely related to renal function. And in our group of ESRD patients, losartan did not reduce serum UA. The LVMI significantly regressed in all three groups, and the regression ratio of the losartan-treated group was greater than that by amlodipine or enalapril. In addition, the RWT decreased significantly only in the losartan-treated group. We divided our study group into four groups according to LVMI and RWT as described previously (*44*). At baseline, all three groups exhibited concentric hypertrophy. After 6 months of treatment, LVH in the losartan-treated group improved closely to the normal LV geometry area. But the enalapril- and amlodipine-treated groups exhibited concentric LV hypertrophy. Reducing and preventing LVH as well as interstitial myocardial fibrosis decreased the risk of cardiovascular events, leading to greater survival and an improvement in the quality of life in ESRD patients (*45–48*). AT1-R antagonists such as losartan might have these potential benefits in ESRD patients.

In conclusion, we demonstrated that losartan was more effective in suppressing myocardial fibrosis than enalapril or amlodipine in patients with ESRD independent of its antihypertensive effects. These data suggested that losartan has cardioprotective and hypotensive effects as well as an ability to suppress myocardial fibrosis in ESRD patients, and should be considered as one of the first-line antihypertensive drugs for ESRD patients.

Limitations of the Study

CITP appears to be cleared from the circulation *via* glomerular filtration. Therefore, the serum concentration of CITP has been considered a useful marker of collagen type I degradation in conditions of normal renal function (*9*). In this study, we examined the serial changes of CITP, PIP and PIP-to-CITP ratio in individual patients. These biochemical assessments of myocardial fibrosis were not contradictory to ultrasonic assessment of myocardial fibrosis under the same hemodialysis conditions. Further studies are needed to determine whether the PIP-to-CITP ratio is a useful prognostic marker of the absolute degree of collagen type I degradation even in ESRD patients.

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