Effects of Long-term Enalapril Therapy on Left Ventricular Diastolic Properties in Patients With Depressed Ejection Fraction

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Background. The aim of the present study was to analyze the changes in left ventricular diastolic function that occur in patients with chronic severe left ventricular systolic dysfunction in the absence or presence of prolonged therapy with an angiotensin converting enzyme inhibitor.

Methods and Results. Left ventricular function data (cineangiography plus Millar, frame-by-frame analysis) and right ventricular volumes (radionuclide angiography) were obtained at baseline and after an average follow-up of 12.4 months in 42 patients with a left ventricular ejection fraction of 35% or less. After baseline measurements, the patients were randomized to placebo (n=16) or enalapril (10 mg BID, n=26).

In the placebo group, the changes in left ventricular function were characterized by increases in end-diastolic (159±43 to 170±44 mL/m²) and end-systolic (119±38 to 128±49 mL/m²) volumes accompanied by a downward and rightward shift of the diastolic pressure-volume relation. In contrast, decreases in end-diastolic (166±43 to 156±47 mL/m²) and end-systolic (125±43 to 111±42 mL/m²) volumes accompanied by a slight upward and leftward shift of the diastolic pressure-volume relation were noted in the enalapril group. These changes in left ventricular volumes were significantly different between groups (both P<.005) but were not attended by changes in left ventricular end-diastolic pressure, in time constant of isovolumic pressure decrease, or in right ventricular volumes. However, the chamber stiffness constant β decreased from 0.044±0.027 to 0.032±0.019 mL⁻¹/m² in the placebo group, whereas it increased insignificantly in the enalapril group (0.040±0.028 to 0.041±0.028 mL⁻¹/m²). These changes in chamber stiffness constant β between baseline and follow-up were significantly different between placebo and enalapril groups (P<.05).

Another index of chamber compliance, ΔV/ΔP, also confirmed the presence of opposite changes in left ventricular chamber compliance in the placebo group and in the enalapril group. The mean diastolic wall stress increased with placebo but not with enalapril (+51 versus −13 kdyn/cm²; P<.04) whereas left ventricular mass and the indexes of left ventricular sphericity tended to improve in the enalapril group. The changes in plasma levels of norepinephrine, atrial natriuretic peptide, and arginine vasopressin were, however, comparable in both groups.

Conclusions. The data indicate that in patients with severe systolic left ventricular dysfunction, the progressive left ventricular dilatation was accompanied by a decrease in left ventricular chamber stiffness; enalapril therapy was able to prevent or partially reverse these changes and tended to reduce left ventricular mass and ventricular sphericity. Those changes were suggestive of partial reversal of left ventricular remodeling by enalapril administration. (Circulation 1993;88:481-491)

Key Words • angiotensin converting enzyme • left ventricle • ejection fraction

Complex changes in left ventricular volumes, shape, and wall structure occur after myocardial infarction in animals and in patients.¹⁻³ These changes, often referred to as “ventricular remodeling,” have been shown to be partially prevented by the administration of an angiotensin converting enzyme (ACE) inhibitor.⁴⁻⁵ Although not explicitly demonstrated, ventricular remodeling is thought also to occur in heart disease of nonischemic etiology and to be responsible for the progression toward congestive heart failure and death in a subset of patients.³ However, even if the benefits of ACE inhibitors are well established in patients with chronic left ventricular dysfunction,⁶⁻⁷ the mechanisms underlying this benefit and the changes in left ventricular function during prolonged therapy remain unclear. The aim of the present study, therefore, was to analyze in detail the changes in left ventricular function observed during prolonged therapy with placebo or enalapril in a subset of patients with chronic left ventricular systolic dysfunc-
### Table 1. Clinical Characteristics of Patients at Baseline and 1 Year After Randomization: Treatment Arm

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NYHA indicates New York Heart Association; P/E, placebo/enalapril; IMI, inferior myocardial infarction; AMI, anterior myocardial infarction; IDCM, idiopathic dilated cardiomyopathy; DIU, diuretics; VSD, vasodilators; DGX, digoxin; CEB, calcium entry blockers; AP, antiplatelet agents; and AA, antiarrhythmic agents.

