Original Article

Non-Corresponding Effects of an Angiotensin-Converting Enzyme Inhibitor on Cardiac and Vascular Hypertrophy in Spontaneously Hypertensive Rats

Masahiko TOZAWA, Shuichi TAKISHITA, Hiromi MURATANI, and Koshiro FUKIYAMA

Angiotensin-converting enzyme inhibitors (ACEIs) may have different effects on cardiac hypertrophy than on vascular hypertrophy. Arginine vasopressin (AVP) may promote cardiac hypertrophy. Our aims were (1) to simultaneously examine the chronic effects of ACEIs on hypertrophy of the heart and hypertrophy of the coronary and renal interlobular arteries, and (2) to clarify the relation between AVP concentration (AVPC) and cardiac hypertrophy. ACEI (delapril: 30 mg/kg/day) or vehicle (5% arabic gum) was administered in a preventive (4 to 28 weeks of age) or a therapeutic (12-24 weeks of age) protocol in spontaneously hypertensive rats. In both protocols, delapril produced a slight but significant decrease in systolic blood pressure. In the therapeutic protocol, the weight of the left ventricle (mean $\pm$ SE) was lower ($p<0.05$) in the ACEI group (64 ± 2 mg/100 g body weight) than in the control group (69 ± 1 mg/100 g body weight). Plasma renin activity was significantly higher in the ACEI group than in the control group in both the preventive ($p<0.01$) and therapeutic ($p<0.01$) protocols. In the therapeutic protocol, AVPC was significantly ($p<0.05$) lower in the ACEI group than in the control group. AVPC was significantly ($p=0.02$, $r=0.46$) correlated with the weight of the left ventricle in the therapeutic protocol. For both protocols, no differences were noted between the ACEI and control groups in the vascular hypertrophy of the coronary and renal interlobular arteries. We conclude that (1) the preventive or therapeutic effect of ACEIs on hypertrophy may not be the same in the heart as in the coronary and renal arteries; and (2) AVP was significantly correlated with the left ventricular weight. This indicates that AVP could play a role in the etiology of cardiac hypertrophy in SHR. (*Hypertens Res* 2000; 23: 483-490)

Key Words: hypertension, cardiac hypertrophy, vascular hypertrophy, renin-angiotensin system, arginine vasopressin

Introduction

Chronic hypertension is associated with hypertrophy of the cardiac muscle (1, 2) and the medial layer of arteries and arterioles (3-5). Angiotensin-converting enzyme inhibitors (ACEIs) have been shown to reduce cardiac hypertrophy (1). ACEIs have been shown to reduce

vascular hypertrophy in the carotid, mesenteric, coronary, and renal arteries of spontaneously hypertensive rats (SHR) (6), and to prevent development of atherosclerosis in the large arteries by reducing vascular ACE activity in monkeys on a high-cholesterol diet (7). In other studies using SHR, ACEIs were found to simultaneously effective on hypertrophy of the heart and hypertrophy of the coronary, renal and mesenteric arteries (8, 9). Kett *et al.*

From the Third Department of Internal Medicine, University of the Ryukyus, Okinawa, Japan.

Address for Reprints: Masahiko Tozawa, M.D., Third Department of Internal Medicine, University of the Ryukyus, 207 Uehara, Nishihara-cho, Nakagami-gun, Okinawa 903-0215, Japan.

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reported that enalapril treatment does not prevent vessel wall hypertrophy of the renal interlobular and arcuate arteries in SHR (10). And, in a regression study on SHR, ACEIs were found to be effective on hypertrophy of heart but not on vascular hypertrophy of the mesenteric artery (11). The effect of ACEIs and the role of the renin-angiotensin system in vascular hypertrophy remains controversial. To test the hypothesis that the effect of ACEIs on cardiac hypertrophy differs from that on vascular hypertrophy, we simultaneously examined the chronic effects of delapril on hypertrophy of the heart and on hypertrophy of the coronary and renal interlobular arteries in SHR using a preventive and a therapeutic protocol. In addition, because arginine vasopressin (AVP) may promote cardiac hypertrophy (12, 13) and, in an experimental study on left ventricular hypertrophy, chronic treatment with ACE attenuated circulatory AVP (14), we also assayed AVP concentration (AVPC) and examined the relation between AVPC and left ventricular hypertrophy.

Methods

Animals

Four-week-old male SHR (Charles River Inc., Atsugi, Kanagawa, Japan) were fed standard rat chow and tap water containing 1% NaCl *ad libitum* throughout the experiment. Systolic blood pressure (SBP) by the tail-cuff method and body weight (BW) were measured weekly. All experiments were performed in accordance with the Guidelines for Animal Experimentation of the University of the Ryukyus, and under the approval of the Animal Care and Use Committee of the University of the Ryukyus.

