Long-Term Effects of Delapril Hydrochloride on Procollagen Type III Amino-Terminal Peptide, Left Ventricular Mass and Left Ventricular Function in Hypertensive Patients

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The long-term effect of delapril hydrochloride, a non-sulfhydryl angiotensin converting enzyme inhibitor, on serum concentrations of procollagen type III amino-terminal peptide (PIIIP) and left ventricular mass (LVM) and function were investigated in 15 hypertensive patients. Patients were treated with delapril hydrochloride 30 mg/day po for 12 months. Blood samples and an echocardiogram were obtained before treatment and after 6 and 12 months of treatment. Blood pressure, PIIIP, and LVM significantly decreased associated with an increase in left ventricular fractional shortening and mean systolic and diastolic posterior wall velocity at 6 and 12 months of treatment. Positive correlations between PIIIP and LVM ($r=0.49$, $p<0.005$) and negative correlations between PIIIP and left ventricular fractional shortening ($r=-0.31$, $p<0.05$) were found. Delapril hydrochloride reduced PIIIP and LVM and improved cardiac function in hypertensive patients. (*Jpn Circ J* 1998; 62: 900–902)

Key Words: Delapril hydrochloride; Left ventricular mass; Procollagen type III amino-terminal peptide

Left ventricular hypertrophy (LVH) is a major hazardous cardiovascular complication in patients with hypertension.^{1,2} The development of LVH depends not only on the renin-angiotensin system generating angiotensin II,³ but also on the mechanical stress, which activates the protein kinase cascade of phosphorylation in cardiac myocytes.⁴ The goal of antihypertensive therapy should be prevention and regression of LVH. It is reported that angiotensin converting enzyme (ACE) inhibitors are more effective than β -blockers, calcium antagonists, and diuretics in reducing left ventricular mass (LVM).⁵ We therefore assessed the clinical effect of delapril hydrochloride (an ACE inhibitor)⁶ from the viewpoint of echocardiographically determined cardiac function and LVH, as well as the serum concentrations of procollagen type III amino-terminal peptide (PIIIP) as reflected in the production of collagen type III.

Methods

Patient Selection

Fifteen hypertensive patients with LVH (10 men and 5 women, mean age 77.2 ± 7.5 years) were entered in the study. Patients were previously untreated with hypertensive drugs or had discontinued the use of these drugs for at least 4 weeks prior. Patients with hyperglycemia, liver dysfunction or pulmonary fibrosis were excluded. The 2 criteria of LVH were an interventricular septal thickness (IVST) of more than 10 mm and left ventricular posterior wall thickness (LVPWT) of more than 10 mm as measured by echocardiography. All study patients complied with these criteria.

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Study Protocol

All patients were treated with an ACE inhibitor (delapril hydrochloride, 30 mg/day po) for 12 months. To evaluate the clinical effect of delapril hydrochloride, blood pressure (BP) and heart rate were measured in a supine position before administration of delapril hydrochloride and then after 6 and 12 months of administration. Blood samples were obtained from each patient. Plasma renin activity (PRA) and concentrations of serum atrial natriuretic peptide (ANP) and serum PIIIP were measured by radioimmunoassay before administration and again after 6 and 12 months of taking the drug. The normal serum concentration of PIIIP, which was 0.40 ± 0.13 U/ml ($0.25-0.70$ U/ml), was obtained from 24 normal volunteers (aged 20–80 years).

Table 1 Changes in Clinical Data Before and After Treatment With Delapril Hydrochloride

