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Renin Angiotensin System-Dependent Hypertrophy as a Contributor to Heart Failure in Hypertensive Rats: Different Characteristics from Renin Angiotensin System-Independent Hypertrophy

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OBJECTIVES This study aimed to characterize the difference between renin angiotensin system (RAS)-dependent and RAS-independent hypertrophy and their differential contribution to the transition to heart failure.

BACKGROUND Hypertensive left ventricular (LV) hypertrophy develops with RAS activation in the heart; however, LV hypertrophy develops even without RAS activation.

METHODS Left ventricular geometry and function were assessed in Dahl salt-sensitive rats placed on an 8% NaCl diet from seven weeks old (hypertensive rats) and in those placed on an 0.3% NaCl diet (control rats, n = 8). The hypertensive rats were randomized to no treatment (n = 8) or treatment with the angiotensin type 1 receptor (AT_1R) antagonist candesartan (1 mg/kg per day, n = 10) after the baseline echocardiography study.

RESULTS From 7 to 13 weeks, AT_1R blockade at a subdepressor dose did not restrain the development of LV hypertrophy but prevented narrowing of LV diastolic dimension, leading to the normalization of abnormally decreased end-systolic wall stress in the untreated rats. Progressive development of LV hypertrophy in spite of lower than normal end-systolic wall stress (excessive hypertrophy) after 13 weeks was suppressed by the AT_1R blockade. Elevation of LV end-diastolic pressure and prolongation of Tau were associated with histological evidence of myocyte hypertrophy and massive interstitial fibrosis in the untreated rats, and none of these was evident in the treated rats.

CONCLUSIONS Renin-angiotensin system activation and AT_1R signaling may be dispensable for the development of early adaptive LV hypertrophy and closely linked to the transition to heart failure. (J Am Coll Cardiol 2001;37:293–9) © 2001 by the American College of Cardiology

Ventricular hypertrophy as a physiological response to chronic pressure overload initially normalizes wall stress but may eventually result in a deterioration of contractile function, alter left ventricular (LV) geometry or decrease chamber compliance. Any of these changes may contribute to the development of heart failure; however, the mechanism accounting for the transition from compensatory hypertrophy to heart failure is not well understood. Evidence from many experimental studies supports the idea that local activation of the renin angiotensin system (RAS) is closely related to the development of cardiac hypertrophy. The expression of angiotensin-converting enzyme (ACE) and angiotensin type-1 receptor (AT_1R) messenger RNA (mRNA) is induced in the hypertrophied rat heart (1,2). Mechanical stress stimulates the secretion of angiotensin (AT) II from myocytes, and AT II, in turn, induces cardiomyocyte hypertrophy through AT_1R (3,4). This evidence supports the idea that RAS plays an important role in the development of pressure overloaded hypertrophy. In fact, pharmacological blockade of RAS with ACE inhibition regresses LV hypertrophy in patients as well as in animal models (5–7). In contrast, there are several pieces of evidence that the activation of RAS may be dispensable for LV hypertrophy. Administration of the AT_1R antagonist did not completely prevent stress-induced hypertrophy in rats with persistent systolic pressure overload due to ascending aortic stenosis (8), and cardiac hypertrophy was induced by pressure overloading in AT_1R knockout mice (9,10). Both of these studies indicate that activation of RAS is not essential for the development of cardiac hypertrophy. Thus, the role of RAS in the development of cardiac hypertrophy is still controversial.

The aim of this study was to characterize the difference between RAS-dependent and RAS-independent hypertrophy in hypertensive rats and to clarify their differential contribution to the transition from compensatory to failing stage. Specifically, we studied the effect of AT_1R antagonist administration on the development of hypertrophy and, hence, heart failure in Dahl salt-sensitive rats in which development of hypertension is followed by compensatory LV hypertrophy at 13 weeks old and, in turn, by the transition to heart failure at 19 weeks old.

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Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
AT	= angiotensin
AT_1 R	= angiotensin II type-1 receptor
CAND(+)	= experimental group receiving candesartan
CAND(−)	= experimental group receiving placebo
ECE	= endothelin-converting enzyme
ET	= endothelin
LV	= left ventricular
LVMI	= the ratio of left ventricular mass to body weight
mRNA	= messenger RNA
RAS	= renin angiotensin system
Tau	= time constant of left ventricular isovolumic pressure fall

METHODS

This study conforms to the guiding principles of the Osaka University School of Medicine with regard to animal care and to the position of the American Heart Association on research animal use. Our study consisted of two experimental protocols.