*This patient had cardiac transplant for refractory arrhythmias.

...tion who were enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) trials. As experimental studies had found evidence of a change in chamber compliance after administration of an ACE inhibitor, special attention was directed in our analysis toward the changes in left ventricular diastolic properties.

### Methods

The SOLVD protocol and main results have been described in detail. Briefly, patients were eligible if they were between 21 and 80 years old, had a left ventricular ejection fraction of 35% or less, and were not receiving an ACE inhibitor. The patients also had to be in stable clinical condition, to be free of noncardiac life-threatening disease, and to not have suffered a myocardial infarction within the past 30 days. All patients gave written informed consent to participate in the study, which was approved by the ethics committee of each participating institution. According to their symptomatic status, the patients were stratified to the treatment arm if they were already treated for heart failure or to the prevention arm if they were in New York Heart Association functional class I or II but did not require therapy for heart failure. All patients were randomized to placebo or enalapril (2.5 to 10 mg BID) therapy. The data reported in this study concern a subset of 65 patients (16 in the treatment arm and 49 in the prevention arm) who were studied at the St Luc University Hospital. There were 54 men and 11 women. The mean age was 55.8±8.3 years for the treatment patients and 56.1±9.9 years for the prevention patients. The etiology of the left ventricular dysfunction was ischemic heart disease in 56 patients and idiopathic dilated cardiomyopathy in 9 patients. Their main individual clinical characteristics are listed in Tables 1 and 2.

### Data Acquisition and Analysis

**Radionuclide angiography.** To assess right ventricular volumes, an equilibrium-gated radionuclide ventriculography was performed with the patient in the supine position on the same day as the left-heart catheterization. All subjects received 10 mg sodium pyrophosphate IV and 1.8 mg stannous chloride followed 30 minutes later by 20 mCi $^{99m}$Tc-pertechnetate to achieve red blood cell labeling. Gated equilibrium radionuclide data were acquired using a mobile Apex 215 M camera (Elscint, Israel) with a low-energy, all-purpose, parallel-hole collimator. The camera was positioned in a left anterior oblique projection with caudal angulation, allowing the best separation between ventricles and atria. The data gated to the patient’s ECG were acquired in frame mode using 32 frames per cycle and a 64×64 pixel matrix. Radionuclide studies were analyzed at a core facility at Tufts University, New England Medical Center, using previously described methods.

For the purpose of this study, the right ventricular end-diastolic and end-systolic regions were drawn manually and redrawn as needed, using simultaneous inspection of stroke volume, ejection fraction, and paradox images. Inspection of these functional images and of an endless loop movie format display aided in delineating both the tricuspid and pulmonary valve planes. Background was subtracted using counts per pixel in a paraventricular background region at the end-systolic frame. After background subtraction, right ventricular ejection fraction was calculated as the number of end-systolic counts subtracted from the end-diastolic counts.
Table 2. Clinical Characteristics of Patients at Baseline and 1 Year After Randomization: Prevention Arm

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NYHA indicates New York Heart Association; P/E, placebo/enalapril; IMI, inferior myocardial infarction; AMI, anterior myocardial infarction; IDCM, idiopathic dilated cardiomyopathy; DIU, diuretics; VSD, vasodilators; DGX, digoxin; HTX, heart transplant; CEB, calcium entry blockers; AP, antplatelet agents; and AA, antiarrhythmic agents.
stolic counts and then divided by the number of end-diastolic counts. Absolute right ventricular end-diastolic volume and end-systolic volume were estimated using a count-based methodology, which incorporated elements of the methods of several previous reports.\textsuperscript{9,13,14}

**Contrast ventriculography.** Left-heart catheterization was performed in the fasting state and without premedication as described previously.\textsuperscript{15} An 8F pigtail Millar catheter (Millar Instruments Instr, Houston, Tex) was introduced through the femoral artery to measure high-fidelity left ventricular pressure and to inject contrast material. After blood sampling for neurohormones, angiographic images were acquired with Philips Polidyagnost C and DVI systems (Philips Instr, Best, The Netherlands). These systems allow the acquisition of nonsubtracted left ventricular images at 50 frames per second with 1024 shades of grey (10 bits) and a geometric resolution of approximately 0.7 mm. During the 3 ms of frame exposure, there is a simultaneous acquisition of the left ventricular pressure and of the ECG signal.\textsuperscript{16}