	Before	After 6 months	After 12 months
Systolic BP (mmHg)	167.5 $\pm$ 11.2	138.3 $\pm$ 17.5***	129.4 $\pm$ 17.4***
Diastolic BP (mmHg)	91.7 $\pm$ 8.7	75.5 $\pm$ 8.0***	71.9 $\pm$ 9.4***
Heart rate (beats/min)	80.0 $\pm$ 10.7	75.9 $\pm$ 12.3	79.3 $\pm$ 10.3
IVST (mm)	17.1 $\pm$ 4.5	13.9 $\pm$ 2.7**	13.5 $\pm$ 3.1**
LVPWT (mm)	11.6 $\pm$ 1.6	10.6 $\pm$ 1.5**	9.6 $\pm$ 1.5**
LVM (g)	336.4 $\pm$ 92.3	264.4 $\pm$ 60.3*	213.3 $\pm$ 62.1***†
LVFS (%)	29.9 $\pm$ 7.2	34.0 $\pm$ 7.6**	39.9 $\pm$ 12.8*†
meanVcf (circ/sec)	1.18 $\pm$ 0.34	1.22 $\pm$ 0.34	1.42 $\pm$ 0.59
MPWVs (mm/sec)	42.8 $\pm$ 13.9	52.3 $\pm$ 14.7	58.4 $\pm$ 16.6*
MPWVd (mm/sec)	63.8 $\pm$ 22.0	69.0 $\pm$ 22.4	81.3 $\pm$ 19.4*†
PIIIP (U/ml)	1.05 $\pm$ 0.26	0.85 $\pm$ 0.21**	0.80 $\pm$ 0.22**
PRA (ng ml ⁻¹ h ⁻¹)	2.09 $\pm$ 1.60	2.40 $\pm$ 1.97	1.92 $\pm$ 1.78
ANP (pg/ml)	24.7 $\pm$ 20.3	31.7 $\pm$ 17.3	21.0 $\pm$ 11.7

IVST, intraventricular septal thickness; LVPWT, LV posterior wall thickness; LVM, left ventricular mass; LVFS, LV fractional shortening; MPWVs, mean systolic posterior wall velocity; MPWVd, mean diastolic PWV; PIIIP, procollagen type III amino-terminal peptide; PRA, plasma renin activity; ANP, atrial natriuretic peptide.

* $p<0.05$, ** $p<0.01$, *** $p<0.001$, † $p<0.05$.

Fig 1. Relationship between serum procollagen type III amino-terminal peptide (PIIIP) concentrations and left ventricular mass (LVM) or left ventricular fractional shortening (LVFS).

M-mode and 2-dimensional echocardiograms were recorded in each patient. Left ventricular fractional shortening (LVFS) and mean Vcf were calculated. LVM was calculated using the Devereux formula.⁷ Mean systolic posterior wall velocity (MPWVs) and mean diastolic posterior wall velocity (MPWVd) were calculated by the methods of Fogelman et al⁸ and Yoshikawa et al⁹.

Statistical Analysis

Differences between the mean values obtained before and after the administration of delapril hydrochloride were analyzed using paired *t* tests, and $p < 0.05$ was considered statistically significant. The correlation between distributed variables was tested by univariate analysis. Data are expressed as the mean $\pm$ standard deviation.

Results

Hemodynamic Effects

Systolic BP significantly decreased from 167.5 ± 11.2 mmHg before treatment to 138.3 ± 17.5 mmHg at 6 months of treatment ($p < 0.001$) and to 129.4 ± 17.4 mmHg at 12 months of treatment ($p < 0.001$). Diastolic BP also significantly decreased. No significant change was observed in heart rate before and after administration of delapril hydrochloride (Table 1). Systolic and diastolic BP achieved the therapeutic goal after the 6-month period of treatment.

Parameters in the Echocardiogram

IVST and LVPWT significantly diminished from 17.1 ± 4.5 mm and 11.6 ± 1.6 mm before treatment to 13.9 ± 2.7 mm and 10.6 ± 1.5 mm at 6 months of treatment ($p < 0.01$ and $p < 0.01$, respectively). Twelve months after treatment, IVST and LVPWT had both significantly diminished. LVM was significantly decreased [before treatment, 336.4 ± 92.3 g; at 6 months, 264.4 ± 60.3 g ($p < 0.05$); and at 12 months, 213.3 ± 62.1 g ($p < 0.001$)]. LVFS significantly increased from $29.9 \pm 7.2\%$ before treatment to $34.0 \pm 7.6\%$ at 6 months ($p < 0.01$) and to $39.9 \pm 12.8\%$ at 12 months ($p < 0.05$). The mean Vcf did not change. MPWVs and MPWVd were significantly increased from 42.8 ± 13.9

mm/s and 63.8 ± 22.0 mm/s to 58.4 ± 16.6 mm/s ($p < 0.05$) and 81.3 ± 19.4 mm/s ($p < 0.05$) at 12 months, respectively. In all patients LVH regressed with an improvement in cardiac function and left ventricular wall motion after treatment with delapril hydrochloride (Table 1).