Protocol 1: 19 weeks end-point study. Laboratory chow containing 0.3% NaCl was continuously fed to the male Dahl-Iwai salt-sensitive (Dahl S) rats (DIS/Eis, Eisai, Tokyo, Japan), and they were defined as control rats (n = 8). Laboratory chow containing 0.3% NaCl was fed to weanling Dahl S rats until their diet was switched at seven weeks old to laboratory chow containing 8% NaCl for the other rats (n = 18). We randomly selected 10 out of 18 rats, and these rats were given candesartan cilextil (1 mg/kg per day, courtesy of Takeda Chemical Industries Ltd: group CAND[+]). The dose of candesartan was determined according to the data in a preliminary study. The other eight rats were given placebo (group CAND[−]). The diet and tap water were given ad libitum throughout the experiment. Systolic blood pressure and heart rate were measured every two to five weeks with a tail-cuff system (BP-98A, Softron, Tokyo, Japan).

Protocol 2: 13 weeks end-point study. Pathological and neurohumoral conditions in the stage of compensatory hypertrophy were studied as protocol 2 using six control rats, seven untreated rats and seven rats treated with candesartan. In these rats post mortem, the ratio of LV mass to body weight (LVMI) and LV mRNA levels were measured at 13 weeks. The production of the model for this protocol is the same as that described in protocol 1.

Doppler echocardiography and hemodynamic studies. Transthoracic echocardiography Doppler studies were performed at 7 (just before starting 8% NaCl diet), 13, 15, 17 and 19 weeks to determine LV mass, relative wall thickness, systolic wall stress, endocardial and midwall fractional shortening, peak early diastolic filling velocity (E velocity) and peak filling velocity at atrial contraction (A velocity) in a fashion previously described (11,12). Hemodynamic studies were performed at 19 weeks. Soon after Doppler echocardiography studies, LV catheterization was performed for the determination of time constant (Tau) and end-diastolic pressure as previously described (11).

Pathological studies. After the hemodynamic studies, adequate anesthesia was achieved, and lung weight and LV mass were measured as previously described (11). Left ventricular myocardium was sampled for measurement of hydroxyproline, histological examination and mRNA quantification. Hydroxyproline content was measured as previously described (13). The rest of the left ventricle was fixed with a phosphate-buffered 10% formalin solution for a week. The specimens were embedded in paraffin, and 2-μm thick transverse sections of the organs were stained with hematoxylin and eosin for routine histological examination and with Azan Mallory stain to evaluate the degree of fibrosis. Myocyte diameter was measured from myocytes that were cut transversely and had both a visible nucleus and an unbroken cellular membrane. At least 100 cells were counted per heart, and the average was used for analysis. The percent area of fibrosis in the left ventricle at the papillary muscle level in the slices stained with Azan Mallory stain at ×100 magnification was determined by previously described computer analysis method (11).

Quantitative reverse-transcriptase polymerase chain reaction analysis. Quantitative reverse-transcriptase polymerase chain reaction analysis was performed using Prism 7700 Sequence Detector (The Perkin-Elmer Corporation, Foster, California) as previously described (13,14). We measured mRNAs of ACE, AT_1a receptor, prepro endothelin (ET)-1, endothelin-converting enzyme (ECE), ET type A receptor, ET type B receptor and glyceraldehyde-3-phosphate-dehydrogenase. These sequences of all oligonucleotides used as forward primers, reverse primers and detection probes were shown in the previous paper (13). To correct the efficiency of cyclic DNA synthesis, the amounts of mRNAs were divided by the amounts of glyceraldehyde-3-phosphate-dehydrogenase mRNA.

Statistical analysis. Results are expressed as mean values ± SEM. All statistical analyses were performed using a commercially available statistical software (STATVIEW version 4.54, Abacus Concepatients, Berkeley, California). The serial data were analyzed by analysis of variance for repeated measurements. Differences at specific stages among groups were assessed using one-factor analyses of variance and Scheffe's test. A p value of <0.05 was considered statistically significant.

