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Effects of Angiotensin-Converting Enzyme Inhibition on Left Ventricular Geometric Patterns in Patients with Essential Hypertension

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Although angiotensin-converting enzyme inhibitors have been shown to affect left ventricular (LV) remodeling favorably in several conditions, it remains unclear whether they can influence LV geometric pattern in hypertension. To address this issue, 122 patients (71 men and 51 women; mean age = 51 ± 10 years) with mild to moderate hypertension were studied prospectively. All underwent clinical evaluation and Doppler echocardiography at entry and more than 2 years of quinapril therapy (10–40 mg/day). According to either LV mass (normal if <131 g/m² for men or <100 g/m² for women) or the ratio of LV posterior wall thickness to diastolic diameter (RWT; normal if <0.45) at baseline, 58 patients had normal mass and RWT, 18 patients had concentric remodeling (i.e., normal mass but increased RWT), 24 patients had eccentric hypertrophy (i.e., increased mass but normal RWT), and 22 patients had concentric hypertrophy (i.e., increase in both mass and RWT). After 6 months of quinapril therapy, all patients with normal left ventricles showed the maintenance of mass and RWT within normal limits. Patients with concentric remodeling showed no increase in mass but had a significant decrease in RWT. Patients with eccentric hypertrophy exhibited a significant reduction in mass with no substantial change in RWT. Patients with concentric hypertrophy had a significant reduction in both mass and RWT. Changes in LV mass and geometry were maintained during the 2-year period of treatment and were paralleled by improvements in Doppler indices of LV diastolic function in each group. It is concluded that quinapril, with its well-known effects on LV hypertrophy, modifies the LV geometric pattern of hypertensive patients favorably, regardless of the presence of an abnormal LV mass or RWT.

Essential hypertension is associated with changes in left ventricular (LV) morphology. LV hypertrophy progressively develops as an adaptive response to pressure overload and is a well-established marker of a poorer prognosis independently of blood pressure.[1] More recent investigations also have considered LV geometry in hypertensive patients. Four mutually exclusive geometric patterns have been classified on the basis of LV mass and relative wall thickness (RWT; the ratio of wall thickness to cavity diameter),[2] and preliminary observations indicate that a more complete definition of LV geometry may be a more effective approach for characterizing the risk factors of patients with hypertension.[3,4]

Multiple studies have demonstrated the favorable effects of various antihypertensive treatments on LV hypertrophy[5,6]; however, no previous investigation has verified in a large series of patients whether the distinct patterns of LV geometry are influenced by

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pharmacologic therapy. To address this issue, the authors prospectively investigated the long-term effects of an angiotensin-converting enzyme (ACE) inhibitor, quinapril, on LV morphology and shape in a cohort of patients with essential hypertension.

PATIENTS AND METHODS

Patients

All hypertensive patients who were referred to the authors' institution between January 1992 and December 1992 were considered eligible to participate in the study. To be included, patients had to demonstrate all of the following criteria: 1) essential hypertension with sitting blood pressure of 140 mmHg or diastolic blood pressure of 90 mmHg on at least three visits in the 3 weeks before admission; 2) discontinuation of any previous antihypertensive therapy for more than 4 weeks; 3) absence of any symptom or sign of heart failure, ischemic heart disease, cardiomyopathy, valvular heart disease, and concomitant important disease; and 4) echocardiograms of adequate quality to assess LV morphologic characteristics. According to these admission criteria, a total of 133 patients entered the study. At admission, all patients underwent clinical and physical evaluation, including a detailed medical history, fundoscopic evaluation, laboratory screening tests (including urinalysis and determination of serum levels of creatinine, glucose, cholesterol, and electrolytes), and Doppler echocardiography. During follow-up, four patients were lost, and seven patients discontinued treatment because of the onset of side effects. The remaining 122 patients completed the 2-year period of treatment with quinapril and therefore constituted the study group included in the analysis. There were 71 men and 51 women. The mean age was 51 ± 10 years (range, 25–70 years).

