Effects of the Angiotensin Converting Enzyme Inhibitor Enalapril on the Long-term Progression of Left Ventricular Dilatation in Patients With Asymptomatic Systolic Dysfunction

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Background. Patients with heart failure and reduced left ventricular (LV) ejection fraction (EF) manifest progressive LV dilatation, which is prevented by angiotensin converting enzyme (ACE) inhibitors. In patients with asymptomatic LV systolic dysfunction, in whom there is less activation of the renin-angiotensin system, ventricular remodeling might be less rapid and the benefit of ACE inhibitors less discernible.

Methods and Results. One hundred eight patients enrolled in the Studies of Left Ventricular Dysfunction (SOLVD) Prevention Trial, with left ventricular ejection fraction ≥0.35 but without clinical heart failure, underwent radionuclide ventriculograms, and 49 underwent left heart catheterizations. Measurements were made before and after double-blinded randomization to enalapril (2.5 to 20 mg/d) or placebo. Repeated-measures analysis of all time points showed significant differences for change in end-diastolic volume (EDV) between enalapril and placebo groups. Significant difference between the enalapril and placebo groups \((P<.05)\) was present for change in EDV at 1 year within the catheterization study and at a mean of 25 months within the radionuclide study. Radionuclide EDV increased in placebo patients \((119\pm28\) to \(124\pm33\) mL/m², mean±SD) and decreased in enalapril patients \((120\pm25\) to \(113\pm25\) mL/m²). Differences between the two groups were significantly less than previously described in patients with symptomatic heart failure \((P<.02)\), with less increase in LV volumes in the placebo group and less decrease in volumes in the enalapril group.

Conclusions. Chronic ACE inhibitor treatment slows or reverses LV dilatation in patients with asymptomatic LV systolic dysfunction. Compared with symptomatic patients, asymptomatic patients manifest a slower rate of spontaneous LV dilatation and less reduction in LV volumes by enalapril. (Circulation. 1993;88[part 1]:2277-2283.)

KEY WORDS • vasodilation • ejection fraction • heart failure

Patients with depressed left ventricular (LV) ejection fraction manifest progressive LV dilatation and systolic functional impairment, findings that have been attributed to excessive wall stress.1,2 We previously observed that this adverse progression may be halted by chronic administration of angiotensin converting enzyme (ACE) inhibitors.2 The relative degree to which LV dilatation and systolic dysfunction progresses and the relative benefit of ACE inhibition in patients with symptomatic versus asymptomatic depression of LV ejection fraction has not been explored. Asymptomatic patients manifest less or absent elevations in plasma renin,3 and this difference may result in less rapid alteration in myocardial architecture and function. Furthermore, it might imply that less benefit is derived from administration of ACE inhibitors in such patients.

In the present study, we performed serial radionuclide measurements of LV volumes and function over an average of 25 months in patients enrolled in the Prevention Trial of Studies of Left Ventricular Dysfunction (SOLVD), who were randomized to long-term enalapril...
or placebo. In this asymptomatic population with LV ejection fractions ≤0.35, we explored the rate of enlargement of ventricular volumes and the influence of ACE inhibitor treatment on ventricular dilatation.

Methods

Study Protocol

The radionuclide study population consisted of 108 patients participating in the SOLVD Prevention Trial at three centers: Tufts University, New England Medical Center, Boston; Vanderbilt University, Nashville, Tenn; and University of Louvain, Brussels, Belgium. At the University of Louvain, 49 prevention trial patients (including 40 patients participating in the radionuclide study) were enrolled in the catheterization study. Both radionuclide and catheterization studies were performed before randomization and 1 year after randomization. At Tufts University and at Vanderbilt University, radionuclide studies were performed at three additional time points: (1) 4 months after randomization; (2) at the completion of SOLVD, 13 to 45 months (mean, 25) after randomization while patients continued to receive study drug; (3) after withdrawal of study drug for a minimum of 5 days, at the completion of SOLVD. 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.