RESULTS

Hemodynamics and heart failure. Aortic pressure was slightly, although statistically significant, decreased in CAND(+) rats at 13 weeks compared with CAND(−) rats (Table 1). The ratio of lung weight to body weight increased, and LV end-diastolic pressure was elevated in most of CAND(−) rats reflecting congestive heart failure at 19 weeks (Table 2). Chronic administration of AT_1R antago-

Table 1. Changes in Echocardiographic Parameters in the Control Rats and Rats of Group CAND(−) and CAND(+)

	SBP (mm Hg)	PWd (mm)	LVDd (mm)	FS (%)	MFS (%)	RWT (%)	LVMI (mg/g)	ESS (10^3 dynes/cm^2)	E/A
Control (n = 8)									
7 weeks	121 ± 3	1.1 ± 0.1	7.3 ± 0.1	41 ± 1	21 ± 1	31 ± 1	2.7 ± 0.1	56 ± 4	1.6 ± 0.1
13 weeks	144 ± 3	1.3 ± 0.1	8.8 ± 0.1	30 ± 2	16 ± 1	29 ± 1	2.2 ± 0.1	107 ± 9	2.4 ± 0.3
19 weeks	146 ± 3	1.5 ± 0.1	8.7 ± 0.2	31 ± 1	14 ± 1	36 ± 2	2.2 ± 0.1	83 ± 5	2.6 ± 0.4
CAND(−) (n = 8)									
7 weeks	126 ± 3	1.1 ± 0.1	7.3 ± 0.1	42 ± 1	22 ± 1	30 ± 1	2.6 ± 0.1	52 ± 5	1.6 ± 0.1
13 weeks	232 ± 2†	2.2 ± 0.1†	7.3 ± 0.3†	41 ± 2†	14 ± 1	61 ± 4†	3.3 ± 0.1†	52 ± 9†	1.1 ± 0.1†
19 weeks	231 ± 2†	2.5 ± 0.2†	8.4 ± 0.2	36 ± 1	15 ± 1	61 ± 5‡	4.4 ± 0.2†	72 ± 6	3.7 ± 0.7
CAND(+) (n = 10)									
7 weeks	122 ± 2	1.1 ± 0.1	7.4 ± 0.1	39 ± 1	22 ± 1	30 ± 1	2.7 ± 0.1	63 ± 3	1.7 ± 0.1
13 weeks	218 ± 4†‡	1.9 ± 0.1†§	8.6 ± 0.2§	29 ± 1§	13 ± 1	44 ± 1†‡	3.1 ± 0.1†	120 ± 11§	0.8 ± 0.1†
19 weeks	220 ± 4†	2.0 ± 0.1*‡	8.7 ± 0.1	35 ± 1	15 ± 1	45 ± 2‡	3.2 ± 0.3†§	94 ± 7	1.4 ± 0.4§
P value by repeated measurements ANOVA									
Main effect									
Group	<0.0001	<0.0001	<0.0001	0.0012	0.70	<0.0001	<0.0001	0.0002	0.0004
Time course	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Interaction	<0.0001	<0.0001	0.0006	0.001	0.27	<0.0001	<0.0001	0.0002	<0.0001

Values are expressed as mean ± SEM. *p < 0.05; †p < 0.01 versus control rats; ‡p < 0.05; §p < 0.01 vs. CAND(−) of same age rats.

ANOVA = analysis of variance; CAND(+) = group treated with candesartan; CAND(−) = placebo group; E/A ratio = the ratio of peak filling velocity at atrial contraction to peak early diastolic filling velocity; ESS = end-systolic wall stress; FS = fractional shortening of LV inner diameter; LV = left ventricular; LVDd = LV end-diastolic dimension; LVMI = ratio of LV mass to body weight; MFS = midwall fractional shortening of LV inner diameter; PWd = LV posterior wall thickness at end-diastole; SBP = systolic blood pressure.

nist prevented the increases. Left ventricular systolic function assessed with midwall fractional shortening was not different among the control, CAND(−) and CAND(+) rats throughout the experiment (Table 1). End-systolic stress increased up to 13 weeks and gradually decreased thereafter in the control rats, and its initial increase was considered an aging process (Table 1). End-systolic stress was significantly lower in CAND(−) rats at 13 weeks compared with the control rats. It gradually increased after 13 weeks and was equal to the level of the control rats at 19 weeks. In CAND(+) rats, there was no decrease in end-systolic stress compared with the control rats at 13 through 19 weeks.

