Effects of the Angiotensin Converting Enzyme Inhibitor Enalapril on the Long-term Progression of Left Ventricular Dysfunction in Patients With Heart Failure

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Background. In patients with heart failure, activation of the renin–angiotensin system is common and has been postulated to provide a stimulus for further left ventricular (LV) structural and functional derangement. We tested the hypothesis that chronic administration of the angiotensin converting enzyme (ACE) inhibitor enalapril prevents or reverses LV dilatation and systolic dysfunction among patients with depressed ejection fraction (EF) and symptomatic heart failure.

Methods and Results. We examined subsets of patients enrolled in the Treatment Trial of Studies of Left Ventricular Dysfunction (SOLVD). Fifty-six patients with mild to moderate heart failure underwent serial radionuclide ventriculograms, and 16 underwent serial left heart catheterizations, before and after randomization to enalapril (2.5–20 mg/day) or placebo. At 1 year, there were significant treatment differences in LV end-diastolic volume (EDV; *p*<0.01), end-systolic volume (ESV; *p*<0.005), and EF (*p*<0.05). These effects resulted from increases in EDV (mean±SD, 136±27 to 151±38 ml/m²) and ESV (103±24 to 116±24 ml/m²) in the placebo group and decreases in EDV (140±44 to 127±37 ml/m²) and ESV (106±42 to 93±37 ml/m²) in the enalapril group. Mean LVEF increased in enalapril patients from 0.25±0.07 to 0.29±0.08 (*p*<0.01). There was a significant treatment difference in LV end-diastolic pressure at 1 year (*p*<0.05), with changes paralleling those of EDV. The time constant of LV relaxation changed only in the placebo group (*p*<0.01 versus enalapril), increasing from 59.2±8.0 to 67.8±7.2 msec. Serial radionuclide studies over a period of 33 months showed increases in LV volumes only in the placebo group. Two weeks after withdrawal of enalapril, EDV and ESV increased to baseline levels but not to the higher levels observed with placebo.

Conclusions. In patients with heart failure and reduced LVEF, chronic ACE inhibition with enalapril prevents progressive LV dilatation and systolic dysfunction (increased ESV). These effects probably result from a combination of altered remodeling and sustained reduction in preload and afterload. (Circulation 1992;86:431–438)

KEY WORDS • vasodilation • ventricular function • cardiomyopathies • ejection fraction

Heart failure caused by left ventricular (LV) systolic dysfunction is characterized by progressive symptomatic deterioration and high mortality.1–3 Angiotensin converting enzyme (ACE) inhibitors improve exercise capacity in patients with heart failure4–9 and improve survival in patients who are severely symptomatic (New York Heart Association [NYHA] class IV).10 The Studies of Left Ventricular Dysfunction (SOLVD) include two large-scale, randomized, placebo-controlled trials designed to assess the effect of the ACE inhibitor enalapril on survival in patients with depressed LV ejection fraction (≤0.35). The recently reported results of the SOLVD Treatment Trial11 indicated a significant reduction in mortality by enalapril in patients with symptomatic heart failure, most of whom were in NYHA class II or III, over a mean follow-up of 42 months.

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To examine the natural history of LV volume and function and the effects of chronic ACE inhibition on this course, we performed serial radionuclide ventriculograms and serial cardiac catheterizations in subsets of patients enrolled in the SOLVD Treatment Trial and randomized to receive either enalapril or placebo. We postulated that patients with symptomatic heart failure are characterized by progressive LV dilatation and systolic dysfunction and that this course is prevented or reversed by chronic therapy with an ACE inhibitor.

Methods

Study Protocol

Fifty-six patients participating in the SOLVD Treatment Trial at three centers who also consented to participate in the substudy were enrolled in the radionuclide study between September 1987 and March 1991. Participating centers were Tufts University/New England Medical Center, Boston; Vanderbilt University, Nashville, Tenn.; and the University of Louvain, Brussels. Sixteen Treatment Trial patients at the University of Louvain (including 14 patients participating in the radionuclide study) were enrolled in the catheterization study. Radionuclide and catheterization protocols were approved by the Human Investigation Review Committees at each institution at which they were performed, and all patients gave written informed consent. Radionuclide and catheterization studies were performed before randomization and 1 year after randomization. At Tufts University and Vanderbilt University, radionuclide studies were performed at three additional time points: 1) 4 months after randomization; 2) at the completion of SOLVD, 20–36 (mean 33) months after randomization, while patients continued to receive the study drug; and 3) after withdrawal of the study drug for an average of 15 days at the completion of SOLVD.