Echocardiography

Echocardiographic studies were performed using a Hewlett-Packard (Andover, MA; model Sonos 1500) ultrasonic sector scanner with a 2.5-MHz transducer. Standard left parasternal long- and short-axis views and apical two- and four-chamber views were obtained in all patients. All examinations were performed by two investigators (DC and SF) and recorded on videotapes. To obviate the potential limitation of a biased evaluation, all Doppler echocardiographic measurements were calculated independently at the end of the study by two other investigators who are experts in echocardiography (SDC and FP) and who were unaware of patients' identities and clinical statuses. Echocardiograms were judged adequate for interpretation if acceptable recognition of the endocardial and epicardial borders of the LV wall was obtained. M-mode echocardiograms were derived from the two-dimensional image under direct anatomic visualization. Measurements were made according to the recommendations of the American Society of Echocardiography with a leading-edge-to-leading-edge convention.[7] Standard echocardiographic values of LV internal dimension, interventricular septum thickness, and posterior wall thickness were assessed at end diastole. Left ventricular mass, in grams, was calculated using the formula introduced by Devereux et al[8,9]:

$$0.80 \times 1.04[(\text{LVID} + \text{PWT} + \text{IVST})3 - (\text{LVID})3] + 0.6,$$

where LVID is LV internal dimension, PWT is posterior wall thickness, and IVST is interventricular septum thickness. Values were indexed by the body surface area. Relative wall thickness was calculated using the formula (IVST + PWT)/LVID.[4]

Reproducibility

Intraobserver variability of echocardiographic data was determined with repeat analysis of all the measurements calculated in all the 122 patients by one investigator (SDC), who evaluated all examinations on two separate occasions 3 months apart. Interobserver variability was assessed in all 122 patients by two different investigators (SDC and FP), who measured all echocardiographic parameters independently and without knowledge of the identities of patients.

Cardiac Doppler

Doppler mitral flow recordings were obtained from the apical four-chamber view using a 2.5-MHz transducer. The pulsed wave beam was positioned in a line parallel to the LV long axis, with the sample volume at the level of the mitral annulus. Tracings of at least five cardiac cycles with the highest velocity pattern of LV diastolic filling were recorded. The following measures were calculated in each patient: peak flow velocities of early filling wave and atrial filling wave, ratio of early to atrial filling waves, deceleration time of early filling wave (i.e., the time required for the early filling wave velocity to decline from its peak to the baseline value), and isovolumic relaxation time (i.e., the time interval from the beginning of the second heart sound to the beginning of the early filling wave). Doppler tracings were evalu-

ated by two investigators (SDC and FP), who were unaware of patient status. For each Doppler echocardiographic parameter in any given patient, at least five consecutive cardiac cycles were analyzed and the average calculated.[10]

Patterns of LV Geometry

In all patients, the LV geometric pattern was evaluated on the basis of their LV mass and RWT. Cut-off points to identify LV hypertrophy were set at 131 g/m^2 for men and 100 g/m^2 for women, corresponding to the 95% confidence limits for the upper range of normal as assessed in the Framingham Heart Study.[11] A cut-off point of 0.45 was used for RWT according to previous reports on the significance of different patterns of LV adaptation to hypertension.[3,4] The study patients were classified as having a normal LV if LV mass and RWT were normal; concentric remodeling if LV mass was normal but RWT was 0.45 or greater; eccentric hypertrophy if LV mass was increased but RWT was normal; or concentric hypertrophy if both LV mass and RWT were higher than normal.[2–4]

Treatment and Follow-up

At discharge and during follow-up, all patients were treated with quinapril (10–40 mg/day) given orally to reduce clinical blood pressure to less than 140/90 mmHg. In 50 patients, it was necessary to add 25 mg/day to 50 mg/day of chlorthalidone to ensure effective treatment. All patients were given instructions regarding life-style changes. No patient received β-adrenergic blocking agents, calcium channel blockers, α1-blockers, or other antihypertensive drugs during the study period. All patients were reevaluated 6 months after the beginning of therapy and at the end of the 2-year follow-up period. Follow-up visits included repeat clinical and physical examination, serum biochemistry, 12-lead electrocardiography, and Doppler echocardiography.