LV geometrical change. Echocardiography determined posterior wall thickness at end-diastole and LVMI increased both in CAND(−) and CAND(+) rats at 13 weeks, and there was no significant difference in LVMI between the two groups (Table 1, Fig. 1). Left ventricle end-diastolic dimension was smaller in CAND(−) rats than it was in the control rats at 13 weeks, and, consequently, relative wall thickness was increased in CAND(−) rats. Angiotensin II type-1 receptor antagonist administration attenuated the increase in relative wall thickness. After 13 weeks CAND(−) rats showed a progressive increase in wall thickness and LVMI, and these changes were attenuated by AT_1R antagonist administration (Table 1, Fig. 1). The data of postmortem LVMI confirmed the echocardiography results (Fig. 2).

Histological study. Myocyte diameter was increased in CAND(−) rats at 19 weeks, and the increase was reduced by AT_1R antagonist administration (Table 2). CAND(−) rats showed perivascular and interstitial fibrosis at 19 weeks (Fig. 3), particularly in the subendocardial portion. Massive fibrosis was not observed in CAND(+) rats. The findings were confirmed by the data of percent area of fibrosis and hydroxyproline content (Table 2).

LV mRNA levels. At 13 weeks LV ACE mRNA levels were slightly, but significantly, higher in the CAND(−)

Table 2. Results of Hemodynamics and Pathology at 19 Weeks

	Control	CAND(−)	CAND(+)	p Value by ANOVA
LV systolic pressure (mm Hg)	149 ± 7	196 ± 4†	218 ± 9†	<0.0001
Lung/wt (mg/g)	3.8 ± 0.1	7.5 ± 1.3†	4.0 ± 0.1‡	0.0023
LVEDP (mm Hg)	9 ± 1	19 ± 2†	7 ± 2§	<0.0001
Tau (ms)	23 ± 2	29 ± 1*	24 ± 1‡	0.0082
Myocyte diameter (μm)	14.0 ± 0.3	17.4 ± 0.4†	14.9 ± 0.3§	<0.0001
Area of fibrosis (%)	2.0 ± 0.4	7.5 ± 1.3†	3.7 ± 0.6§	0.0001
Pro-OH (μmol/g)	2.4 ± 0.2	4.1 ± 0.2†	2.8 ± 0.5‡	0.0003

Values are expressed as mean ± SEM. *p < 0.05; †p < 0.01 versus control group; ‡p < 0.05; §p < 0.01 versus CAND(−) group.

ANOVA = analysis of variance; CAND(+) = group treated with candesartan; CAND(−) = placebo group; lung/wt = ratio of lung weight to body weight; LV = left ventricular; LVEDP = LV end-diastolic pressure; Pro-OH = hydroxyproline concentration; Tau = time constant of left ventricular isovolumic pressure fall.

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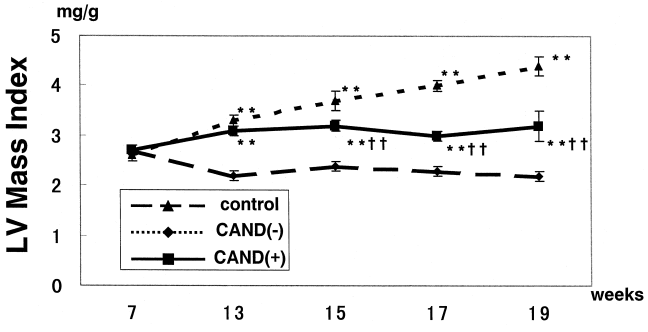

Figure 1. Serial changes in LV mass index in control, CAND(−) and CAND(+) rats. p value of analysis of variance main effects: group, <0.0001; time course, <0.0001. p value of analysis of variance interaction, <0.0001. **p < 0.01 versus control group; †† p < 0.01 versus CAND(−) group at same time point. Values are means ± SEM. LV = left ventricular.

group than they were in the control group and were similar between CAND(−) and CAND(+) rats (p < 0.0001). At 19 weeks LV ACE mRNA level was increased in CAND(−) compared with control and was significantly attenuated in CAND(+) (p < 0.0001). Left ventricular AT_1a mRNA level was not different between any of the three groups at 13 or 19 weeks (p = 0.27 and 0.17, respectively) (Fig. 4).