Enrollment criteria were that LV ejection fraction, measured within the preceding 3 months, be ≥0.35 and that patients be receiving medication for treatment of symptomatic heart failure. Patients were excluded if any of the following were present: age >80 years, hemodynamically significant valvular disease requiring surgery, unstable angina, angina thought to be severe enough to require revascularization procedures, myocardial infarction within the past 30 days, severe pulmonary disease, serum creatinine >2 mg/dl, or other diseases that might significantly shorten survival or impair participation in a long-term trial. Before baseline measurements, all patients received single-blind enalapril, 2.5 mg orally twice daily, for 2–7 days to screen for intolerance to this lowest dosage, followed by single-blind placebo for 14 to 17 days to screen for noncompliance or worsening of clinical condition upon drug withdrawal.

After initial baseline radionuclide and catheterization measurements, patients were randomized to receive either placebo or enalapril, 5 mg orally twice daily. The drug dosage was increased to 10 mg twice daily if tolerated or decreased if necessitated by adverse effect. Radionuclide and catheterization studies were performed with the patient supine for at least 30 minutes after an overnight fast. Diuretics and non–ACE inhibitor vasodilators were withheld for a minimum of 12 and 4 hours, respectively. All studies except before randomization and after withdrawal were performed 2–6 hours after a dose of the study drug.

Radionuclide Studies

Red blood cells were labeled by a modified in vivo method as previously described.13 Equilibrium-gated radionuclide ventriculograms were acquired in a modified left anterior oblique projection with caudal angulation.14–16 Scans were acquired for 8 minutes (minimum 5 million counts), with each cardiac cycle divided into 32 frames. Blood pressure was recorded with a sphygmomanometer at least twice during the course of the scan acquisition, and the recordings were averaged.

Radionuclide studies were analyzed at the SOLVD Radionuclide/Ventricular Performance Core Laboratory at Tufts University/New England Medical Center by previously described techniques.14–17 Studies were analyzed and reviewed by a technologist and a physician who were blinded to treatment. LV end-diastolic and end-systolic volumes were calculated on the basis of the ratio of background-subtracted LV counts to counts within a 5-ml blood sample, corrected for tissue attenuation.17 LV stroke volume was calculated as end-diastolic volume minus end-systolic volume, LV output was calculated as stroke volume times heart rate, and ejection fraction was calculated as stroke volume divided by end-diastolic volume.

We tested intraobserver variability of our radionuclide measurements by analysis of duplicate scans with duplicate blood sample acquisitions in a series of 10 patients. Coefficients of variation were as follows: LV ejection fraction, 3.9% (percent of measured ejection fraction) and LV end-diastolic and end-systolic volumes, 3.4% and 3.1%, respectively. In all cases, the correlation coefficient between duplicate measurements was 0.99.

Catheterization

Left heart catheterization was performed without premedication, as described previously.18 An 8F pigtail Millar catheter (Millar Instruments Inc., Houston, Tex.) was introduced through the femoral artery to measure high-fidelity LV pressure and to inject contrast material. Angiographic images were acquired with Philips PolyaDiagnost C and DVI systems (Phillips Instruments, Best, The Netherlands). These systems allow the acquisition of nonsubtracted LV images at 50 frames per second with 1,024 shades of gray (10 bits) and a geometric resolution of approximately 0.7 mm. During the 3 m sec of frame exposure, there was simultaneous acquisition of the LV pressure and the ECG signal.19 LV pressure, together with the ECG signal, was continuously recorded on analog magnetic tape (Honeywell 101, Honeywell Information Systems, Inc., Waltham, Mass.).