Entrance criteria for the prevention trial included LV ejection fraction ≤0.35 measured within the preceding 3 months by radionuclide ventriculography, echocardiography, or contrast ventriculography and absence of medication prescribed for treatment of heart failure.6 7 The protocol permitted use of digoxin if prescribed for supraventricular arrhythmia, diuretics, or vasodilators if prescribed for hypertension and nitrates if prescribed for angina. This population differed from that of the previously reported treatment trial,2 in whom treatment for heart failure was considered indicated. Patients were excluded if any of the following were present: age greater than 80 years, hemodynamically significant valvular disease requiring surgery, unstable angina, angina thought to be severe enough to require revascularization, myocardial infarction within the previous 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 to 7 days to screen for intolerance to this lowest dose, 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) twice daily, orally. The drug dose 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 prerrandomization and postwithdrawal were performed 2 to 6 hours after a dose of study drug.

Radionuclide Studies

Red blood cells were labeled by a modified in vivo method, as previously described.6 Equilibrium-gated radionuclide ventriculograms were acquired in a modified left anterior oblique projection with caudal angulation.7 8 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, using previously described techniques.7-10 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 based on the ratio of background-subtracted LV counts to counts within a 5-mL blood sample, corrected for tissue attenuation.10 LV stroke volume was calculated as end-diastolic volume minus end-systolic volume, LV output as stroke volume times heart rate, and ejection fraction as stroke volume divided by end-diastolic volume.

We previously 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); 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.11 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 Polylagnost C and DVI systems (Philips Instruments, Best, The Netherlands). These systems allow the acquisition of nonsubtracted LV images at 50 frames/s with 1024 shades of gray (10 bits) and a geometric resolution of approximately 0.7 mm. During the 3 milliseconds of frame exposure, there was simultaneous acquisition of the LV pressure and the ECG signal.12 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

Analog data were digitized every 2 milliseconds 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 LV end-diastolic pressure, LVEDP) were automatically detected by a set of subroutines for generation of average pressure-volume loops.12 The angiographic data were analyzed by two blinded observers. Masked ventricular silhouettes were outlined frame by frame on a video screen using an electronic cursor. Both prema-
ture and premature beats were excluded from analysis. A computer system (APU Philips, Philips Electronic Instrument Co, Mahwah, NJ) was used to derive the correction factor for x-ray magnification and calculated volumes every 20 milliseconds by applying Simpson's rule. The LV pressure-volume loop was constructed after data smoothing for each patient, and the individual loops were averaged using the method described previously.12

**Plasma Renin Assay**

With the patient supine for at least 30 minutes, blood samples were drawn via an indwelling intravenous line into a tube containing sodium-EDTA. Plasma samples were shipped on dry ice and were analyzed at the SOLVD Neuroendocrine Core Laboratory at the University of Texas, Galveston, later relocated to the University of Texas Health Science Center, Houston. Plasma renin activity was measured using a standard radioimmunoassay.3

**Statistics**

Statistical analyses were performed at the Collaborative Studies Coordinating Center, University of North Carolina. All data were analyzed according to intention to treat and were adjusted for center variations. Results are expressed as mean±SD. Significance of change from baseline in each parameter within each treatment group was analyzed using paired t tests. Significance of treatment effect (enalapril group vs placebo group) and of between-trial (prevention trial vs treatment trial) comparisons was determined by analyses of covariance, adjusting for baseline values. Repeated-measures analysis was performed to examine treatment differences across the multiple sets of measurements performed at two study sites.

**Results**

Of the 108 patients entered into the radionuclide study, 53 were randomized to receive enalapril and 55 to receive placebo. Of the 49 patients entered into the catheterization study (including 40 enrolled in the radionuclide study), 27 were randomized to enalapril and 22 to placebo. Five enalapril patients and 4 placebo patients died before 1 year (4 enalapril and 3 placebo patients within the catheterization study). Six additional enalapril patients (5 refusals, 1 intercurrent coronary bypass surgery) and 7 additional placebo patients (3 refusals, 2 heart transplants, 2 coronary bypass surgery) did not undergo repeat radionuclide study at 1 year (4 enalapril and 9 placebo patients within the catheterization study). Thus, 86 patients (42 enalapril and 44 placebo) had radionuclide studies, and 29 patients (19 enalapril and 10 placebo) had catheterizations performed at baseline and 1 year and were included in the analysis.

