Effect of Antihypertensive Agents on the Regression of Hypertensive Cardiac Hypertrophy —— Comparison of Angiotensin converting enzyme(ACE) inhibitor and Ca^{++} blocking agent ——

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ABSTRACT. A study was conducted to examine differences in the effects of an angiotensin converting enzyme (ACE) inhibitor (cilazapril) and a Ca^{++} blocking agent (nifedipine) on regression of hypertensive left ventricular hypertrophy. Effects of these drugs on the regression of cardiac hypertrophy were examined at one year after administration in 13 patients (7 patients: cilazapril group, 6 patients: nifedipine group) by evaluating findings obtained from ultrasonic echocardiograms and electrocardiograms. A similar degree of reduction in blood pressure was obtained in both groups. The thickness of the interventricular septum (IVS), thickness of the posterior wall (PW) or SV_1+RV_5 (ECG) was, to a similar extent, different significantly between both groups. However, the left ventricular mass index (LVM) decreased more remarkably in the cilazapril group ($184.5\pm30.9\rightarrow147.6\pm25.1$, $P<0.01$) as compared with that of the nifedipine group ($172.7\pm34.4\rightarrow159.0\pm28.3$, $P<0.05$). In conclusion, this study presents the possibility that cilazapril may be superior to nifedipine in its effects on the regression of left vetricular hypertrophy.

Key words: hypertensive left ventricular hypertrophy — ACE inhibitor — Ca^{++} antagonist — ultrasonic echocardiography.

Left ventricular hypertrophy accompanied by hypertension has been considered to be induced by adjustment to a chronic elevated level of afterload. However, recent studies have revealed that left ventricular hypertrophy is not always a favorable adjustment. It may also be a harmful reaction that increases the risk of cardiovascular complications. Therefore, regression of cardiac hypertrophy is becoming one of the targets of the therapy of hypertension.[1,2] Administration of antihypertensives has been shown to have an effect on the regression of cardiac hypertrophy, but the degree of regression depends on the characteristics of antihypertensives.[3-5] Ca^{++} blocking agent and angiotensin converting enzyme (ACE) inhibitors, which are used frequently in recent years, are known to have different effects on hemodynamic factors, represented by

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pressure load as a cause of cardiac hypertrophy, and on humoral factors, mainly the renin and sympathetic nerve systems.[6-9] The difference between these drugs in their effect on the regression of cardiac hypertrophy would seem to be an important problem in therapy of hypertension.[3]

Thus, the present study compared the effects on the regression of left ventricular hypertrophy between cilazapril (an ACE inhibitor) and nifedipine (a Ca^{++} blocking agent), which exhibit different functional mechanisms against hypertensive hypertrophy.

SUBJECTS

Hypertensive patients met the following criteria.

(1) Blood pressure: Blood pressure must always be either above 160 mmHg (systolic) or above 95 mmHg (diastoic) at two or more different measuring timepoints. The change in blood pressure must not exceed 20 mmHg (systolic) or 10 mmHg (diastolic).
(2) Severity: According to the WHO disease classification, the subjects in the Stage II or III without severe complications were selected.
(3) Age and sex: 30-69 years, male or female.
(4) Left ventricular hypertrophy: ECG findings ($SV_1+RV_5 \geq 35$ mm during the observation period) and UCG findings (thickness of IVS or PW $\geq$ 12 mm in a clear ultrasonic cardiogram) were adopted for evaluation of left ventricular hypertrophy.

Patients were randomly divided into the following two groups and the effects of cilazapril and nifedipine on blood pressure and cardiac hypertrophy were examined before and after administration of the drugs. No significant differences were seen in clinical characteristics (age, blood pressure, heart rate,

TABLE 1. Effects of cilazapril and nifedipine on hemodynamics and left ventricular thickness.