Left ventricular pressure, together with the ECG signal, was recorded continuously on analog magnetic tape (Honeywell 101, Honeywell Informations Systems, Inc, Waltham, Mass). Analog data were digitized every 2 ms and processed off-line by means of a Hewlett-Packard A900 computer (Hewlett-Packard Co, Palo Alto, Calif). Specific points of the signals (such as the peak of the R wave or the left ventricular end-diastolic pressure) were automatically detected with a set of subroutines. With a least-squares regression technique, left ventricular pressure data after peak (-)dP/dt were fitted to a monoeponential relation with time or to a linear relation with the first derivative of the pressure, and the time constants t (0 to 80 ms after peak (-)dP/dt) or \( \tau \) (dP/dt versus pressure method) of these relations were used as indexes of left ventricular relaxation.\textsuperscript{17,18} As isovolumic indexes of inotropic state, we used peak (+)dP/dt and the dP/dt measured and normalized at a developed pressure of 40 mm Hg, (dP/dt)\textsubscript{40}. For evaluation of left ventricular function, masked ventricular silhouettes were outlined on a frame-by-frame basis on a video screen using a joystick. Both premature and post premature beats were excluded from analysis.

A computer system (APU Philips, Philips Electronic Instr Co, Mahwah, NJ) derived the correction factor for x-ray magnification and calculated volumes every 20 ms by applying Simpson’s rule. For that purpose, the ventricular contour was divided into 64 equally spaced slices, perpendicular to the long axis, and the volume of each slice was calculated assuming a cylindrical geometry. The ejection fraction was calculated according to the classic formula using the frame with the maximal pressure-to-volume ratio as end systole.\textsuperscript{20} Volume data were corrected for the body surface area. Myocardial wall thickness was determined on the last diastolic frame and was computed for subsequent frames assuming a constant left ventricular mass. Left ventricular wall stress was computed as:

\[
\text{Stress} = \frac{Pb}{h}[1 - (h/2b) - (b^2/2a^2)]
\]

where P is pressure, h is wall thickness, and a and b are the semimajor and semiminor axes at mid wall, respectively;\textsuperscript{21} the mean systolic wall stress was obtained by averaging data from the start of ejection to end systole, and mean diastolic stress was calculated by averaging data from end systole to the peak of the R wave. Left ventricular wall volume was calculated assuming an ellipsoid of revolution, using the formula:

\[
\text{Wall volume} = 4.189[(a + h/2)^2(a + h/2) - (b - h/2)^2(a - h/2)]
\]

The left ventricular mass was derived by multiplying the wall volume by the myocardial specific weight assumed to be 1.05 g/cm\(^3\). The left ventricular pressure-volume loop was constructed after data smoothing for each patient (Fig 1). For the assessment of left ventricular chamber stiffness, the left ventricular pressure-volume data from the lowest diastolic pressure end diastole were fitted to an exponential pressure-volume relation with a three-parameter model:

\[
P = \alpha \cdot e^{\beta V} + \gamma
\]

where P is left ventricular pressure (mm Hg), \( \alpha \) is material constant (mm Hg), \( \beta \) is constant of left ventricular chamber stiffness (mL\(^{-1}\)/m\(^2\)), \( V \) is volume (mL/m\(^2\)), and \( \gamma \) is asymptote pressure (mm Hg).\textsuperscript{22} The chamber stiffness constant (\( \beta \)) was derived by use of a nonlinear curve-fitting algorithm. For illustration purposes, the last equation was transformed to the linear relationship

\[
\ln(P - \gamma) = \beta V + \ln(\alpha)
\]