Statistics

Data are expressed as means ± standard deviations. Data within a group among baseline and follow-up evaluations were compared by repeated-measures analysis of variance. The Student-Newman-Keuls post hoc test was used to detect differences between two evaluations whenever the analysis of variance showed a significant difference. The Statistical Package for the Social Sciences software (SPSS, Inc., Chicago, IL) was used. A P value of less than 0.05 was considered statistically significant.

RESULTS

Patients

According to the criteria adopted, 58 patients (47%) were considered to have a normal left ventricle, 18 patients (15%) showed concentric remodeling, 24 patients (20%) had an eccentric hypertrophy, and 22 patients (18%) had concentric hypertrophy. Clinical features and indices of disease severity for each group are reported in Table I. Patients with eccentric and concentric hypertrophy had a longer duration of hypertension. Also, those with LV hypertrophy had been treated more often with antihypertensive drugs before entry in the study than those with normal LV mass.

Effects of Quinapril on Blood Pressure

The effects of quinapril on blood pressure are shown in Table II. Systolic arterial blood pressure at the 6-month and 2-year visits appeared significantly decreased in all study groups compared with baseline values. Also, significant reductions in diastolic arterial pressure were recorded in the four study groups during follow-up.

Effects of Quinapril on Left Ventricular Geometry

The effects of quinapril on LV geometry are shown in Table III. During the 2-year therapy period, the LV mass index decreased significantly in all four study groups. Although major reductions in LV mass index occurred in patients with eccentric hypertrophy (a 9% decrease after 6 months and a 12% decrease after 2 years) and concentric hypertrophy (an 8% decrease after 6 months and a 15% decrease after 2 years), treatment with quinapril also was associated with a decrease in LV mass index in patients with no evidence of LV hypertrophy at baseline (a 1% decrease after 6 months and a 4% decrease after 2 years in patients with a normal LV, and a 3% decrease after 6 months and a 12% decrease after 2 years in those with concentric remodeling).It is noteworthy that none of the 58 patients with normal left ventricles and none of the 18 patients with concentric remodeling showed the progression toward LV hypertrophy during follow-up. Reductions in LV mass index were similar in the 72 patients who received only quinapril and in the 50 patients that were treated with quinapril plus chlorthalidone. At 2 years, LV mass index in the former group decreased by 5% in those with normal left ventricles, 14% in those with concentric remodeling, 15% in those with eccentric hypertrophy, and 13% in those with concentric hyper-

TABLE I

Clinical Characteristics and Indices of Disease Severity at Referral in Patients with Essential Hypertension

	Study Group				
	Normal Left Ventricle (n = 58)	Concentric Remodeling (n = 18)	Eccentric Hypertrophy (n = 24)	Concentric Hypertrophy (n = 22)	P Value
Gender (M/F)	38/20	13/5	10/14	10/12	
Age (yrs)	49 ± 10	53 ± 10	50 ± 8	55 ± 9	NS
Duration of hypertension (yrs)	3.5 ± 2.7	3.1 ± 3.4	5.4 ± 4.1	5.9 ± 5.4	<0.02
Never treated, no. (%)	44 (76)	11 (61)	8 (33)	8 (36)	<0.0001
Heart rate (bpm)	71 ± 11	74 ± 9	79 ± 15	77 ± 19	NS
Fundoscopic grade, no. (%)					
≤1	55 (95)	17 (95)	20 (83)	19 (86)	NS
>1	3 (5)	1 (5)	4 (17)	3 (14)	NS
Serum glucose (mg/dL)	95 ± 15	100 ± 17	98 ± 18	97 ± 21	NS
Serum cholesterol (mg/dL)	215 ± 35	220 ± 25	210 ± 31	223 ± 28	NS
Serum creatinine (mg/dL)	0.94 ± 0.21	0.97 ± 0.17	0.98 ± 0.15	0.99 ± 0.25	NS
Serum triglycerides (mg/dL)	141 ± 77	138 ± 55	159 ± 63	166 ± 73	NS

Values are presented as the mean ± standard deviation, unless otherwise indicated. bpm, beats per minute; NS, not significant.

trophy. Similarly, in the latter group, LV mass index decreased by 3% in those with normal left ventricles, 11% in those with concentric remodeling, 11% in those with eccentric hypertrophy, and 18% in those with concentric hypertrophy.