	Cilazapril group		Nifedipine group	
Number of patient	7		6	
Sex (M : F)	5 : 2		4 : 2	
Age	52.3±10.7		49.4±7.9	
	Basal	12 Months	Basal	12 Months
SBP	164.3±11.7	148.8±14.2*	146.7±15.2	126.3±11.4*
DBP	91.2±13.5	87.4±13.3	91.7±11.1	82.0± 8.4
mBP	125.1±17.9	108.5±10.9*	119.3±11.6	100.7± 8.2*
HR	66.2± 1.7	65.6± 2.1	66.3± 0.8	66.7±1.03
SV_1+RV_5	38.1±12.2	36.5±10.9	36.7±20.4	35.3±26.1
IVS	14.7± 2.9	12.6± 4.4**	15.1± 3.7	11.8± 2.8*
PW	14.1± 2.7	12.5± 5.7*	15.1± 3.7	14.0± 3.2
LVM	184.5±30.9	147.6±25.1**	172.7±34.4	159.0±28.3*
⊿LVM		−36.8±26.9†		−13.8±30.3
%FS	30.5± 4.3	31.1± 6.8	27.1± 5.5	30.8±11.7
A/E	1.63±0.44	1.44±0.36	1.3± 0.3	0.9± 0.2*

Values are shown as mean±S.D. *p<0.05, **P<0.01, versus basal data.
†: P<0.01, versus Nifedipine group.

ECG findings, and UCG indices) between the groups before administration of the drug (Table 1).

(1) Cilazapril group: 7 patients (5 male), mean age 52.3 years
Cilazapril 1-2 mg was administered once a day.

(2) Nifedipine group: 6 patients (4 male), mean age 49.4 years
Nifedipine 10-20 mg was administered twice a day.

In both groups, administration of any other drugs which were considered to have any influence on blood pressure was prohibited. The administration period was at least one year.

ITEMS MEASURED

1) Systolic blood pressure, diastolic blood pressure, mean blood pressure, and heart rate.
2) Echocardiogram (M-mode): IVS (interventricular septum), PW (thickness of posterior wall), %FS (% rate of shortening of left ventricular dimension), A/E (ratio of A wave to E wave measured by the pulsed Doppler method during the left ventricular inflow period), and LVM (truncated ellipsoid method).
3) ECG: SV_1+RV_5
Statistical analysis was performed by a paired t test and $P<0.05$ was considered to be significant.

RESULTS

(1) Cilazapril group: Although systolic blood pressure and mean blood pressure decreased significantly, diastolic blood pressure and heart rate remained unchanged. The degree of reduction in blood pressure was similar to that in the nifedipine group. No significant difference was seen in ECG (SV_1+RV_5) between both groups. In UCG findings, no significant differences were seen in A/E and %FS between both groups. Wall thickness (LVM, IVS, and PW) showed significant regression in both groups after administration of drug (Table 1, Figures 1 and 2). A

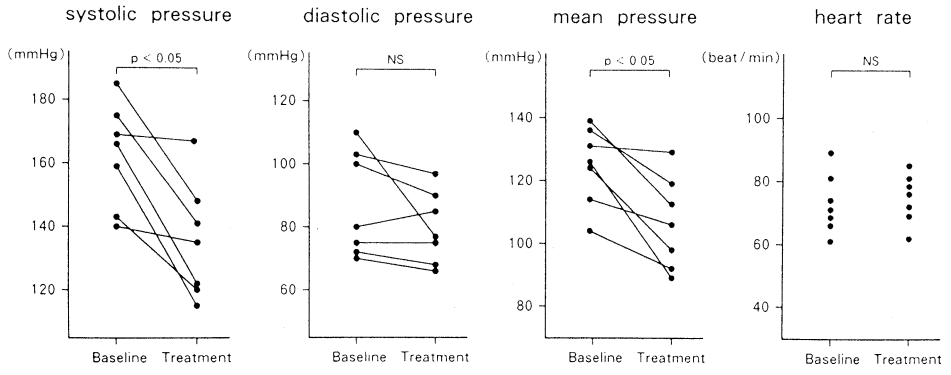

Fig 1. Effects of cilazapril on systolic pressure, diastolic pressure, mean pressure and heart rate. Systolic pressure and mean pressure decreased significantly ($P<0.05$), but diastolic pressure and heart rate remained unchanged.