FIG 1. Plots of typical pressure-volume relations in two patients of the prevention trial obtained at baseline (o) and after 12 months of therapy (●) with aspirin and placebo (top) or aspirin and enalapril (10 mg BID, bottom). Both patients had comparable end-systolic and end-diastolic volumes at baseline but opposite changes in left ventricular volumes during follow-up. Despite these opposite volume changes, ejection fraction improved slightly during follow-up in both cases.
posed, as illustrated in Fig 3. The beat with the smallest end-diastolic volume of the two was determined, and the volume value of this beat immediately prior to the R wave (150 mL/m² in the beats of Fig 3) was selected as V High for both beats; the other volume used in the calculation of this index (V Low, 125 mL/m² in Fig 3) was arbitrarily chosen as being 25 mL/m² smaller than V High. The corresponding pressure values were determined for the baseline beat and the follow-up beat, and the index ΔV/ΔP then was calculated for each beat as (V High minus V Low)/(P High minus P Low).

As an index of sphericity to assess the effect of treatment on the shape of the ventricle, the ratio of the left ventricular volume to the volume of a sphere of a diameter equal to the long axis of the ventricle was calculated. This ratio was expressed in percent, with 100% representing a spherical ventricle, and the lower values corresponding to more ellipsoid shapes. The ratio (long axis to short axis) also was used as an index of sphericity, with a value equal to 1 for this index corresponding to a spherical shape, and values of more than 1 representing more ellipsoid shapes. The angiographic data were analyzed by two blinded observers; interobserver variability, as assessed by having baseline angiographs analyzed twice by the two observers (A and B) and defined as [(2(A−B)/(A+B))]×100, equaled 1.8% for end-diastolic volume, 4.2% for end-systolic volume, and 4.4% for ejection fraction.

Radionuclide angiography, left-heart catheterization, and neurohumoral measurements were repeated after an average interval of 12.4 months (range, 10 to 17 months) in 42 patients. The reasons for not reassessing left ventricular function are listed in Tables 1 and 2. Death, cardiac transplantation, or new cardiac events precluding a meaningful interpretation of the changes in left ventricular function, such as atrial fibrillation, occurred during follow-up in 10 of 29 patients in the placebo group (34.5%) and in 6 of 36 patients in the enalapril group (16.7%).

Neurohumoral measurements. Blood for neurohumoral measurements was drawn after 30 minutes of supine rest and collected in chilled tubes appropriate each for neurohumoral assay. Within 60 minutes of collection, blood was centrifuged at 3000g at 4°C for 20 minutes to separate the plasma. Plasma was stored at −82°C and assayed for plasma norepinephrine, plasma renin activity, atrial natriuretic peptide, and arginine
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TABLE 3. Hemodynamic and Ventricular Function Data for Placebo and Enalapril Groups

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<td>Baseline (n=29)</td>
<td>Baseline (n=16)</td>
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<td>HR (bpm)</td>
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<td>LVDP (mm Hg)</td>
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<td>LVSP (mm Hg)</td>
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<td>(dP/dt)_{max} (mm Hg/s)</td>
<td>1363±307</td>
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<td>(dP/dt)/DP_{40} (s^-1)</td>
<td>18.7±5.9</td>
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<td>T (ms)</td>
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<td>τ (ms)</td>
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<td>LVEDVI (mL/m²)</td>
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<td>LVESVI (mL/m²)</td>
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<td>LVEF (%)</td>
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<td>LV mass (g)</td>
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<td>RVESVI (mL/m²)</td>
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<td>RVEF (%)</td>
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<td>47.1±14.1</td>
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HR indicates heart rate; bpm, beats per minute; LVDP, left ventricular end-diastolic pressure; (dP/dt)/DP_{40}, T, and τ, see “Methods”; LVSP, left ventricular systolic pressure; LVEDVI and LVESVI, left ventricular end-systolic and end-diastolic volume index; LVEF, left ventricular ejection fraction; RVEDVI and RVESVI, right ventricular end-systolic and end-diastolic volume index; RVEF, right ventricular ejection fraction; and Δ placebo and Δ enalapril, difference between baseline and follow-up values in the placebo and enalapril groups, respectively. Value are mean±SD.

*P<.005 Δ placebo vs Δ enalapril.