Experimental Protocol

Delapril hydrochloride was administered by gavage from the 4th to the 28th week of age in rats ($n=13$) in the preventive protocol and from the 12th to the 24th week of age in rats ($n=8$) in the therapeutic protocol. The daily oral dose of delapril hydrochloride was 30 mg/kg·body weight. Delapril hydrochloride (Takeda Chemical Industries, Ltd., Osaka, Japan) was suspended in 5% arabic gum. Five percent arabic gum solution was given to control rats in both protocols ($n=16$ each). At the end of each protocol, rats were killed by decapitation and trunk blood was collected in an experimental tube with EDTA-2Na. After the samples were centrifuged for 15 min at 3,000 rpm at 4°C, the plasma was collected and stored at -20°C until use. Plasma renin activity (PRA), arginine vasopressin concentration (AVPC), and plasma aldosterone concentration (PAC) were assayed. PRA was determined by radioimmunoassay using a RENIN RIABEAD

kit (Dainabot Ltd., Tokyo, Japan). AVPC was measured by radioimmunoassay using an AVP-RIA kit (Mitsubishi-yuka Ltd., Tokyo, Japan). PAC was measured by radioimmunoassay using an ALDOSTERONE RIAKIT II kit (Dainabot Ltd.).

Tissue Preparations

Owing the final week of each protocol, at the end of the final week of each protocol, each rat was decapitated, and the heart and kidney were dissected. The right ventricle was removed from the heart and the left ventricle was weighed. Immediately after tissue extraction, the left ventricle and kidney were fixed with phosphate buffered 10% formalin solution. The left ventricles were cut into the three parts (the upper, middle, and lower thirds), and kidneys were cut sagittally into two parts. All these tissues were prepared routinely, and then 4- μ m thick cross-sections were stained with hematoxylin-eosin, periodic acid-Schiff (PAS) and azan. Infiltration of lymphocytes and fibrosis of the heart were classified as follows: 0, none; 1, slight; 2, mild; or 3, moderate.

Cardiometry

Coronal sections of the upper, middle and lower regions were made from each ventricle. Free wall thickness, wall area, lumen area, and perimeter of coronal-sectioned left ventricles were measured by an image-analyzer (IBAS-2000, Carl Zeiss Japan, Tokyo, Japan). Mean values of the three regions (the upper, middle, and lower thirds) in each were used for comparison.

Evaluation of Vascular Thickness

Thickening of the coronary and renal interlobular arteries were graded as normal, mild or moderate (Fig. 1). Histologic findings of coronary and interlobular arteries were graded as follows: Stage 0, no thickened vessels observed; Stage 1, one or two vessels in the mild grade and the moderate grade are observed; or Stage 2, two or three vessels in the mild grade and three or four vessels in the moderate grade are observed. The stage of each sample was determined according to the findings of three sections from the left ventricles and one section from the kidney. Three transverse sections were obtained, one each from the upper, middle, and lower thirds of the left ventricle. One central sagittal section was obtained from each kidney. The stages of all samples were determined by a single examiner (AS). For quantitative evaluation of the vascular thickening, the cross-sectional area (CSA) of a vessel wall was calculated as the CSA of the whole vessel minus the CSA of the lumen.

Fig. 1. Three grades of vascular thickening of the coronary arteries, normal (a), mild (b), and moderate (c), and of the renal interlobular arteries, normal (d), mild (e), and moderate (f). Scale bars equal 100 μ m. According to these grades, the histologic findings of the coronary and interlobular arteries are classified into three stages (described in the text).

Statistics

Values are expressed as the means $\pm$ SE. The statistical significance of blood pressure (ACEI group vs. control group) was tested by analysis of variance and Bonferroni *t*-test. The statistical significance of cardiac measurement and CSA of vessels (ACEI group vs. control group) was tested by Student's unpaired *t*-test. The statistical significance of vascular thickening as determined by histological stage (ACEI group vs. control group) was tested by Mann-Whitney *U* test. *P* values less than 0.05 were considered to indicate statistical significance.

Results

Body Weights and Systolic Blood Pressure

In the preventive protocol, BW in the final week was lower in the ACEI group than in the control group ($p < 0.05$). This difference was absent in the therapeutic protocol (Table 1). In both protocols, SBP in the final week was lower in the ACEI group than in the control group ($p < 0.05$).