Hemodynamic and Ventriculographic Data Analysis

One patient who had been randomized to enalapril was excluded from analysis because a severely abnormal LV contour precluded accurate assessment of ventricular volumes. In the remaining patients, analog data were digitized every 2 m sec and processed off-line with 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 LV end-diastolic
pressure) were automatically detected by a set of sub-
routines for generation of average pressure-volume
loops.19 LV pressure data after peak negative dp/dt
were also fitted to an exponential relation by a least-
squares regression technique, and the time constant \( T_c \)
(0–40 msec after peak negative dp/dt) of this relation
was used as an index of LV isovolumic relaxation.20
Peak positive dp/dt and the dp/dt measured and nor-
malized at a developed pressure of 40 mm Hg, (dp/dt)/
DP\(_{40}\),21 were used as isovolumic indexes of inotropic
state. For evaluation of LV function, masked ventricular
silhouettes were outlined frame by frame on a video
screen with an electronic cursor. Both premature and
post premature beats were excluded from analysis. A
computer system (APU Philips, Philips Electronic In-
struments Co., Mahwah, N.J.) was used to derive the
correction factor for x-ray magnification and calculated
volumes every 20 msec by applying Simpson’s rule. The
ejunction fraction was calculated using the frame with
the maximal pressure–volume ratio as end systole.22,23 The
LV pressure–volume loop was constructed after data
smoothing for each patient, and the individual loops
were averaged by the method described previously.19
The angiographic data were analyzed by two blinded
observers.

**Plasma Renin Assay**

Blood samples were drawn via an indwelling intrave-
nous line, with the patient supine for at least 30
minutes. Plasma samples were shipped on dry ice and
were analyzed at the SOLVD Neuroendocrine Core
Laboratory at the University of Texas Health Science
Center, Houston. Plasma renin activity was measured
by radioimmunoassay.24,25

**Statistics**

Statistical analyses were performed at the Collabora-
tive Studies Coordinating Center, University of North
Carolina. All data were analyzed according to intention
to treat and were adjusted for center variations. The
primary analysis examined group means and treatment
effects among patients who underwent study both
before randomization and at 1 year. In addition, attempts
were made to identify potential biases resulting from
patient death or dropout. For this purpose, imputation
of data was performed by three methods: 1) use of last
available data, 2) linear regression applied to all avail-
able data from the individual patients, and 3) rank
observations, assigning the worst ranks to patients who
died soonest. All treatment effects remained consistent
regardless of analysis strategy. The significance of
changes from baseline in each parameter within each
treatment group was analyzed by paired \( t \) test. Signifi-
cance of treatment effect (enalapril group versus pla-
acebo group) was determined by ANCOVA, adjusting
for baseline values, for radionuclide measurements, and
by unpaired \( t \) test for catheterization study parameters.
Repeated-measures analysis was performed to examine
treatment differences across the five sets of measure-
ments performed at two study sites.

**Results**

Of the 56 patients entered into the radionuclide
study, 31 were randomized to receive enalapril and 25 to
receive placebo. Two patients randomized to enalapril

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics</th>
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<tr>
<td>Age (years; mean±SD)</td>
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<tr>
<td>Males (%)</td>
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<tr>
<td>Cause (%)</td>
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<tr>
<td>Coronary disease</td>
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<td>Idiopathic</td>
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<tr>
<td>NYHA class (%)</td>
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<td>I</td>
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<td>II</td>
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<td>III</td>
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<td>IV</td>
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<tr>
<td>Medications (%)</td>
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<tr>
<td>Digoxin</td>
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<tr>
<td>Diuretics(^a)</td>
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<td>Vasodilators(^a)</td>
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<tr>
<td>(non–ACE inhibitors)</td>
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<td>EF (%; mean±SD)</td>
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NYHA, New York Heart Association; ACE, angiotensin con-
verting enzyme; EF, ejection fraction.

\(^a\)Two deaths, four refusals, one cardiac transplant. \(^b\)Seven
deaths, three refusals. \(^c\)With previous clinical evidence of heart
failure. \(^d\)Withheld before each radionuclide and catheterization
study.

and seven randomized to placebo died before 1 year.
Five additional enalapril patients (four refusals, one
cardiac transplant) and three additional placebo pa-

Table 1 lists clinical characteristics of the study
population at baseline, comparing findings between the
enalapril and placebo groups for the 39 patients who
contributed to the 1-year radionuclide analysis and the
17 who did not. There were no significant differences
between enalapril and placebo groups for any baseline
characteristic. Patients who were not studied at 1 year
appeared slightly sicker at baseline, with a higher pro-
portion of patients in NYHA class III and a higher
portion receiving digoxin. However, none of these
differences were statistically significant, and these char-
acteristics were similar in groups randomized to enala-
pril and to placebo.