Left ventricular dimension did not show any change in patients with normal LV geometry during the study period. In those with concentric remodeling, treatment with quinapril was associated with a substantial reversal of LV dimension to normal; LV dimension increased 5% after 6 months and 11% after 2 years. Conversely, patients with eccentric hy-

TABLE II

Arterial Blood Pressure Values at Baseline and at 6-Month and 2-Year Evaluations

	Study Group			
	Normal Left Ventricle (n = 58)	Concentric Remodeling (n = 18)	Eccentric Hypertrophy (n = 24)	Concentric Hypertrophy (n = 22)
Systolic blood pressure (mm Hg)				
baseline	157 ± 11	164 ± 6	158 ± 15	165 ± 18
6 mos	140 ± 12*	145 ± 9*	142 ± 11*	138 ± 15*
2 yrs	135 ± 13*	140 ± 8*	141 ± 14*	135 ± 14*
P†	<0.001	<0.001	<0.001	<0.001
Diastolic blood pressure (mm Hg)				
baseline	100 ± 13	95 ± 8	105 ± 15	101 ± 15
6 mos	89 ± 10*	90 ± 6*	87 ± 12*	86 ± 11*
2 yrs	85 ± 12*	85 ± 5*	85 ± 13*	83 ± 13*
P†	<0.001	<0.001	<0.001	<0.001

** P < 0.05 versus corresponding value at baseline.*
† P values were determined by means of analysis of variance.
Values are presented as the mean ± standard deviation.

TABLE III

Echocardiographic Parameters of Left Ventricular Morphology at Baseline and at 6-Month and 2-Year Evaluations

	Normal Left Ventricle (n = 58)	Concentric Remodeling (n = 18)	Eccentric Hypertrophy (n = 24)	Concentric Hypertrophy (n = 22)
LV mass (g/m^2)				
baseline	92 ± 19	84 ± 10	124 ± 15	125 ± 15
6 mos	91 ± 17	81 ± 15	113 ± 18*	115 ± 16*
2 yrs	88 ± 16*†	72 ± 14*†	109 ± 19*	106 ± 19*
P	<0.001	<0.001	<0.001	<0.001
LV end-diastolic diameter (cm)				
baseline	4.92 ± 0.37	4.37 ± 0.22	5.25 ± 0.32	4.77 ± 0.35
6 mos	4.93 ± 0.36	4.59 ± 0.24*	5.19 ± 0.27*	4.90 ± 0.39*
2 yrs	4.91 ± 0.37	4.83 ± 0.11*†	5.13 ± 0.32†	5.04 ± 0.33†
P	NS	<0.001	<0.001	<0.001
LV posterior wall thickness (cm)				
baseline	1.00 ± 0.13	1.02 ± 0.08	1.13 ± 0.09	1.28 ± 0.14
6 mos	0.98 ± 0.10*	0.93 ± 0.09*	1.06 ± 0.09*	1.11 ± 0.12*
2 yrs	0.95 ± 0.08*†	0.82 ± 0.11	1.03 ± 0.10*	1.01 ± 0.09
P	<0.001	<0.001	<0.001	<0.001
Interventricular septum thickness (cm)				
baseline	0.89 ± 0.12	1.04 ± 0.07	1.08 ± 0.08	1.16 ± 0.09
6 mos	0.90 ± 0.11	0.96 ± 0.10*	1.04 ± 0.09*	1.10 ± 0.10*
2 yrs	0.89 ± 0.10	0.79 ± 0.10*†	1.03 ± 0.09*	1.01 ± 0.09*†
P	NS	<0.001	<0.001	<0.001
Relative wall thickness				
baseline	0.38 ± 0.03	0.47 ± 0.02	0.42 ± 0.03	0.51 ± 0.05
6 mos	0.38 ± 0.03	0.41 ± 0.04*	0.40 ± 0.02*	0.45 ± 0.05*
2 yrs	0.37 ± 0.02*†	0.33 ± 0.04*†	0.40 ± 0.02*	0.40 ± 0.03*†
P	<0.001	<0.001	<0.001	<0.001

P < 0.05 versus corresponding value at baseline.
† P < 0.05 versus corresponding value at 6-month visit.
*Values are presented as the **mean ± standard deviation**; P values were determined by means of analysis of variance.*
LV, left ventricular; NS, not significant.

pertrophy exhibited a statistically significant trend toward a progressive decrease in LV end diastolic diameter. In those with concentric hypertrophy, there was a slight increase in baseline values of LV internal dimension during the 2-year follow-up.