The prepro ET-1 mRNA level was not different among the three groups at 13 weeks (p = 0.044). At 19 weeks prepro ET-1 RNA levels were significantly elevated in CAND(−) (p < 0.0001). This elevation was significantly attenuated in the CAND(+) group. Nor were ECE, ET type A and ET type B receptor mRNA levels different among the three groups at 13 weeks (p = 0.17, 0.11 and 0.70, respectively). At 19 weeks these mRNA levels were increased in CAND(−) rats, and the induction was attenuated by AT_1R antagonist administration (p = 0.0099, 0.0007 and <0.0001, respectively) (Fig. 5).

AT_1R antagonist versus ACE inhibitor. Renin-angiotensin system activation may be blocked at different levels and result in different outcomes (15). We studied an additional 15 rats in our model treated with enalapril (5 mg/kg/day) from 8 weeks to 19 weeks. Effects of ACE inhibition were comparable with those of candesartan in this study (Table 3).

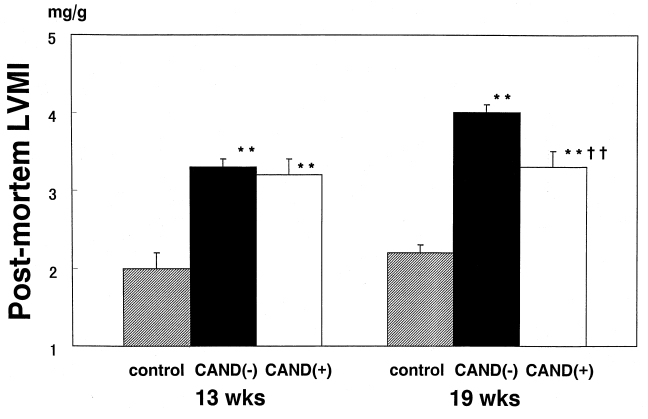

Figure 2. Postmortem LVMI at 13 and 19 weeks in control, CAND(−) and CAND(+) rats. **p < 0.01 vs. control group; ††p < 0.01 vs. CAND(−) group. p value of analysis of variance main effects: 13 weeks: <0.0001; 19 weeks: <0.0001. Values are means ± SEM. LVMI = left ventricular mass index.

DISCUSSION

In this study, administration of the AT_1R antagonist, candesartan, did not suppress initial development of LV hypertrophy although it attenuated the geometrical changes in LV chamber dimensions at 13 weeks. However, further development of hypertrophy and interstitial fibrosis was suppressed after 13 weeks by candesartan, which likely contributed to the prevention of transition to heart failure in hypertensive rats. These results indicate that RAS signaling through AT_1R may be dispensable for initial hypertension-induced adaptive LV hypertrophy in this model. In contrast, AT_1R signaling appears to be involved in the maintenance of LV hypertrophy and closely linked with the transition to heart failure.

RAS-dependent versus RAS-independent hypertrophy. Left ventricular hypertrophy developed from 7 to 13 weeks both in CAND(−) and CAND(+) rats to the same degree, indicating that LV hypertrophy at this stage occurs independent of RAS activation. This result is supported by the data of recent experimental studies. Cardiac hypertrophy was induced by pressure overload in AT_1a knockout mice (10), and extracellular signal-regulated protein kinases were strongly activated in myocytes of AT_1a knockout mice (16). Left ventricular hypertrophy was suppressed by the administration of tyrosine kinase inhibitor and selective inhibitors of epidermal growth factor receptor in AT_1a knockout mice (16). Activation of signal-regulated protein kinase was observed also in wild type myocytes, and mechanical stretch may likely evoke hypertrophic responses in cardiac myocytes lacking in the AT_1 signaling pathway, possibly through tyrosine kinase activation. Another in vitro study showed that LV c-fos and c-myc mRNA levels and the rate of phenylalanine incorporation into cardiac proteins were increased in isolated perfused adult rat hearts subjected to increased systolic load and that AT_1R blockade with losartan did not prevent these hypertrophic responses (17). Thus, there is considerable evidence indicating independence of development of LV hypertrophy from RAS activation. However, previous studies failed to characterize the difference between RAS-dependent and RAS-independent LV hypertrophies.