Increased slightly in the remaining patients. Nevertheless, the changes in the stiffness constant during the follow-up period were significantly different between groups (Δ placebo: -0.011±0.019 mL^-1/m²; Δ enalapril: 0.001±0.016 mL^-1/m²; P<.05).

A closer inspection of the individual data indicated that the greatest decreases in stiffness constant were found in the placebo patients who had β values above the mean at baseline (Fig 2, upper left). In this subgroup, β indeed decreased by 39% in the placebo group (from 0.072±0.019 to 0.044±0.025 mL^-1/m²), whereas it remained unchanged with enalapril (0.061±0.027 to 0.061±0.029 mL^-1/m²; P<0.01 Δ placebo versus Δ enalapril). Furthermore, with placebo, these patients had a decrease in their ejection fraction from 28% to 24% during follow-up, whereas ejection fraction increased from 28% to 33% when these patients were treated with enalapril (P<.1). In patients with chamber stiffness below the mean at baseline (Fig 2, right), no significant change was seen after 1 year in the placebo group (0.025±0.010 to 0.025±0.010 mL^-1/m²) or in the enalapril group (0.021±0.07 to 0.023±0.08 mL^-1/m²), and the ejection fraction tended to increase in both groups.

The chamber compliance index, on the other hand, increased in 80% of the placebo patients from a median of 2.00 (mL/m²)/mm Hg at baseline (range, 0.87 to 8.50) to a median of 2.19 (range, 1.00 to 5.50) during follow-up, whereas this index decreased in 85% of the enalapril patients from a median of 2.34 (range, 1.00 to 13.5) to a median of 1.92 (range, 0.87 to 4.25) (P<.001 placebo versus enalapril). The individual changes from baseline are plotted in Fig 4.

This conclusion that chamber distensibility had changed in opposite directions was also supported by the comparison of the empirical distribution of the changes in left ventricular end-diastolic volume and end-diastolic pressure and of the changes in left ventricular volume and in left ventricular pressure throughout diastole. In both cases, the volume changes were significantly different between groups (P<.001 and P<.0016, respectively), whereas the pressure changes were not, confirming the presence of a significant displacement of the pressure-volume relation not only at end diastole but also throughout diastolic filling.

Apart from these changes in left ventricular volumes and in chamber compliance, there were no other consistent changes in hemodynamic parameters. Left ventricular systolic pressure, (dP/dt)/dt_{max}, and (dP/dt)/DP_{40} all tended to decrease, and the indexes of isovolumic relaxation were slightly prolonged in the enalapril group, but none of these changes reached statistical significance compared with placebo. The changes in left ventricular peak filling rate were also comparable in both groups, whether expressed as absolute values (placebo: 240±89 to 251±102 mL · s^-1 · m^-2; enalapril: 266±89 to 257±65 mL · s^-1 · m^-2; P=NS) or when normalized for the end-diastolic volume (placebo: 8.4±14.1 to 6.8±11.2; P<.001).
Changes in Left Ventricular Wall Stress, Wall Mass, and Sphericity Index

The mean diastolic wall stress increased from 106±29 to 157±40 kdyn/cm² in the placebo group but decreased from 117±57 to 104±60 kdyn/cm² in the enalapril group, and the difference between baseline and follow-up was significantly different between groups (+51 versus −13 kdyn/cm²; P<.04). The mean systolic wall stress, on the other hand, tended to increase in both groups, from 419±107 to 492±277 kdyn/cm² in the placebo group and from 450±171 to 511±275 kdyn/cm² in the enalapril group (enalapril versus placebo, P=NS). Wall thickness decreased insignificantly in the placebo group (8.9±2.3 to 8.5±2.7 mm) and in the enalapril group (8.7±2.6 to 8.2±2.7 mm). Left ventricular wall mass increased slightly in the placebo group and tended to decrease in the enalapril group (Table 3). When expressed in percent of baseline, there appeared to be a slight decrease in calculated left ventricular mass in the enalapril group compared with the placebo group (Fig 5).