Course of Systolic Blood Pressure

Throughout the study, SBP in the preventive protocol was lower in the ACEI group than in the control group (Fig. 2). Until week 11, in the therapeutic protocol, SBP

in the ACEI group was similar to that in the control group. At week 11, ACEI was introduced, and SBP decreased in the ACEI group.

Cardiometry of the Left Ventricle

In the preventive protocol, no intergroup differences in left ventricular (LV) weight were observed. In the therapeutic protocol, the LV weight was lower in the ACEI group (64 ± 2 mg/100 g body weight) than in the control group (69 ± 1 mg/100 g body weight, $p < 0.05$). In the preventive protocol, the LV wall area was less in the ACEI group (56 ± 1 mm²) than in the control group (61 ± 1 mm², $p < 0.05$). No such difference was observed in the therapeutic protocol. In both protocols, no intergroup differences were noted in LV wall thickness. In the preventive protocol, the LV perimeter was smaller in the ACEI group (30 ± 0.4 mm) than in the control group (33 ± 0.3 mm, $p < 0.05$). No such intergroup difference was observed in the therapeutic protocol. In both protocols, the LV lumen area was less ($p < 0.05$) in the ACEI group than in the control group.

Histological Change of the Heart

In the preventive protocol, the mean grade $\pm$ SE of lymphocyte infiltration was 1.3 ± 0.1 in the ACEI group and 1.1 ± 0.1 in the control group ($p = 0.24$, ACEI vs. control). In this protocol, the mean grade of fibrosis was 2.2

Fig. 2. Weekly systolic blood pressure of spontaneously hypertensive rats. The left panel shows the preventive effects of the angiotensin-converting enzyme inhibitor (ACEI) on blood pressure. The right panel shows the therapeutic effect of the ACEI on blood pressure in spontaneously hypertensive rats. Values are means $\pm$ SE.

Table 1. Body Weight and Systolic Blood Pressure in the Final Week of the Experiment

	BW (mg)	SBP (mmHg)
Preventive protocol		
ACEI ($n=13$)	374 ± 6	199 ± 4
Control ($n=16$)	406 ± 3	219 ± 3
p	<0.05	<0.05
Therapeutic protocol		
ACEI ($n=8$)	386 ± 7	200 ± 6
Control ($n=16$)	389 ± 3	218 ± 3
p	NS	<0.05

Values are expressed as mean $\pm$ SE.

± 0.1 in the ACEI group and 2.1 ± 0.1 in the control group ($p=0.84$). In the therapeutic protocol, the mean grade of lymphocyte infiltration was 1.0 ± 0 in the ACEI group and 0.9 ± 0.1 in the control group ($p=0.49$). In the therapeutic protocol, the mean grade of fibrosis was 1.3 ± 0.1 in the ACEI and 1.6 ± 0.1 in the control group ($p=0.26$).

Vascular Thickening

In both protocols, no intergroup differences were observed in the vasculature composition (intima, media, fibrous tissue). In addition, no intergroup differences were noted in the grade of vascular thickening in the coronary or renal interlobular arteries (Table 2). And no significant intergroup differences were noted in the CSA of the coronary or renal interlobular arteries (Fig. 4).

Radioimmunoassay

PRA was significantly higher in the ACEI group than in the control group in both the preventive ($p<0.01$) and therapeutic ($p<0.01$) protocols (Table 3). AVPC in the preventive protocol was similar in both groups in the therapeutic protocol. In the therapeutic protocol, AVPC was significantly ($p<0.05$) lower in the ACEI group than in the control group. In the therapeutic protocol, PAC was similar between the two groups. In the preventive protocol, PAC was significantly ($p<0.05$) lower in the ACEI group than in the control group. In the preventive protocol, no significant correlation existed between LV weight and either PRA ($p=0.66$) or AVPC ($p=0.17$). In the therapeutic protocol, a negative correlation ($p=0.02$, $r=-0.47$) was observed between PRA and LV weight, and a positive correlation ($p=0.02$, $r=0.46$) was observed between AVPC and LV weight (Fig. 5).