Apart from those patients with normal LV morphology at baseline, there were significant reductions during follow-up in interventricular septum and LV posterior wall thicknesses in all study groups.

Beneficial effects of ACE inhibition on both LV dimension and thickness resulted in substantial changes in RWT during the 2-year treatment period. RWT decreased 13% after 6 months and 30% after 2 years in patients with concentric remodeling, and 12% after 6 months and 22% after 2 years in patients with concentric hypertrophy. It is noteworthy that RWT was 0.45 in 40 of the 122 study patients at baseline, whereas it was within normal limits in all but 1 patient at the end of the follow-up period.

As a consequence of the progressive changes in LV mass and RWT that occurred during the study, patients could be reclassified. At the end of the study, the number of patients with a normal LV geometric pattern had increased from 58 to 87, no patient showed concentric remodeling, and concentric hypertrophy remained in only 1 patient.

Effects of Quinapril on Left Ventricular Filling

The effects of quinapril on LV filling are shown in Table IV. Changes in LV geometric patterns during the 2-year period of treatment with quinapril were paralleled by improvements in Doppler indices of LV diastolic function. All study groups showed trends toward progressive increases in peak early velocity

TABLE IV

Doppler Indices at Left Ventricular Filling at Baseline and at 6-Month and 2-Year Evaluations

	Normal Left Ventricle (n = 58)	Concentric Remodeling (n = 18)	Eccentric Hypertrophy (n = 24)	Concentric Hypertrophy (n = 22)
E wave (cm/s)				
baseline	62.2 ± 11.9	62.3 ± 12.2	62.9 ± 13.3	62.2 ± 14.7
6 mos	65.2 ± 9.0*	64.2 ± 10.9	62.4 ± 8.6	65.2 ± 7.1
2 yrs	67.4 ± 10.5*†	67.4 ± 11.1	65.0 ± 10.3	66.8 ± 7.9
P	<0.001	NS	NS	NS
A wave (cm/s)				
baseline	72.9 ± 14.9	70.9 ± 17.1	72.8 ± 13.4	78.1 ± 15.9
6 mos	69.1 ± 11.8*	69.2 ± 12.0	64.0 ± 13.6*	74.1 ± 14.0
2 yrs	68.7 ± 12.2*	68.6 ± 13.2	64.0 ± 14.6*	73.9 ± 14.6
P	0.003	NS	<0.001	NS
E/A ratio				
baseline	0.87 ± 0.19	0.91 ± 0.12	0.87 ± 0.16	0.81 ± 0.21
6 mos	0.96 ± 0.16*	0.93 ± 0.12	1.0 ± 0.20*	0.89 ± 0.14
2 yrs	1.0 ± 0.18*†	0.99 ± 0.09	1.0 ± 0.21*	0.95 ± 0.14*
P	<0.001	NS	<0.001	0.04
DT (ms)				
baseline	210 ± 78	194 ± 55	203 ± 59	197 ± 84
6-mos	177 ± 49*	188 ± 50	186 ± 39*	187 ± 54
2 yrs	178 ± 53*	185 ± 52*	181 ± 44*	184 ± 56
P	<0.001	0.03	0.005	NS
IRT (ms)				
baseline	81.0 ± 16.5	91.1 ± 14.9	91.1 ± 21.3	91.6 ± 14.3
6 mos	91.9 ± 15.2*	101.3 ± 13.2*	95.3 ± 19.0*	103.9 ± 15.6*
2 yrs	92.1 ± 15.1*	100.5 ± 16.5*	95.2 ± 19.9*	103.8 ± 16.0*
P	<0.001	0.01	0.02	<0.001

* $P < 0.05$ *versus corresponding value at baseline.*
† $P < 0.05$ *versus corresponding value at 6-month visit.*
Values are presented as the mean ± standard deviation; P values were determined by means of analysis of variance. E wave, early diastolic peak left ventricular inflow velocity; A wave, late diastolic peak inflow velocity; DT, early diastolic flow deceleration time; IRT, isovolumic relaxation time; NS, not significant.

and decreases in peak late velocity of transmitral flows. As a consequence, early to late ratio of peak velocities increased both at 6-month and 2-year examinations. Also, deceleration time of early filling wave and isovolumic relaxation time improved during follow-up in the four groups.