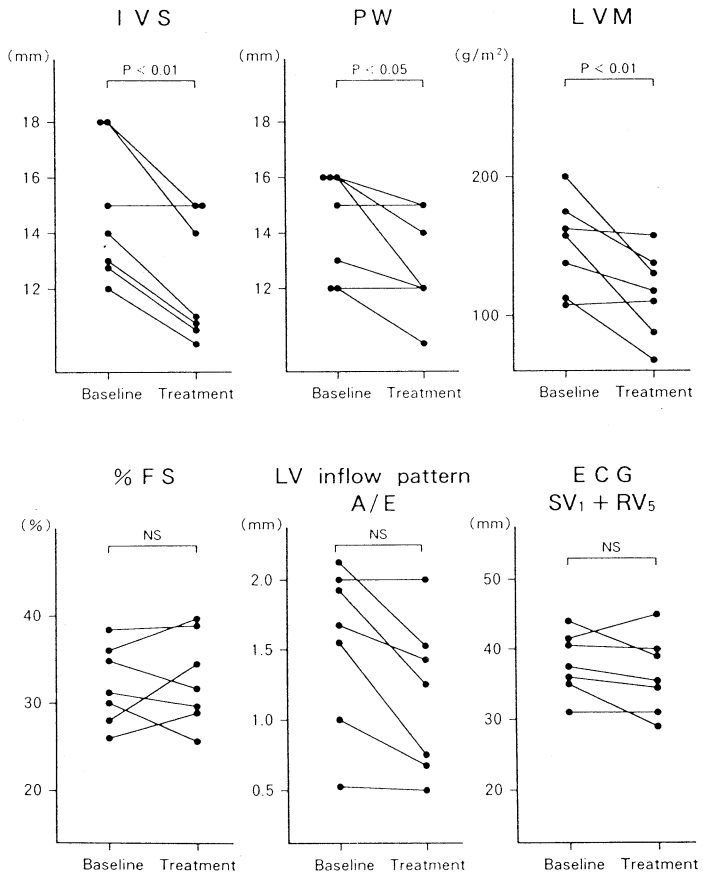

Fig 2. Changes in wall thickness of the interventircular septum (IVS), posterior wall (PW), left ventricular mass index (LVM), % fractional shortening (%FS), and left ventricular inflow pattern (A/E) in ultrasonic echocardiography and SV_1+RV_5 in 12 lead electrocardiography after 12 months of treatment with cilazapril. No significant changes were seen in A/E, %FS and SV_1+RV_5. But IVS, PW and LVM showed significant regression. A larger significant difference in LVM was seen in comparison with the nifedipine group.

greater difference was seen in LVM in comparison with the nifedipine group ($P<0.01$, Table 1). In M mode echocardiography cilazapril showed a regression of hypertrophy (IVS and PW) at one year after the administration (Fig 3).

(2) Nifedipine group: Although systolic blood pressure and mean blood pressure decreased significantly, diastolic blood pressure and heart rate remained unchanged. No significant change was seen in ECG (SV_1+RV_5) after administration of nifedipine. As for UCG, A/E decreased significantly, but %FS did not change. Although a regression was seen in the thickness of LVM and IVS, the thickness of PW did not change after nifedipine (Table 1, Figures 4 and 5).