Heart rate, blood pressure, and radionuclide-derived
parameters measured before randomization and 1 year
after randomization to either placebo or enalapril are
listed in Table 2. There was no difference between
enalapril and placebo groups with regard to any param-
eter at baseline. At 1 year, both systolic and diastolic
blood pressure were reduced compared with baseline in
enalapril-treated patients. Heart rate was significantly reduced at 1 year in the enalapril group, and the difference between the two groups with regard to heart rate change was statistically significant.

The enalapril and placebo groups differed significantly in terms of change in LV end-diastolic volume and end-systolic volume, with ventricular volumes increasing in the placebo group and decreasing in the enalapril group. The groups also differed with regard to change in ejection fraction, which increased compared with baseline in enalapril-treated patients but not in placebo-treated patients. There were no significant differences between the two patient groups with regard to change in LV stroke volume or LV minute output.

Of patients undergoing catheterization before randomization, two placebo patients died and one enalapril patient underwent cardiac transplant before one year. One additional enalapril patient refused repeat catheterization. Of the 11 patients who underwent repeat catheterization at 1 year, six had been randomized to enalapril and five to placebo. Data derived during catheterization performed before randomization and 1 year after randomization are presented in Table 3. Changes in ventricular volumes were consistent with radionuclide findings. In addition, the two groups differed significantly in terms of treatment effect on LV end-diastolic pressure, with changes paralleling those in end-diastolic volume. Isovolumic indexes of contractility trended downward in the placebo group, with statistical significance reached for peak positive dP/dt, although these changes were not significantly different from those observed in the enalapril group. In contrast, changes from baseline to 1 year in the time constant of relaxation differed significantly between the two patient groups, increasing in the placebo group and remaining unchanged in the enalapril group.

Figure 1 depicts the average LV pressure–volume loops at baseline and at 1 year for patients randomized to placebo and to enalapril. The entire curve was shifted rightward in the placebo group and leftward in the enalapril group. There was no obvious upward or downward displacement or alteration in the slope of the curve during diastole.

Figure 2 shows radionuclide findings and systolic blood pressure before randomization; at 4 months, 1 year, and an average of 33 months after randomization; and an average of 15 days after withdrawal from enalapril (n=11) or placebo (n=7) from the two centers at which these multiple time points were sampled. Repeat-measures analyses revealed significant treatment differences in both end-diastolic (p<0.05) and end-systolic volumes (p<0.05) with either exclusion or inclusion of postwithdrawal data points. Progressive increases from baseline in LV volumes in the placebo group and an early and sustained reduction in LV volumes in the enalapril group contributed to these treatment differences. After withdrawal from enalapril, both systolic blood pressure and LV volumes increased to approximately the level observed before randomization. However, ventricular volumes did not reach the higher levels observed in the placebo group. Measurements of plasma renin activity indicated that ACE inhibitor effect had been removed after withdrawal of enalapril.

In the enalapril group, plasma renin activity increased from 2.2±1.6 ng/ml/hr at baseline to 11.7±13.7 ng/ml/hr (p<0.05) just before drug withdrawal. This value decreased to 1.4±1.4 ng/ml/hr at the time of the postwithdrawal radionuclide study (not significantly different compared with baseline). In placebo patients, plasma renin activity did not change significantly during the study period.

Between 11 and 19 days after withdrawal from the study drug at the completion of SOLVD, four patients, all of whom had been withdrawn from enalapril, developed adverse events. Of these, two patients suffered myocardial infarction, and one of these two developed