Reproducibility

Intraobserver variability percentages at baseline, 6 months, and 2 years for LV mass were 5.3% ± 1.2%, 4.4% ± 1.6%, and 5.5% ± 1.9%, respectively. For LV diameter, they were 4.6% ± 1.8%, 4.9% ± 1.7%, and 4.1% ± 1.5%, respectively. For LV posterior wall thickness, they were 4.1% ± 1.1%, 3.9% ± 0.9%, and 4.9% ± 1.5%, respectively. For interventricular septum thickness, they were 6.6% ± 1.3%, 5.1% ± 1.6%, and 4.9% ± 1.9%, respectively. Interobserver variability percentages at baseline, 6 months, and 2 years for LV mass were 7.5% ± 4.2%, 6.9% ± 3.2%, and 7.3% ± 5.2%, respectively. For LV diameter, they were 6.1% ± 3.2%, 7.3% ± 4.2%, and 6.7% ± 3.3%, respectively. For LV posterior wall thickness, they were 5.5% ± 3.2%, 6.0% ± 4.2%, and 6.2% ± 3.2%, respectively. For interventricular septum thickness, they were 7.3% ± 3.2%, 6.8% ± 3.9%, and 6.0% ± 3.8%, respectively.

DISCUSSION

The results of this study suggest that long-term ACE inhibition in hypertensive patients, along with its well-known favorable influence on LV mass, also is

associated with beneficial effects on LV geometric patterns.

Several, but not all, hypotensive drugs are useful for either treating arterial hypertension or reducing LV mass.[5,6] The results of the present study demonstrate that quinapril is effective in reversing LV hypertrophy. This result is consistent with those of previous long-term, placebo-controlled studies, which showed that a significant decrease in LV mass can be obtained with ACE inhibition.[12]

Apart from showing that quinapril reverses LV hypertrophy, the findings of this study also suggest that its long-term administration prevents the development of LV hypertrophy in hypertensive patients. This observation is consistent with the experimental evidence that quinapril, probably because of its major affinity for cardiac tissue ACE, is particularly effective in hypertension, in which the cardiac renin–angiotensin system acts as a trophic factor.[13] Conversely, other drugs, despite decreasing the cardiac volume overload, are not able to attenuate the hypertrophic response of the heart.[14]

The presence of LV hypertrophy is a risk factor for cardiovascular morbidity and mortality.[1] Recent investigations have shown that further classification of hypertensive patients by their LV geometric patterns, including concentric or eccentric hypertrophy, concentric ventricular remodeling, or normal geometry, can identify groups with different pathophysiologic patterns and may add to LV mass for stratification of risk.[3,4]

Although it remains to be shown whether cardiovascular risk can actually be attenuated by reducing increased LV mass or modifying an abnormal LV shape, it has been speculated that restoration of a normal LV geometric pattern may have implications for cardiac function and prognosis.[3,6] To the authors' knowledge, previous reports on the effects of antihypertensive drugs on LV dimension have been performed only on small series of patients and have yielded conflicting findings.[15,16] The results of the present study, therefore, are relevant because they demonstrate that the various LV geometric patterns of hypertensive patients can be changed substantially with long-term ACE inhibition. Indeed, treatment with quinapril was effective both in reversing LV hypertrophy and in influencing LV size and shape. In fact, patients with eccentric hypertrophy exhibited a significant decrease in LV mass and a reduction of the enlarged cavity size. Also, patients with concentric remodeling, who, by definition, had no LV hypertrophy but did have a restricted LV dimension at baseline, showed a major increase in LV size, which reverted to normal after the 2-year period of treatment with quinapril.