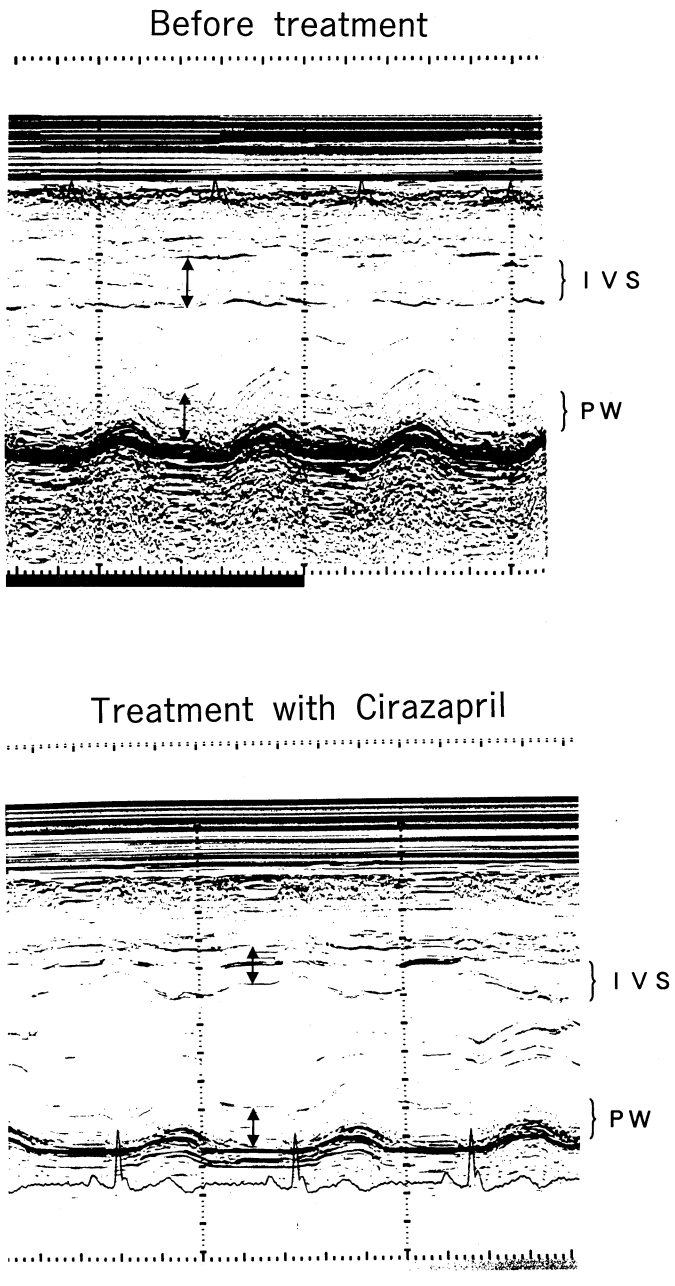

Fig 3. M mode echocardiography after treatment with cilazapril shows regression of thickness of the interventricular septum (IVS) and posterior wall (PW).

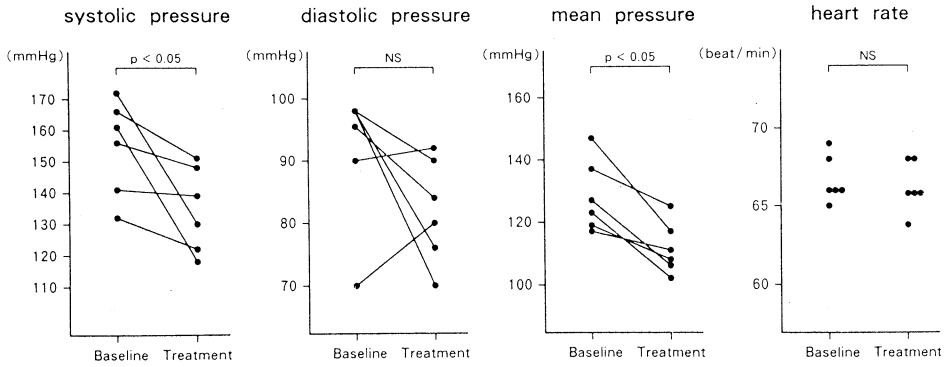

Fig 4. Effect of nifedipine on systolic pressure, diastolic pressure, mean pressure and heart rate. Systolic pressure and mean pressure decreased significantly ($P<0.05$), but diastolic pressure and heart rate remained unchanged.