Characteristics of RAS-dependent hypertrophy. First, RAS activation may be involved in concentric geometrical LV chamber remodeling at 13 weeks old. Relative wall thickness was greater in CAND(−) rats than it was in the control rats, and the increase was attenuated by chronic AT_1R antagonist administration without any effect on LVMI. The difference in chamber size accounts for subnormal systolic wall stress in CAND(−) rats and for normal systolic wall stress in CAND(+) rats. The significant

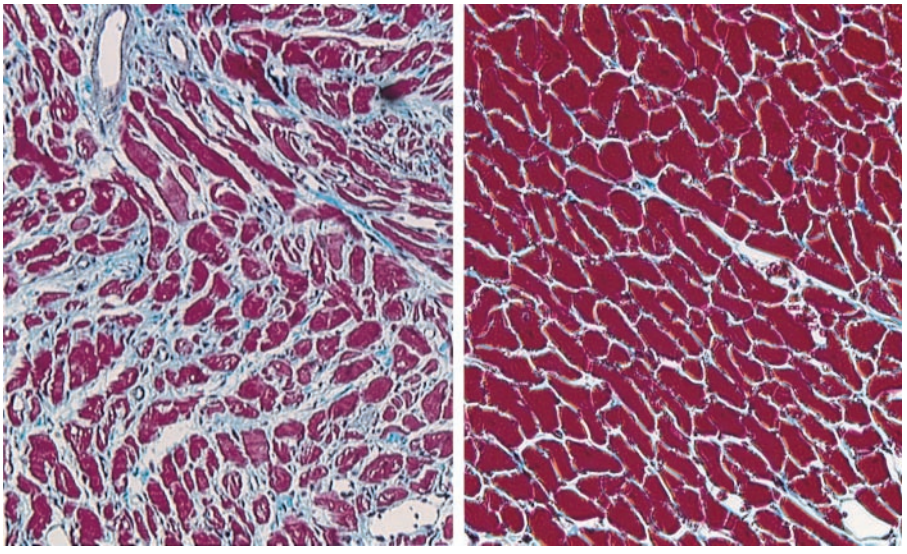

Figure 3. Photomicrographs of Azan Mallory staining of left ventricle in a CAND(−) rat **(left panel)** and a CAND(+) rat **(right panel)** (×40). Interstitial and perivascular fibrosis is evident only in CAND(−) rats.

elevation of ACE mRNA at 13 weeks in CAND(−) rats may support the idea that RAS activation is already, although partially, involved in compensatory hypertrophy in CAND(−) rats. Sugishita et al. (18) showed in hypertensive patients that regression of LV hypertrophy was not achieved with the administration of the antihypertensives, such as Ca channel antagonist and diuretics, in the condition of subnormal systolic wall stress. They speculate the involvement of neurohumoral factors in LV geometrical changes in such patients. Our data may explain the failure to obtain regression of LV hypertrophy with the use of Ca channel antagonist or diuretics in their patients. The RAS may have been abnormally activated in their patients. Future studies are needed both from the molecular and clinical viewpoints to disclose the relation between RAS activation and geometrical remodeling.

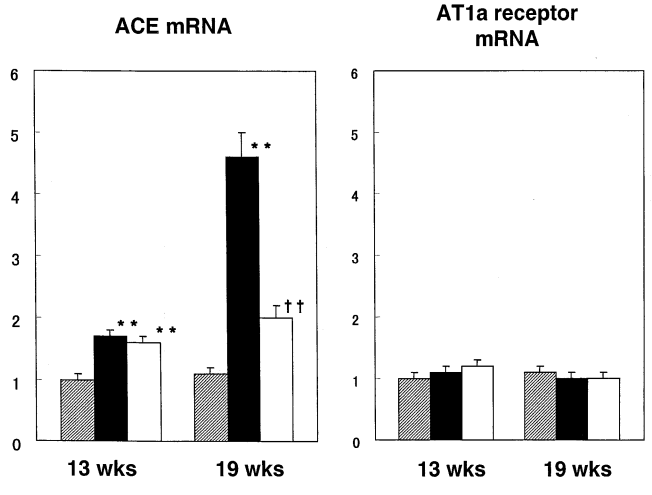

Figure 4. The mRNA levels of ACE, AT1a receptor at 13 and 19 weeks old. Each mRNA level was corrected for an mRNA level of glyceraldehyde-3-phosphate-dehydrogenase and was then normalized to a mean value of age-matched control group, respectively. **$p < 0.01$ versus control group; ††$p < 0.01$ versus CAND(−) group. Values are means ± SEM. **Hatched bar**= control; **solid bar**= CAND(−); **open bar**= CAND(+). ACE = angiotensin-converting enzyme; mRNA = messenger RNA.