In 1 of the 42 enalapril patients (none within the catheterization study), study drug had been discontinued because of adverse effect; the remainder were receiving active study drug. In 4 of the 44 placebo patients, study drug had been discontinued (none within the catheterization study): In 2 patients, adverse effects had occurred, and in 2 patients, open-label ACE inhibitor had been instituted because of clinical deterioration. At 1 year, the mean study drug dose was 18.6 mg/d among patients randomized to enalapril and 18.6 mg/d for patients continuing to take study drug. Corresponding doses for patients randomized to placebo were 15.2 and 18.0 mg/d, respectively.

Sixty-eight patients were enrolled at the two centers that performed radionuclide studies at the completion of SOLVD, with 31 randomized to enalapril and 37 to placebo. Of these, 2 enalapril and 6 placebo patients died before the final study. In addition, 6 enalapril patients and 1 placebo patient refused the final two studies (before and after drug withdrawal), and 1 placebo patient could not be studied for a technical reason (inability to gate). Study drug had been discontinued before study end in 2 enalapril patients (1 because of adverse effect and 1 with institution of open-label ACE inhibitor because of clinical deterioration) and in 4 placebo patients (all with institution of open-label ACE inhibitor because of clinical deterioration). Thus, 46 patients—21 enalapril and 25 placebo patients—had data available through completion of SOLVD, before and after withdrawal of study drug.

<table>
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<td><strong>EF, % (mean±SD)</strong></td>
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ACE indicates angiotensin converting enzyme and EF, ejection fraction.

*Includes 40 patients participating in the catheterization study; †for supraventricular arrhythmia; §for hypertension; ¶¶withheld before each radionuclide and catheterization study; ||for hypertension or angina.
trended downward in placebo-treated patients as well, and the difference between the two groups was not statistically significant. Heart rate was not significantly changed in either group.

Over the entire study period, LV end-diastolic and end-systolic volumes trended upward in the placebo group and downward in the enalapril group. Repeated-measures analysis applied to all time points indicated a significant difference ($P<.05$) between enalapril and placebo groups in change from baseline in end-diastolic volume. Differences between the two groups by analysis of covariance were not statistically significant at 1 year. However, at the end of the study (an average of 25 months after randomization), the difference between the enalapril and placebo groups was significant in terms of change from baseline in end-diastolic volume ($P=.02$) and was of marginal significance in terms of change in end-systolic volume ($P=.055$). In the enalapril group, LV ejection fraction increased from baseline slightly but significantly ($P<.002$) at 1 year, although this change did not represent a significant difference from the placebo group. There were no significant differences between the two patient groups with regard to change in LV stroke volume or LV minute output. There was no significant difference in enalapril effect on LV volumes for patients receiving digoxin, diuretics, or non-ACE inhibitor vasodilators at baseline compared with those who were not receiving these drugs.

Fig 1 depicts the average LV pressure-volume loops for 29 patients (19 enalapril, 10 placebo) undergoing catheterization at baseline and at 1 year. The entire curve was shifted slightly rightward in the placebo group and leftward in the enalapril group. Within this group of patients in whom baseline LV volumes were somewhat larger than within the overall radionuclide study group, the 1-year changes in both end-diastolic and end-systolic volumes were significantly different for the enalapril group vs the placebo group (both $P<.01$). There were no significant changes from baseline and no significant differences between the two groups in LV end-diastolic, end-systolic, or peak-systolic pressures.

After withdrawal of study drug, LV volumes trended upward in the enalapril group but did not reach the higher levels observed in the placebo group. Repeated-measures analyses were applied to volumetric data in two ways: (1) restricting the analysis to all data points before drug withdrawal and (2) including the withdrawal data point. By both analyses, differences between the two groups were significant in terms of end-diastolic volume ($P=.03$ before drug withdrawal and $P=.03$ including withdrawal data). However, after withdrawal, treatment differences in LV volumes between enalapril and placebo groups were no longer significant based on analysis of covariance. There were no adverse clinical events observed after withdrawal of study drug.