### Table 2. Results: Heart Rate, Blood Pressure, and Radionuclide Measurements

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 year</th>
<th>P (B vs. 1 year)</th>
<th>P (P vs. E*)</th>
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<tbody>
<tr>
<td>Heart rate (min⁻¹)</td>
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<tr>
<td>P</td>
<td>78±11</td>
<td>74±6</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>77±14</td>
<td>68±12</td>
<td>0.01</td>
<td>0.04</td>
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<tr>
<td>Systolic BP (mm Hg)</td>
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<tr>
<td>P</td>
<td>129±17</td>
<td>125±12</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>130±25</td>
<td>122±19</td>
<td>0.05</td>
<td>NS</td>
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<tr>
<td>Diastolic BP (mm Hg)</td>
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<td></td>
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<tr>
<td>P</td>
<td>78±10</td>
<td>78±7</td>
<td>NS</td>
<td></td>
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<tr>
<td>E</td>
<td>76±11</td>
<td>72±9</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>LVEDV (ml/m²)</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>P</td>
<td>136±27</td>
<td>151±38</td>
<td>0.10</td>
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<tr>
<td>E</td>
<td>140±44</td>
<td>127±37</td>
<td>0.02</td>
<td>0.008</td>
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<tr>
<td>LVESV (ml/m²)</td>
<td></td>
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<tr>
<td>P</td>
<td>103±24</td>
<td>116±24</td>
<td>0.08</td>
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<tr>
<td>E</td>
<td>106±42</td>
<td>93±37</td>
<td>0.01</td>
<td>0.002</td>
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<tr>
<td>LVEF (%)</td>
<td></td>
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<td></td>
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<tr>
<td>P</td>
<td>25±5</td>
<td>24±8</td>
<td>NS</td>
<td></td>
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<tr>
<td>E</td>
<td>25±7</td>
<td>29±8</td>
<td>0.01</td>
<td>0.04</td>
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<tr>
<td>LSVV (ml/m²)</td>
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<tr>
<td>P</td>
<td>33±8</td>
<td>35±12</td>
<td>NS</td>
<td></td>
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<tr>
<td>E</td>
<td>33±8</td>
<td>34±8</td>
<td>NS</td>
<td>NS</td>
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<tr>
<td>LVCO (l/min/m²)</td>
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<tr>
<td>P</td>
<td>2.5±0.6</td>
<td>2.6±0.9</td>
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<td></td>
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<tr>
<td>E</td>
<td>2.5±0.6</td>
<td>2.3±0.6</td>
<td>NS</td>
<td>NS</td>
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</tbody>
</table>

B, baseline; P, placebo; E, enalapril; BP, blood pressure; LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; SV, stroke volume; CO, cardiac output. Data are mean±SD. P, n=15; E, n=24.

*Significance for difference in treatment effect.
cardiogenic shock and died. One patient developed unstable angina and underwent emergency coronary artery bypass graft surgery. One patient was hospitalized with ventricular tachycardia and worsening heart failure and subsequently died.

### Discussion

Activation of the renin–angiotensin–aldosterone axis in patients with heart failure provides rationale for the therapeutic use of ACE inhibitors. ACE inhibitors have been documented to improve hemodynamics acutely and functional capacity chronically in patients with heart failure caused by LV systolic dysfunction. Two large-scale placebo-controlled trials have documented that the ACE inhibitor enalapril improves survival in patients with NYHA functional class IV10 and class II–III heart failure.11 In both of these studies, enalapril-induced improvement in survival resulted principally from a reduction in mortality related to worsening heart failure. In addition, enalapril was found to reduce the frequency of hospitalization for worsening heart failure.11

In the present study, we observed that chronic ACE inhibition substantially improved the natural history of changes in LV cavity size and mechanical performance in patients with mild to moderate heart failure caused by LV systolic dysfunction. It is tempting to speculate that the beneficial effects of enalapril on ventricular dilatation and performance are related to the reduction in the clinical expression and mortality of heart failure.10,11

Ventricular remodeling has been best described in the setting of prior myocardial infarction. After myocardial infarction, the LV cavity dilates because of thinning and expansion within the infarcted zone. Subsequent LV dilatation appears to be related to hypertrophy with expansion of the endocardial surface in noninfarcted regions. Several studies have suggested that inhibition of the renin–angiotensin system may reduce the propensity to myocardial hypertrophy and remodeling after acute myocardial infarction, possibly through vasodilation and reduction in myocardial wall stress. In all of these studies, ACE inhibition was initiated early after myocardial infarction.

Our study population comprised patients with clinical heart failure caused by coronary artery disease or