Finally, for the entire groups, small changes in the left ventricular index of sphericity also were observed. The sphericity index at end diastole increased in the placebo group from 47% to 51% but remained unchanged in the enalapril group; the difference between groups (+3.8±7.2% versus 0±4.8%; P=.053) was of borderline significance. At end systole, the differences were more consistent with a deterioration in the placebo group (39.0% to 41.5%) and an improvement with enalapril (40.7% to 38.9%), with the differences between groups (+2.5±7.8 versus −1.8±5.5; P<.05) reaching statistical significance. The long axis–to–short axis ratio yielded similar conclusions. At end diastole, the ratio decreased from 1.56 to 1.42 in the placebo group, indicating a more spherical shape, but was unchanged with enalapril (1.49 to 1.49; P=.06 for Δ enalapril versus Δ placebo). At end systole, the index decreased from 1.64±0.19 to 1.58±0.67 with placebo but increased from 1.64±0.27 to 1.68±0.28 with enalapril (P<.03 for Δ enalapril versus Δ placebo).

Correlation Between Changes in Ventricular Function and Changes in Plasma Neurohormones

At baseline, no correlation was found between plasma renin activity, plasma norepinephrine, or arginine vasopressin and the indexes of right ventricular or left ventricular function. There was, however, a weak correlation between left ventricular end-diastolic pressure and plasma atrial natriuretic peptide (r=.45 in both groups; P<.01). Table 4 presents the values of these plasma neurohormones at baseline and during follow-up. Except for plasma renin activity, which increased markedly in the enalapril group, no statistically significant differences were noted between groups. Plasma norepinephrine and arginine vasopressin essentially were unchanged, and plasma atrial natriuretic peptide decreased substantially in both groups (both P<.001 versus baseline but P=NS between groups). In the placebo group, plasma atrial natriuretic peptide still correlated with left ventricular end-diastolic pressure during follow-up (r=−.70, n=15; P<.001), but this was no longer the case in the enalapril group (r=.21; n=23; P=NS).

Table 4. Neurohumoral Data for Placebo and Enalapril Group

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<tr>
<th>Neurohormone</th>
<th>Placebo group</th>
<th>Enalapril group</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (ng·mL⁻¹·h)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>3.1</td>
<td>1.8</td>
</tr>
<tr>
<td>Median (range)</td>
<td>(0.1-22.2)</td>
<td>(0.1-25.8)</td>
</tr>
<tr>
<td>AVP (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>Median (range)</td>
<td>(0.8-3.8)</td>
<td>(1.2-7.2)</td>
</tr>
<tr>
<td>ANP (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>99</td>
<td>109</td>
</tr>
<tr>
<td>Median (range)</td>
<td>(27-348)</td>
<td>(24-508)</td>
</tr>
<tr>
<td>PNE (pg/mL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>422</td>
<td>443</td>
</tr>
<tr>
<td>Median (range)</td>
<td>(199-886)</td>
<td>(165-881)</td>
</tr>
</tbody>
</table>

*P<.001 vs baseline.
†P<.001 Δ placebo vs Δ enalapril.

PRA indicates plasma renin activity; AVP, arginine vasopressin; ANP, atrial natriuretic peptide; and PNE, plasma norepinephrine.
Discussion

The main findings of this study were that in chronic left ventricular systolic dysfunction, left ventricular dilatation continued to progress in the absence of therapy or with conventional heart failure therapy; left ventricular dilatation was accompanied by a decrease in left ventricular chamber stiffness; and enalapril therapy could prevent or partially reverse these changes in left ventricular volumes and diastolic properties.