Discussion

Delapril is a nonsulfhydryl ACEI (15) and potently inhibits ACE in plasma, aorta, kidney, lung and brain in SHR (16), and is used in the clinical treatment of hypertension (17). In the present study, circulatory PRA was higher in the ACEI group than in the control group. This finding indicated that the renin angiotensin system was inhibited and that plasma renin increased through positive feedback following blockade of angiotensin II generation (18). Delapril produced a slight but significant decline in SBP. Cardiac dilation was reversed, and cardiac weight was decreased. Vascular hypertrophy continued in the coronary and interlobular arteries. These results suggest that delapril does exert both preventive and therapeutic

Table 2. Effect of ACEI on Vascular Thickening in Coronary and Renal Interlobular Arteries

		Stage of vascular hypertrophy			<i>p</i> value
		0	1	2	
Coronary arteries					
Preventive protocol	ACEI (<i>n</i> =13)	0	4	9	0.160 (NS)
	Control (<i>n</i> =16)	0	0	16	
Therapeutic protocol	ACEI (<i>n</i> =8)	0	0	8	>0.999 (NS)
	Control (<i>n</i> =16)	0	0	16	
Renal interlobular arteries					
Preventive protocol	ACEI (<i>n</i> =13)	1	2	10	0.430 (NS)
	Control (<i>n</i> =16)	0	7	9	
Therapeutic protocol	ACEI (<i>n</i> =8)	0	4	4	0.624 (NS)
	Control (<i>n</i> =16)	0	10	6	

Values are the number of animals. Definition of the stage (0, 1, and 2) is described precisely in the text. NS: not significant difference in the ACEI group vs. control group. ACEI, angiotensin-converting enzyme inhibitor.

Fig. 3. Bar graphs show data from cardiometry of the left ventricle in the preventive protocol (Px), and the therapeutic protocol (Tx), with angiotensin converting enzyme inhibitor (ACEI) and control vehicle (C) in spontaneously hypertensive rats. The weight, wall area, wall thickness, perimeter, and lumen area of the left ventricle are shown. Note that the left ventricular weights are shown as a ratio: weight of left ventricle/body weight (mg/100 g body weight). NS, not significant. * $p < 0.05$, vs. control group. Values are means $\pm$ SE.

effects on hypertrophy of the heart, but that it does not have the corresponding effects on hypertrophy of the coronary and renal arteries. In addition, ACEI treatment reduced circulatory AVPC. AVPC was significantly correlated with the left ventricular weight. AVP could thus play a role in the etiology of cardiac hypertrophy in SHR.

We used 1% NaCl as drinking water to expand the intravascular volume to make the hypertension relatively refractory to the administration of ACEI. The difference of blood pressure between the control and ACEI groups was significant although small. In this experiment, we were able to test the effect of delapril on the pressure-independent mechanisms of tissue hypertrophy more extensively than on the pressure-dependent mechanisms.

In both the preventive and therapeutic protocols, delapril did not change the left ventricular wall thickness, but it did improve or regress the cardiac lumen area (Fig. 3). ACEIs have been shown to be more effective at improving left ventricular dilation of the lumen, *i.e.*, eccentric hypertrophy (*I*), than thickening of the left ventricular wall, *i.e.*, concentric hypertrophy (*I*). Eccentric hypertrophy is volume-dependent (*I*), and aldosterone may play a role in developing this type of hypertrophy. Aldosterone production is decreased during ACE inhibition by ACEI (*19-21*), and ACEI might ameliorate volume overload by reducing both aldosterone production and left ventricular dilation. In the preventive protocol, PAC was lower in the ACEI group than in the control group, which apparently supports this hypothesis.

The effect of delapril on cardiac hypertrophy was consistent with that observed in experiments using other types of ACEIs (*8, 9, 11, 22-24*). Cardiac hypertrophy in hypertension is thought to be induced by both the hypertension itself and various humoral circulating growth factors. One of these growth factors, tissue angiotensin II is known to be an endogenous growth factor (*25, 26*), and thus may account for be implicated in the pathophysiolo-

Table 3. Plasma Renin Activity, Arginine Vasopressin, and Plasma Aldosterone Concentration

		PRA (ng/ml/h)	AVPC (pg/ml)	PAC (ng/dl)
Preventive protocol	ACEI (<i>n</i> =13)	7.60±1.74	2.91±0.18	1.78±0.32
	Control (<i>n</i> =16)	1.54±0.41	2.59±0.14	3.48±0.54
	<i>p</i>	<0.01	NS	<0.05
Therapeutic protocol	ACEI (<i>n</i> =8)	7.56±0.97	2.52±0.20	3.06±0.49
	Control (<i>n</i> =16)	1.11±0.20	3.02±0.08	3.10±0.40
	<i>p</i>	<0.01	<0.05	NS

Values are mean±SE. PRA, plasma renin activity; AVPC, arginine vasopressin concentration; PAC, plasma aldosterone concentration.

Fig. 4. Bar graphs show data obtained from digitizer analysis of the coronary arteries (upper panel) and renal interlobular arteries (lower panel) of the preventive protocol (Px) and therapeutic protocol (Tx), with angiotensin-converting enzyme inhibitor (ACEI) and control vehicle (C) in spontaneously hypertensive rats. CSA, wall cross-sectional area; NS, not significant. Values are means±SE.

gy of left ventricular hypertrophy (22). Suppression of the renin-angiotensin system could improve cardiac hypertrophy.