Biochemical Variables

Serum PIIIP concentrations were significantly diminished from 1.05 ± 0.26 U/ml before treatment to 0.85 ± 0.21 U/ml ($p < 0.01$) at 6 months of treatment with delapril hydrochloride and to 0.80 ± 0.22 U/ml ($p < 0.01$) at 12 months. Fig 1 shows the relationship between serum PIIIP concentrations and LVM or LVFS. There were significant positive correlations between PIIIP and LVM ($r = 0.49$, $p < 0.005$), and negative correlations between PIIIP and LVFS ($r = -0.31$, $p < 0.05$). No significant changes in either PRA or ANP were measured before or after treatment (Table 1).

Discussion

It has been reported that serum PIIIP is a useful marker of fibrogenesis.¹⁰ The major components of the cardiac interstitium are fibrillar collagens type I and III.^{11,12} The fibrillar collagens form a network of structural continuum in the myocardium. PIIIP is an extension peptide of the procollagen type III during the conversion of procollagen type III to collagen type III. Serum concentrations of PIIIP (1.05 ± 0.26 U/ml) in hypertensive patients in this study were higher compared with the normal serum range of 0.25–0.7 U/ml. These elevations of serum PIIIP appear to reflect an increase in collagen type III production in the hypertensive heart. Type I and III collagen gene expression is increased during the early evolutionary phase of hypertrophy.¹³ Further experiments show that TGF- β 1 in the myocardium may play an important role in the regulation of collagen biosynthesis and myocardial fibrosis.^{14,15} The half-life of collagen decreased to 17 days in the hypertrophic myocardium compared with that of 80–120 days in the normal myocardium. Furthermore, fibroblasts and fibroblast proliferation may also contribute to an elevation in collagen synthesis. This remodeling of collagen structure

has been reported in hypertension,^{16,17} heart failure,¹⁸ stunned myocardium¹⁹ and acute myocardial infarction.²⁰ In the present study, we excluded hypertensive patients accompanied by liver disease,²¹ lung disease,²² and diabetes²³ because they have other causes of the elevation of PIIIP.

ANP is mainly released by overloaded atria. During chronic pressure and volume overload the ventricular myocardium may produce ANP in hypertension. In the present study ANP did not change after improvement of LVH by the ACE inhibitor. The changes in plasma ANP were blunted in this study's patients, which may have contributed to the attenuated natriuretic response. Neurohormonal compensation may occur during long-term administration of delapril hydrochloride. The vascular ACE activity is higher in hypertension. In this study the inhibition of vascular ACE activity by delapril hydrochloride seemed to bring about a reduction in BP, irrespective of the circulating renin-angiotensin system.

Delapril hydrochloride is a non-sulfhydryl ACE inhibitor that has a potent and long-lasting inhibitory effect on plasma and tissue angiotensin converting enzyme.²⁴ A reduction in BP and LVH was reported in animals with systemic hypertension^{25,26} and in humans with arterial hypertension.^{27,28} Our data suggest that treatment with delapril hydrochloride normalizes serum PIIIP and LVH in hypertensive patients. A reduction in LVH may be produced by interventricular septum and left ventricular posterior wall thinning caused by a decrease in myocardial collagen. Angiotensin II increases collagen synthesis and inhibits collagenase. Therefore, inhibition of angiotensin II generation with delapril hydrochloride actively removes collagen from the cardiac interstitium. Myocardial stiffness may concurrently improve during the treatment. In this study LVFS was significantly increased at 6 months of treatment, and MPWVs and MPWVd were significantly increased at 12 months of treatment as compared with before treatment. This increase of left ventricular wall motion implies an improvement of systolic and diastolic function. The restoration of the fibrillar collagen network in the myocardium accounts for an improvement in left ventricular dysfunction.

In summary, an increase in serum concentration of PIIIP indicates that collagen type III synthesis increases in hypertensive patients. Delapril hydrochloride significantly reduced serum PIIIP, BP and LVM with a significant improvement in left ventricular function.

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