Measurements of plasma renin activity indicated that ACE inhibitor effect had been lost after withdrawal of enalapril. In the enalapril group, plasma renin activity increased from $0.6+0.4$ ng · mL$^{-1}$ · h$^{-1}$ at baseline to $6.9+7.7$ ng · mL$^{-1}$ · h$^{-1}$ ($P<.005$) just before drug withdrawal. This value decreased to $1.0+0.8$ ng · mL$^{-1}$ · h$^{-1}$ ($P<.005$) at the time of the postwithdrawal radionuclide study. In placebo patients, plasma renin activity did not change significantly during the study period ($1.0+0.8$, $1.3+0.9$, $1.7+1.4$ ng · mL$^{-1}$ · h$^{-1}$ at the same three time points, respectively).

Fig 2 compares changes in LV volumes throughout the entire study period in the two patient groups with those previously reported in patients with symptomatic heart failure (SOLVD treatment trial). The average duration of follow-up was greater in the treatment trial because patient recruitment was more rapid than in the prevention trial. At 1 year, the treatment difference between enalapril and placebo groups was significantly greater for symptomatic than for asymptomatic patients in terms of both end-diastolic ($P<.02$) and end-systolic ($P<.02$) volumes. At end of study, $P$ values for comparison of treatment differences (asymptomatic vs symptomatic patients) were .06 and .04 for end-diastolic and end-systolic volumes, respectively. These differences resulted from both greater increases in volumes in the placebo group and greater decreases in the enalapril group for symptomatic patients compared with asymptomatic patients.

**Discussion**

We previously reported results of serial ventricular volumetric and hemodynamic measurements from patients enrolled in the SOLVD treatment trial. These findings indicated that the left ventricle progressively dilates in patients with symptomatic LV systolic dysfunction because of dilated cardiomyopathy or remote myocardial infarction, and this progression is prevented by administration of an ACE inhibitor. The present investigation examined patients enrolled in the SOLVD prevention trial, a study designed to determine the effects of ACE inhibitor treatment among patients with LV systolic dysfunction, but without overt heart failure. Within the overall prevention trial, the difference in all-cause mortality was not statistically significant, but enalapril significantly reduced the frequency of development of symptomatic heart failure and of heart failure–related hospitalizations.
Our findings indicate that among asymptomatic patients, the progression of ventricular dilatation and systolic dysfunction is slower than what we previously observed within symptomatic patients. Partly for this reason, differences between enalapril- and placebo-treated patients are smaller. Nevertheless, at an average of 25 months, enalapril had prevented the left ventricular dilatation observed within the placebo group. It seems likely that asymptomatic and symptomatic patients represent a continuum of pathology, the progression of which accelerates at later stages. ACE inhibitors appear to exert a beneficial influence at any stage, but this benefit is more evident in the presence of more advanced disease.

Numerous prior studies in animal models and in humans have demonstrated LV myocardial hypertrophy and remodeling in the days and weeks after myocardial infarction. These changes resulting in progressive ventricular dilatation appear to continue for years after the initial myocardial insult. Although the exact stimuli effecting these changes in myocardial structure remain unknown, increased myocardial wall stress has been postulated to represent an initiating factor. Activation of the renin-angiotensin system appears to play an important role in the pathogenesis of ventricular remodeling by contributing to the increase in wall stress and possibly by direct myocardial effects.