ACEI did not alter vascular hypertrophy in the present study, a finding in contradiction to previous reports that have shown a preventive effect of ACEIs on vascular hypertrophy in the cerebral (27), carotid (6), mesenteric (6, 8, 9, 11), coronary (6, 8, 9) and renal (6, 8, 9) arteries. Li *et al.* (8) and Clozel *et al.* (6, 8, 27) used cilazapril as an ACE inhibitor. Delapril and cilazapril are prodrugs, and the IC₅₀ values (the concentration of drugs required for the 50% inhibition of rabbit lung ACE) of CV-3317-COOH (the active form of delapril)/captopril and Ro 31-

Fig. 5. Relation between plasma renin activity (PRA) or arginine vasopressin concentration (AVPC) and left ventricular weight in the therapeutic protocol. ACEI, angiotensin-converting enzyme inhibitor; LVW, left ventricular weight; BW, body weight.

3113 (the active form of cilazapril)/captopril were 4.0×10^{-8} M/ 5.8×10^{-7} M (16) and 1.93 nM/6.93 nM (28), respectively. The potency measured by IC₅₀ values for CV-3317-COOH over Ro 31-3113 was 4-fold. The dose (30 mg/kg/day) and potency of delapril in the present study were greater than those of cilazapril (10 mg/kg/day) in previous studies (6, 27). In these prior studies, cilazapril was administered for 19 weeks, which was longer than the 12 weeks of our therapeutic protocol but shorter than the

24 weeks of our preventive protocol. Based on these facts, the discrepancy in the results of vascular hypertrophy between our experiments and previous studies (6, 27) may not be related to the dose, character or duration of ACEI administration.

In the vasculature and myocardium, hypertension and the pressure-independent mechanisms are considered mechanisms of hypertrophy (29). The pressure-dependent mechanism that includes stretch or wall stress in pressure overload may stimulate hypertrophy of the heart (30) and blood vessels (31). In the studies of Li *et al.* (8) and Sharifi *et al.* (9), ACEI simultaneously reduced cardiac and vascular hypertrophy in SHR. In these experiments, the blood pressure reduction (>60 mmHg) was larger than that seen here (≤ 20 mmHg). Thus the benefit of pressure reduction in the present study was smaller than that seen in previous studies. We observed a reduction only in cardiac hypertrophy but not in vascular hypertrophy. These findings support the notion that the pressure-dependent mechanism is more dominant in the hypertrophy of these vessels than in that of the heart, or that the effects of ACEI on the pressure-independent mechanisms of cardiac and vascular hypertrophy may not be the same.

Kett *et al.* (10) reported that ACEI treatment did not prevent vessel wall hypertrophy in renal interlobular and arcuate arteries in SHR. In their study, ACEI reduced blood pressure substantially (>50 mmHg), although they did not include the heart and coronary arteries. Together, our data and the findings of Kett *et al.* (10) — which are at least partially consistent — suggest that the renin-angiotensin system may make only a limited contribution to vessel wall hypertrophy of the renal arteries in SHR.

AVP has been shown to increase the rate of protein synthesis in neonatal rat cardiomyocytes (12) and isolated perfused adult rat hearts *via* the V1 receptor (13). This increase indicates that AVP may promote cardiac hypertrophy. Chronic blockade of the renin-angiotensin system by ACEI (ramipril) significantly attenuated circulating and central vasopressin in rats with LVH due to aortic banding (14). In our study, AVPC was significantly suppressed in the therapeutic protocol group following ACEI treatment. And AVPC was significantly correlated with LV weight in the protocol group. Given its antidiuretic, vasoconstrictive, and growth-promoting effects, vasopressin may participate in the cardiovascular alterations in LV hypertrophy (14).

In summary, we investigated the preventive and therapeutic effects of ACEI on hypertrophy of the heart and coronary and renal interlobular arteries. The circulatory renin-angiotensin system seemed to be inhibited. In our study, the BP reduction was mild, and cardiac mass and volume regressed. Hypertrophy of the coronary and renal interlobular arteries did not change. In the therapeutic protocol, ACEI treatment was able to reduce AVPC and cardiac hypertrophy in SHR. AVPC was correlated with

the left ventricular weight. In conclusion, the inhibitory effects of ACEI on the tissue renin-angiotensin system in cardiac hypertrophy may differ from those in coronary and renal vascular hypertrophy. In addition, AVP may play a role in the etiology of cardiac hypertrophy in SHR.

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