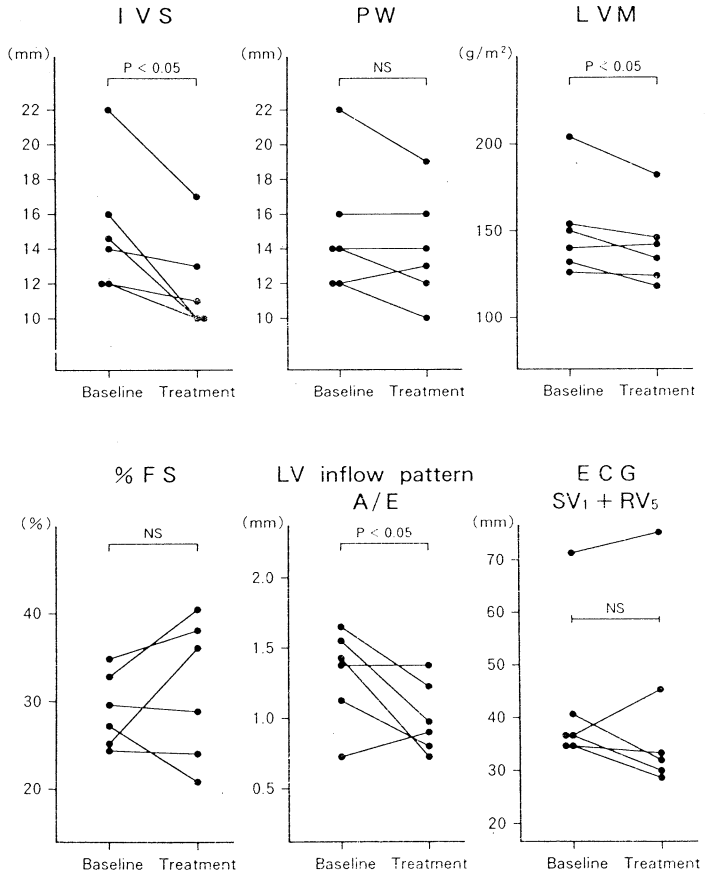

Fig 5. Changes in wall thickness of the interventricular septum (IVS), posterior wall (PW), left ventricular mass index (LVM), % fractional shortening (%FS), left ventricular inflow pattern (A/E) in ultrasonic echocardiography and SV_1+RV_5 in 12 lead electrocardiography after 12 months of treatment with nifedipine. No significant changes were seen in %FS and SV_1+RV_5. But IVS, PW and LVM showed significant regression. A/E decreased after treatment.

DISCUSSION

Left ventricular hypertrophy has been shown to be associated with ischemic heart disease, arrhythmia and heart failure and to be a risk factor in independent life prognosis. Therefore, the regression of cardiac hypertrophy must be considered to be one of the main therapeutical targets in the treatment of high blood pressure. However, various reports have shown that the degree of regression of the hypertrophy is not always consistent with that of reduction in blood pressure. Dahlof *et al* compared the degree of reduction in blood pressure observed after administration of ACE inhibitor and Ca^{++} blocking agent with the degree of the regression of cardiac hypertrophy measured by meta analysis, and the ACE inhibitor had a greater effect on the regression even though reduction in blood pressure was similar.[3] A single and a long-term administration of antihypertensives as first choice showed no relationship between the effect on blood pressure and the hypertrophy. These findings indicate that non-mechanical factors (the regression effect due to the hypertensive itself) are closely related to the regression process in addition to mechanical ones. However, all these studies were only reconfirming the results obtained from previous studies ; a few prospective studies have been pemformed to see the effect of various antihypertensives on the regression of hypertrophy seen in long-term single administration.

In this study, a similar degree of reduction in blood pressure was observed in both groups (cilazapril and nifedipine) in long-term administation of single drug.

As for the regression of cardiac hypertrophy, similar chages were seen in the left ventricular septum, in posterior wall thickness and in ECG ($SV_1 + RV_5$), but there was a larger degree of regression of LVM in the cilazapril group than in the nifedipine group. Left ventricular systolic function examined using %FS as an index remained unchanged in both groups.

Why did the ACE inhibitor have a superior effect on the regression of left ventricular hypertrophy even though both drugs exhibited an equivalent effect on the reduction of blood pressure ? Nifedipine reduced blood pressure by decreasing the resistance of peripheral blood vessels, mainly through the enlargement of arteries. However, it is known that this action causes compensatory tension in sympathetic nerves, secretion of catecholamine, and activation of the renin system in relation to the action of reducing blood pressure.[7,8] The reduction in blood pressure decreases the afterload on the left ventricular wall to bring about regression of hypertrophy. It is expected, however, that this regression of hypertrophy will be inhibited since the activation of the renin system promotes the accumulation of angiotensin II in cardiac muscles, and the angiotensin II stimulates the production of myocardial growth factors.[10–12] ACE inhibitors, on the other hand, reduce blood pressure by inhibiting the renin and sympathetic nerve systems, as well as by extending the peripheral arteries and veins. The present study suggests the possibility that the effect of ACE inhibitors on the regression of hypertrophy may be superior to that of Ca blocking agent, since they can inhibit the activation of renin system as well as reduce the afterload on the hypertrophied left ventricular wall.

CONCLUSIONS

Administration of antihypertensives has the recognized effect on the regression of cardiac hypertrophy, but the problem has emerged that the degree of regression depends on the kind of antihypertensive. The present study showed similar results in the degree of reduction in blood pressure in both cilazapril and nifedipine groups. In the regression of cardiac hypertrophy, similar effects were seen in the septum and posterior wall thickness of the left ventricle and ECG (SV_1+RV_5), but the effect of cilazapril on the regression of LVM was significantly superior to that of nifedipine.

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