To our knowledge, evidence that a progressive decrease in chamber stiffness might play a role in the progression of left ventricular dysfunction has never been provided. The assessment of the left ventricular diastolic properties is notoriously difficult in humans for two main reasons. First, external factors (e.g., pericardium, right-sided cardiac cavities, pleural pressure) may affect the left ventricular chamber distensibility independent of any change in the physical properties of the left ventricular walls. Second, it is difficult, both theoretically and practically, to calculate specific indexes of the diastolic properties such as the myocardial stiffness constant in these markedly enlarged and inhomogeneous ventricles. To determine the “stress-strain” relation from a single diastolic stress-volume relation, it is necessary to extrapolate the data to zero stress to determine the unstressed ventricular volume. However, as the diastolic stress-volume relation of these ventricles is relatively flat and displaced upward, negative volumes frequently are obtained when an extrapolation is made. This procedure therefore is unreliable, and to calculate myocardial stiffness in these patients, it would be necessary to modify the left ventricular loading conditions to obtain a series of end-diastolic stress-volume data. This is, however, impractical using angiographic techniques and also is subject to artifacts as in intact subjects, maneuvers such as volume loading also modify the right-sided pressure and dimensions.

Accordingly, our analysis was limited to indexes of chamber stiffness and chamber compliance, and to facilitate interpretation of the collected data, several additional measurements were performed. To determine if the shift in diastolic pressure-volume data could be related to a mechanical interference between cardiac chambers, the right ventricular volumes were measured at baseline and at follow-up using radionuclide angioscopy. The complex shape of the right ventricular cavity makes it not suitable for the classic geometric methods used to calculate volume from single-plane projections. Accordingly, a count-based methods, which does not require geometric assumption, was thought to be the most adequate to detect right ventricular volume changes within the same patient. As the rate and extent of myocardial relaxation may also affect the left ventricular distensibility, the indexes of isovolumic relaxation rate and were calculated in all patients. In addition, by measuring left ventricular end-systolic volume, the directional changes in recoil forces, another determinant of left ventricular distensibility during early filling, also could be predicted.

Based on these data, it appeared that the most likely hypothesis to explain the increase in left ventricular diastolic distensibility in the placebo group is that it reflected a true reduction in left ventricular chamber stiffness. This change could not be explained by any of the other indirect mechanisms discussed above, such as a decrease in right ventricular volume, an acceleration in the rate of relaxation, or a reduction in end-systolic volume. An effect of the pericardium also was unlikely as it generally produces parallel shifts of the diastolic pressure-volume data, without the change in slope observed here (Fig 2). The conclusion that left ventricular dilatation was accompanied by changes in the diastolic properties of the ventricle that could be prevented by ACE inhibition is consistent with the changes in passive left ventricular pressure-volume curves reported in rat ventricles after myocardial infarction, in the presence or absence of captopril treatment. The effect of enalapril observed in this study is also similar to that reported in a small uncontrolled study that used the impedance catheter to measure left ventricular volumes.

Interestingly, the changes in left ventricular volumes and in left ventricular compliance appeared to be the main differences related to therapy. Enalapril administration had no effect on the indexes of the inotropic state, on the end-systolic stress–to–end-systolic volume relation, on the slope of the end-systolic pressure–to–end-systolic volume relation, or on the isovolumic relaxation rate. Although there was a trend for ejection fraction to be better preserved in the treated group, the effect was significant in patients with heart failure only; in the prevention patients and when all patients were pooled, ejection fraction improved slightly in the placebo group, despite the left ventricular dilatation.

It is therefore tempting to suggest that the benefit of enalapril on pump failure deaths and in preventing the development of overt congestive heart failure in previously asymptomatic patients was at least partially mediated through an effect of ACE inhibitors on the diastolic properties of the left ventricle. The abnormally high values of systolic and diastolic wall stress and the depressed ejection fraction evidenced at baseline in all cases indicated that myocardial hypertrophy was insufficient to compensate in these patients for the initial myocardial injury. It is therefore likely that during the follow-up period, the mechanical and neurohumoral stimuli for hypertrophy remained active even in the asymptomatic patients. In the placebo group, this may have resulted in further eccentric myocardial hypertrophy. This by itself could explain the progressive left ventricular dilatation. Alterations in the collagen matrix, involving ruptures, changes in collagen type, and turnover rate, also have been described in several models of heart failures and also may have contributed to the dilatation process and to the increase in chamber compliance. As ventricular enlargement in the presence of inadequate hypertrophy increases wall stress via the Laplace mechanism, a vicious cycle is maintained that will eventually lead to the afterload mismatch phenomenon and to a decrease in ejection fraction, as were observed in the treatment group.