Second, we showed that RAS activation and signaling through the AT_1R is associated with excessive hypertrophy and a transition to heart failure. After 13 weeks, LVMI in CAND(−) rats progressively increased in spite of lower than or equal to normal systolic wall stress up to 19 weeks. Although AT_1R antagonist administration did not affect LVMI at 13 weeks old, it suppressed the progressive development of additional LV hypertrophy thereafter. These results suggest that LV hypertrophy in CAND(−) rats after 13 weeks may be related to RAS activation. This idea is supported by the data of ACE mRNA levels, which were elevated in CAND(−) rats and were reduced by AT_1R antagonist administration at 19 weeks. A recent in vitro study showed that AT_1R antagonist, losartan, inhibited AT II-induced upregulation of ACE mRNA in neonatal cardiac myocytes (19).

In addition, excessive hypertrophy was accompanied by interstitial fibrosis in this study. We previously reported that interstitial fibrosis also occurred after 13 weeks in the CAND(−) rats (13). These structural changes may well contribute to LV dysfunction, particularly to diastolic dysfunction, because the effects of fibrosis on LV diastolic properties are well known (20,21). In fact, although midwall fractional shortening was not different among the three groups, LV diastolic filling pattern was characterized by high E and low A waves (restrictive pattern) at 19 weeks in the CAND(−) rats, suggesting the presence of advanced LV diastolic dysfunction without severe systolic dysfunction (22). This interpretation was supported by the abnormal values of LV high fidelity pressure-derived parameters, that is, LV end-diastolic pressure and a reference of LV relaxation, Tau. Thus, both excessive hypertrophy and massive

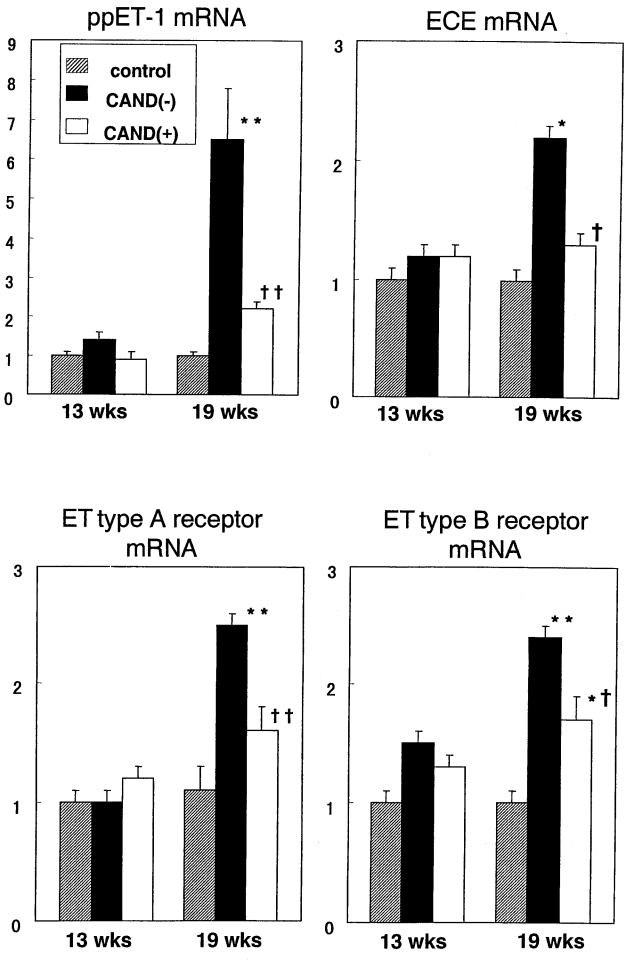

Figure 5. The mRNA levels of ppET-1, ECE, ET type A receptor and ET type B receptor at 13 and 19 weeks. Each mRNA level was corrected for an mRNA level of glyceraldehyde-3-phosphate-dehydrogenase and was then normalized to a mean value of the age-matched control group, respectively. $^{*}p < 0.05$; $^{**}p < 0.01$ versus control group; †$p < 0.05$; ††$p < 0.01$ versus CAND(−) group. Values are means ± SEM. ECE = endothelin-converting enzyme; ET = endothelin; ppET-1 = prepro endothelin-1.

interstitial fibrosis are characteristics of RAS-dependent hypertrophy, which is likely to contribute to the progression of LV diastolic dysfunction and, hence, to the transition to heart failure, particularly diastolic heart failure.