These findings are important because they show that ACE inhibition influences the so-called process of LV remodeling in hypertension favorably, as has already been ascertained in acute myocardial infarction,[17] congestive heart failure,[18] and valvular regurgitation.[19]

Left ventricular diastolic dysfuction is common in patients with hypertension[5] and represents an important cause of morbidity, as it is responsible for pulmonary congestion and systolic dysfunction during exercise.[20,21] Although the effects of different antihypertensive agents on diastolic filling dynamics have been evaluated in several studies,[5] it remains unclear which patients might benefit from treatment.[20] In addition, although it has been shown recently that the extent of LV dysfuction depends on the type of anatomic remodeling,[21] no previous investigation has verified the effects of treatment in patients with different LV geometric patterns. In the present study, changes in LV geometry during the 2-year period of treatment with quinapril were paralleled by significant improvements in Doppler indices of LV diastolic function in all patient groups, regardless of the presence at baseline of an abnormal LV mass or RWT. These findings, therefore, do not support the concept that diastolic function can improve only in patients with LV hypertrophy.[20,22] Rather, they are consistent with previous investigations that have suggested that an amelioration of LV filling can reasonably be expected only if a drug can produce, along with a decrease in LV mass, changes in LV dimensions and distensibility.[23]

Although performed prospectively in a large series of patients and with a long follow-up period, this study suffers from the important limitation of being an open investigation. As a consequence, results indicate only that the abnormal LV geometric changes that occur in hypertensive patients can be modified substantially by antihypertensive treatment. Additional controlled trials are needed to verify whether these favorable effects can be obtained with ACE inhibitors only or with other antihypertensive agents as well. It has been suggested, however, that LV remodeling may be more affected by ACE inhibition than by other types of pharmacologic treatment.[24] Apart from the unloading action similar to that of most antihypertensive agents, ACE inhibitors have peculiar nonhemodynamic properties, as they modulate both cellular hypertrophy and collagen deposition, which are the main pathologic substrates of LV remodeling.[24]

Another limitation of the study was the relatively small sample size of the groups of patients with distinct geometric patterns. This factor prevented the use of a more powerful statistical analysis to assess the strength of the association between long-term ACE inhibition and changes in LV geometry after adjustment for indices of disease severity or the use of diuretics.

The addition of diuretics in a subset of patients constitutes a potential limitation of the study. Although the

results of multiple trials and recent meta-analysis of several treatment studies have ascertained that diuretics have the least effect on LV mass compared with other antihypertensive agents,[25–27] the possibility exists that addition of chlorthalidone in some cases may have potentiated the effects of ACE inhibition. The subset of patients who received only quinapril throughout the study, however, exhibited reductions in LV mass index similar to those detected in patients treated with the combination of quinapril and chlorthalidone. These findings indicate that chlorthalidone played a role in improving the control of blood pressure but not in determining substantial morphologic changes; therefore, it seems reasonable to conclude that the effects of long-term treatment on LV morphology of the patients in this study should be ascribed mainly to quinapril.

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REFERENCES

1. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP: Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. *N Engl J Med* 1990;322:1561–1566.

2. Ganau A, Devereux RB, Roman MJ, De Simone G, Pickering TG, Saba PS, et al: Patterns of left ventricular hypertrophy and geometric remodeling in essential hypertension. *J Am Coll Cardiol* 1992;19:1550–1558.

3. Verdecchia P, Schillaci G, Borgioni C, Ciucci A, Battistelli M, Bartoccini C, Santucci A, et al: Adverse prognostic significance of concentric remodelling of the left ventricle in hypertensive patients with normal left ventricular mass. *J Am Coll Cardiol* 1995;25:871–878.

4. Krumholz HM, Larson M, Levy D: Prognosis of left ventricular geometric pattern in the Framingham Heart Study. *J Am Coll Cardiol* 1995;25:879–884.

5. Frohlich ED, Apstein C, Chobanian AV, Devereux RB, Dustan HP, Dzau V, Fouad-Tarazi F, et al: The heart in hypertension. *N Engl J Med* 1992;327:998–1008.

6. Devereux RB, Dashlof B: Criteria for an informative trial of left ventricular hypertrophy regression. *J Hum Hypertens* 1994;8:735–739.

7. Sahn DJ, DeMaria A, Kisslo J, Weyman A: The committee on M-mode standardization of the American Society of Echocardiography; recommendations regarding quantitation in M-mode echocardiographic measurements. *Circulation* 1978;58:1072–1083.