Over a 1-year period, enalapril therapy was able to stop this progression or to partially reverse it in some cases. At the group level, the chamber compliance index decreased, the sphericity indexes tended to improve, and the hypertrophy tended to regress, all of which are arguments in favor of “reversed remodeling.” One can only speculate on the mechanisms underlying the beneficial effects of enalapril in this clinical setting. The
mean diastolic wall stress improved compared with placebo but still remained abnormal; the mean systolic wall stress also remained elevated. There were little changes in systolic pressure, and in the placebo group, a decrease in systolic pressure did not prevent dilatation. Thus, we have no evidence to suggest that enalapril acted primarily by lowering systolic blood pressure or by reducing the mechanical stimuli for hypertrophy. ACE inhibitors, on the other hand, have been shown to improve the collagen matrix remodeling in experimental heart failure, and angiotensin II is known to promote myocardial hypertrophy. Many questions remain unanswered, however, if it is proposed that enalapril acted solely by reducing the levels of angiotensin II. Indeed, in several experimental models of pressure-overload hypertrophy with high levels of circulating angiotensin II and aldosterone, the changes in left ventricular chamber compliance are opposite those observed in the placebo group. Furthermore, in the present study, there appeared to be no correlation between changes in plasma neurohormones over time and the changes in ventricular function. Accordingly, much remains to be done to elucidate the action of ACE inhibitors on the progression of left ventricular dysfunction and, in particular, to determine to what extent their effect is mediated through a reduction of angiotensin II receptor stimulation at the level of the fibroblasts and myocytes.

In addition to these difficulties of interpretation, the present study also has several practical limitations. The groups were small, and a significant proportion of patients could not be restudied, particularly in the placebo group. The fact that diuretic therapy had to be increased or started during follow-up may also have affected the changes in left ventricular function, left ventricular filling pressure, and neurohormones in those patients who were restudied. Nevertheless, the individual changes were consistent in each group, and when patients matched for baseline ejection fraction and end-systolic volume were compared, the conclusions remain unchanged (data not shown). It is likely, therefore, that the natural history of the changes in left ventricular chamber compliance described in this study is correct, although the large number of dropouts in the placebo group and the fact that no patients were recontrolled when they were in end-stage heart failure may have been responsible for an underestimation of the magnitude of the changes. It also seems clear that enalapril was not able to block progression toward congestive heart failure in all patients, as indicated by the fact that six prevention patients in this group developed heart failure during follow-up; furthermore, left ventricular chamber stiffness was increased by enalapril in only half of the patients who could be restudied.

Another limitation lies in the measurement of wall thickness and in the calculation of left ventricular wall mass and wall stress in these distorted ventricles. In this context, it is noteworthy that in another subset of SOLVD patients, left ventricular mass derived by an echocardiographic method was also found to be less in the enalapril group than in the placebo group. Our data also draw the attention to the lack of sensitivity of the indexes of rapid left ventricular filling to detect these changes in left ventricular chamber compliance during progression or regression of left ventricular dysfunction.

Finally, it is worth remembering that a benefit of captopril on left ventricular dilatation, progression toward congestive heart failure, and survival has also been observed when the therapy was initiated within days of an acute myocardial infarction. As many factors contribute to left ventricular enlargement immediately after an acute myocardial infarction, a comparison between these results and those of the present study should be made only with caution. Qualitatively, the effects of ACE inhibitors administered early after myocardial infarction are consistent with the present findings. It is possible, however, that quantitatively the benefit of ACE inhibitor therapy could be different when introduced later during the evolution of left ventricular dysfunction. Large individual variations in chamber stiffness, volume, and mass were present at baseline in our patients, and further studies would be needed to determine if earlier treatment could have prevented these wide variations.

In conclusion, the data indicate that in patients with severe systolic left ventricular dysfunction, the progressive left ventricular dilatation was accompanied by a decrease in left ventricular chamber stiffness; enalapril therapy was able to prevent or partially reverse these changes and tended to reduce left ventricular mass and ventricular sphericity. Those changes were suggestive of a partial reversal of left ventricular remodeling by enalapril administration.

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