Interaction with ET pathway in RAS-dependent hypertrophy. Renin-angiotensin system activation has been considered to interact with other neurohumoral factors, particularly ET-1. Endothelin-1 as well as AT II are G-protein-coupled receptor agonists that induce hypertrophy and interstitial fibrosis (23,24). In in vitro studies, AT II stimulated cultured bovine endothelial cells to release ET-1 to activate the expression of prepro endothelin-1 mRNA (25). Further, endogenous ET-1, locally generated and secreted by cardiomyocytes, facilitates AT II-induced cardiac hypertrophy via autocrine/paracrine fashion (26). Prepro endothelin-1 mRNA and ECE-1 mRNA levels were enhanced with upregulation of ET type A and ET type B receptors mRNAs in CAND(−) rats at 19 weeks old. Chronic AT_1R blockade modulated the expression of prepro endothelin-1 mRNA and attenuated the upregulation of ET receptors at failing stage. These results suggest that RAS activation and signaling through the AT_1R contribute to the development of heart failure at least partially via the activation of the ET pathway in vivo. Further studies using ET receptor blocker may help in understanding the interaction between the RAS and the ET pathway in vivo in the pathology of heart failure because this is only a model of hypertrophy and heart failure, and the findings may be somewhat different in other models or in humans.

Table 3. Effects of Candesartan and Enalapril on Geometry, Hemodynamics and Pathology at 19 Weeks

	Candesartan (n = 10)	Enalapril (n = 15)	
Echocardiographic parameters			
PWd (mm)	−0.5 ± 0.1	−0.5 ± 0.1	NS
LVDd (mm)	0.3 ± 0.1	0.3 ± 0.1	NS
FS (%)	−1.4 ± 1.6	−1.0 ± 1.5	NS
MFS (%)	−0.3 ± 0.6	0.5 ± 0.8	NS
RWT (%)	−16 ± 2	−16 ± 2	NS
LVMI (mg/g)	−1.2 ± 0.3	−1.2 ± 0.1	NS
ESS (10^3 dynes/cm^2)	22 ± 7	17 ± 7	NS
E/A	−2.3 ± 0.4	−2.2 ± 0.4	NS
Hemodynamic parameters			
LV systolic pressure (mm Hg)	22 ± 9	35 ± 7	NS
LVEDP (mm Hg)	−12 ± 1	−8 ± 2	NS
Tau (ms)	−5 ± 1	−4 ± 1	NS
Pathological parameters			
LVMI (mg/g)	−0.7 ± 0.2	−0.8 ± 0.1	NS
Myocardial diameter (μm)	−2.4 ± 0.3	−2.8 ± 0.3	NS
Area of fibrosis (%)	−4.0 ± 0.5	−5.5 ± 0.2	p = 0.0083
Pro-OH (μmol/g)	−1.1 ± 0.3	−0.7 ± 0.3	NS

Effects of ACE inhibitor were studied in the same model by the administration of enalapril of 5 mg/kg/day from 8 to 19 weeks. The value was determined by subtracting the untreated data from the treated data. Values are expressed as mean ± SEM.

E/A ratio = the ratio of peak filling velocity at atrial contraction to peak early diastolic filling velocity; ESS = end-systolic wall stress; FS = fractional shortening of LV inner diameter; LV = left ventricular; LVDd = LV end-diastolic dimension; LVEDP = LV end-diastolic pressure; LVMI = ratio of LV mass to body weight; MFS = midwall fractional shortening of LV inner diameter; Pro-OH = hydroxyproline concentration; PWd = LV posterior wall thickness at end-diastole; RWT = relative wall thickness.

Conclusions. Chronic AT_1R blockade with candesartan at a subdepressor dose-attenuated concentric geometrical changes accounting for subnormal end-systolic wall stress at the compensatory stage but did not suppress compensatory hypertrophy. However, excessive LV hypertrophy and interstitial fibrosis were prevented in the advanced stage by AT_1R antagonist administration in association with attenuated activation of the ET pathway. These results demonstrate that initial adaptive LV hypertrophy develops independently from RAS activation and that RAS activation and AT_1R/ET system signaling are closely linked to the transition to heart failure. Thus, the blockade of RAS by AT_1R blockade may be effective to inhibit the maladaptive components of LV hypertrophy that contribute to the development of failure.

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