The SOLVD population, identified on the basis of reduced LV ejection fraction, was divided into treatment and prevention cohorts solely on the basis of clinical findings. In contrast to treatment trial patients, patients randomized into the prevention trial had no overt manifestations of heart failure and were therefore not thought by their physicians to require treatment for heart failure. As further evidence that their disease was less severe or less advanced at baseline, prevention trial patients had a higher mean ejection fraction and lower mean LV end-diastolic and end-systolic volumes. In addition, they had significantly less activation of the renin-angiotensin system. The median plasma renin...
level within prevention trial patients was only slightly higher than in a normal control group. Thus, our finding that ventricular dilatation progressed more slowly in prevention trial patients is consistent with the concept that the rate of ventricular remodeling is related to the severity of baseline LV dysfunction, to the magnitude of diastolic wall stress, and to the degree of activation of the renin-angiotensin system. It seems likely that the lesser baseline ventricular dysfunction and the slower progression of ventricular dilatation in prevention trial patients relate directly to the substantially lower mortality rates observed in the prevention trial as compared with the treatment trial.4,22

By design, patients within the two SOLVD trials differed with regard to background therapy. A far larger proportion of treatment trial patients compared with prevention trial patients were receiving digitalis and/or diuretics, and we cannot exclude the possibility that one or both of these classes of agents accelerates the progression of LV dilatation. Additional investigation may be warranted to explore this possibility.

ACE inhibitors have been found to slow or halt the progression of ventricular remodeling and dilatation in animal models and in humans.1,2,19,20,23,24 This effect is likely to be partly or solely responsible for the observed reduction in mortality among patients with symptomatic LV systolic dysfunction22 and among patients with recent myocardial infarction and reduced ejection fraction.25 The effect of ACE inhibitors on LV dilatation does not appear to be limited to patients in whom therapy is initiated soon after myocardial infarction. Among patients with myocardial infarction, entry into either of the SOLVD trials was delayed until at least 30 days after the event. Our present findings extend the observed inhibition of ventricular remodeling by ACE inhibitors to patients without overt heart failure.

The difference in ventricular volumetric changes between placebo- and enalapril-treated patients partly results from an ongoing effect by the ACE inhibitor on ventricular systolic and diastolic load. After withdrawal of enalapril, ACE inhibitor effect was lost, as evidenced by a return in plasma renin activity to the level observed in the placebo group. LV volumes returned toward baseline but did not reach the higher levels observed within placebo patients. Thus, it appears likely that net effects represent a combination of ongoing alteration in load and prevention of remodeling.

The distinction between patients with asymptomatic and symptomatic ventricular systolic dysfunction is not absolute. Rather, it is likely that a continuous progression exists with regard to ventricular dysfunction, neurohormonal activation, and clinical manifestations of heart failure. The progression of these physiological and functional derangements may be nonlinear. After recovery from an initial myocardial insult but while LV dysfunction remains subclinical, the rate of ventricular

**Fig 1.** Mean left ventricular pressure-volume loops at baseline and 1 year in patients randomized to placebo and to enalapril. At 1 year, the entire curve was shifted to the right for the placebo group and to the left for the enalapril group.

**Fig 2.** Left ventricular (LV) end-diastolic volumes (mean±SE) in enalapril and placebo patients within the prevention trial and the previously reported treatment trial who had measurements made at all five time points. Measurements are at baseline, 4 months, 1 year, and at study end (mean of 25 months and 33 months for prevention trial and treatment trial patients, respectively). The final data point on each graph is after withdrawal (wd) of study drug for a minimum of 5 days. *P* values shown are for comparison of placebo and enalapril groups by repeated-measures analysis applied to all time points. Baseline volumes were significantly higher in treatment trial patients (*P*<.005). In the prevention trial and the treatment trial, placebo-treated patients manifested progressive increases in ventricular volumes, whereas enalapril-treated patients showed an early and sustained reduction in LV volumes. Treatment difference between placebo and enalapril groups was significantly greater within the treatment trial than within the prevention trial (*P*<.02 at 1 year).
dilatation and remodeling is slow, and discernible benefits of ACE inhibition are relatively slight. Nevertheless, these effects on ventricular dilatation appear to be important and coincide with a demonstrable reduction in the rate of transition to overt heart failure. In patients with more advanced ventricular dilatation and symptoms of heart failure, progressive ventricular dilatation appears to be more rapid, and clinical events, including deaths, are more common. In this population, ACE inhibitor effects on ventricular remodeling and on mortality are more evident. Thus, during the early stages of ventricular dilatation, therapeutic efforts should be directed toward preventing the transition to a stage of accelerated progression of structural and functional derangement.

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