8. Devereux RB, Alonso DR, Lutas EM, Gottlieb GJ, Campo E, Sachs I, Reichek N: Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. *Am J Cardiol* 1986;57:450–458.

9. Devereux RB: Detection of left ventricular hypertrophy by M-mode echocardiography: anatomic validation, standardization and comparison to other methods. *Hypertension* 1987;9(suppl II):II-19–II-26.

10. Appleton CP, Hatle LK, Popp RL: Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988;12:426–440.

11. Levy D, Savage DD, Garrison RJ, Keaven MA, Kannel WB, Castelli WP: Echocardiographic criteria for left ventricular hypertrophy: the Framingham Heart Study. *Am J Cardiol* 1987;59:956–960.

12. Frohlich ED, Horinaka S: Cardiac and aortic effects of angiotensin converting enzyme inhibitors. *Hypertension* 1991;18(suppl II):II-2–II-7.

13. Ruzicka M, Leenen FHH: Relevance of blockage of cardiac and circulatory angiotensin-converting enzyme for the prevention of volume overload-induced hypertrophy. *Circulation* 1995;91:16–19.

14. Ruzicka M, Yuan B, Armsen E, Leenen FHH: The renin-angiotensin system and volume overload-induced cardiac hypertrophy in rats: effects of angiotensin-converting enzyme inhibitor versus angiotensin II receptor blocker. *Circulation* 1993;87:921–930.

15. Galderisi M, Celentano A, Garofalo M, Tammaro P, Oliviero M, Petrocelli A, De Divitiis O: Reduction of left ventricular mass by short-term antihypertensive treatment with isradipine: a double comparison with enalapril. *Int J Clin Pharmacol Ther* 1994;32:312–316.

16. Franz IW, Ketelhut R, Behr U, Tonnesmann U: Time course of reduction in left ventricular mass during long-term antihypertensive therapy. *J Hum Hypertens* 1994;8:191–198.

17. Pfeffer MA, Braunwald E: Ventricular remodeling after myocardial infarction: experimental observations and clinical implications. *Circulation* 1990;81:1161–1172.

18. Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, et al (for the SOLVD investigators): Effects of angiotensin converting enzyme inhibitor enalapril on the long-term progression to left ventricular dysfunction in patients with heart failure. *Circulation* 1992;86:431–438.

19. Schon HR: Hemodynamic and morphologic changes after long-term angiotensin-converting enzyme inhibition in patients with chronic valvular regurgitation. *J Hypertension* 1994;12(suppl 4):S95–S104.

20. Agabiti-Rosei E, Muiesan ML: Hypertension and diastolic function. *Drugs* 1993;46(suppl 2):61–67.

21. Ren JF, Pancholy SB, Iskandrian AS, Lighty GW, Mallavarapu C, Segal BL: Doppler echocardiographic evaluation of the spectrum of left ventricular diastolic dysfunction in essential hypertension. *Am Heart J* 1994;127:906–913.

22. Oren S, Grossman E, Frohlich ED: Reduction in left ventricular mass in patients with systemic hypertension treated with enalapril, lisinopril, or fosinopril. *Am J Cardiol* 1996;77:93–96.

23. Daholf B, Hansson L: Regression of left ventricular hypertrophy in previously untreated essential hypertension: different effects of enalapril and hydrochlorothiazide. *J Hypertens* 1992;10:1513–1524.

24. Goldstein S, Sabbah H: Ventricular remodeling and angiotensin-converting enzyme inhibitors. *J Cardiovasc Pharmacol* 1994;24(suppl 3):S27–S31.

25. Liebson PR: Clinical studies of drug reversal of hypertensive left ventricular hypertrophy. *Am J Hypertens* 1990;3:512–517.

26. Cruickshank JM, Lewis J, Moore V, Dodd C: Reversibility of left ventricular hypertrophy by different types of antihypertensive therapy. *J Hum Hypertens* 1992;6:85–90.

27. Dahlof B, Pennert K, Hansson L: Reversal of left ventricular hypertrophy in hypertensive patients: a meta-analysis of 109 treatment studies. *Am J Hypertens* 1992;5:95–110.