### Table 3. Catheterization Results

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 year</th>
<th>P (B vs. 1 year)</th>
<th>P (P vs. E*)</th>
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<tbody>
<tr>
<td>LVEDV (ml/m²)</td>
<td>P</td>
<td>185±53</td>
<td>200±41</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>193±38</td>
<td>180±42</td>
<td>0.03</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>P</td>
<td>19±5</td>
<td>18±3</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>21±9</td>
<td>27±5</td>
<td>NS</td>
</tr>
<tr>
<td>LVESV (ml/m²)</td>
<td>P</td>
<td>149±41</td>
<td>167±54</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>152±35</td>
<td>133±38</td>
<td>0.03</td>
</tr>
<tr>
<td>LVEDP (mm Hg)</td>
<td>P</td>
<td>25±9</td>
<td>30±5</td>
<td>NS</td>
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<tr>
<td></td>
<td>E</td>
<td>30±10</td>
<td>23±7</td>
<td>0.04</td>
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<td>LVSP (mm Hg)</td>
<td>P</td>
<td>123±28</td>
<td>128±15</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>133±35</td>
<td>131±14</td>
<td>NS</td>
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<tr>
<td>Peak positive dP/dt (mm Hg/sec)</td>
<td>P</td>
<td>1,196±269</td>
<td>1,021±214</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>E</td>
<td>1,328±705</td>
<td>1,116±318</td>
<td>NS</td>
</tr>
<tr>
<td>(dP/dt)/DP_{a0} (sec⁻¹)</td>
<td>P</td>
<td>15.2±6.2</td>
<td>13.0±3.1</td>
<td>NS</td>
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<tr>
<td></td>
<td>E</td>
<td>17.3±10.8</td>
<td>16.5±6.5</td>
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<td>T₁ (msec)</td>
<td>P</td>
<td>59.2±8.0</td>
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<tr>
<td></td>
<td>E</td>
<td>62.0±10.6</td>
<td>62.0±8.0</td>
<td>NS</td>
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</tbody>
</table>

B, baseline; P, placebo; LV, left ventricular; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; EDP, end-diastolic pressure; SP, peak systolic pressure; dP/dt, rate of LV pressure change; DP_{a0}, at developed pressure of 40 mm Hg; T₁, time constant of early relaxation. Data are mean±SD. P, n=5; E, n=6.

*Significance for difference in treatment effect.
dilated cardiomyopathy, with specific exclusion of patients with recent myocardial infarction. Our findings, therefore, support the concept that the LV protective effect of chronic ACE inhibition is not confined to patients with coronary disease or to those with recent myocardial infarction. Rather, it is likely that LV remodeling is a chronic, progressive process that continues after the clinical expression of heart failure and occurs regardless of the primary cause of myocardial disease. This process may be slowed or reversed by ACE inhibitor therapy, even if instituted at a time remote from that of the initial insult. Return of LV volumes to baseline levels after withdrawal of enalapril indicates that a component of ACE inhibitor effect results from an ongoing influence on ventricular load. LV volumes did not reach the higher levels observed within the placebo group, however. The latter finding supports the view that enalapril altered the progression of ventricular remodeling.

Within our placebo group, the rate of isovolumic LV pressure rise decreased significantly at 1 year, suggesting further depression in contractility, although the difference between the two patient groups in terms of the change in this parameter was not statistically significant. However, the ventricular pressure–volume curves showed a rightward shift at end systole in placebo-treated patients, which was opposite to that seen in the enalapril group, suggesting that enalapril prevented or reversed progression of myocardial contractile dysfunction.

Changes in end-diastolic pressure paralleled changes in end-diastolic volume in a manner that could represent movement along a fairly constant diastolic pressure–volume curve. There was a significant difference in change in the time constant of relaxation between the enalapril and placebo groups, however, with the latter group manifesting progressive aberration in myocardial relaxation. It cannot be determined whether this difference is independent of differences in load and in end-systolic volume between the two groups.

We are uncertain about the relation between enalapril withdrawal and the adverse events observed after discontinuation of the study drug. Within the SOLVD Treatment Trial, a reduction in the incidence of fatal myocardial infarction contributed to the reduction in
mortality among patients randomized to enalapril.11 Recently, levels of plasma renin activity have been found to be related to the incidence of myocardial ischemic events independently of the degree of hypertension.38 The events in our patients raise the possibility that abrupt withdrawal of enalapril, through undefined mechanisms, results in acute myocardial ischemia, perhaps mediated through increased levels of angiotensin II.

In summary, long-term enalapril administration to patients with symptomatic LV systolic dysfunction results in favorable changes in ventricular volumes that are significantly different from the progressive dilatation observed in placebo-treated controls. These differences are likely to result both from prevention of adverse ventricular remodeling and from ongoing effects on ventricular systolic and diastolic load. Additional investigation is needed to gain further insight into the mechanisms by which ACE inhibition achieves these effects and into the relation among the effects of ACE inhibitors on ventricular performance, symptoms, functional capacity, and survival.

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