Intracardiac Angiotensin-Converting Enzyme Inhibition Improves Diastolic Function in Patients With Left Ventricular Hypertrophy due to Aortic Stenosis

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Background Cardiac hypertrophy is associated with elevated intracardiac angiotensin-converting enzyme activity, which may contribute to diastolic dysfunction.

Methods and Results We infused enalaprilat (0.05 mg/min) for 15 minutes into the left coronary arteries of 20 adult patients with left ventricular (LV) hypertrophy due to aortic stenosis (mean aortic valve area, 0.7±0.2 cm²) and 10 patients with dilated cardiomyopathy (mean ejection fraction, 35±4%) and assessed (1) simultaneous changes in LV micromanometer pressure and dimensions, (2) LV regional wall motion analyzed by the area method, and (3) Doppler flow-velocity profiles. Systemic neurohormonal activation did not occur with the selective left coronary artery infusion; there were no changes in plasma renin activity, angiotensin-converting enzyme activity, or atrial natriuretic peptide. In patients with aortic stenosis, LV end-diastolic pressure declined from 25±2 to 20±2 mm Hg (P<.05). LV pressure-volume and LV pressure-dimension relations showed downward shifts by ventriculography and echocardiography, respectively, indicating improved diastolic distensibility. Regional area change during isovolumic relaxation increased in the anterior segments perfused with enalaprilat but decreased in the inferior segments, indicating acceleration of isovolumic relaxation in the anterior segments and reciprocal shortening in the inferior segments. Regional peak filling rate increased in the anterior segments but not in the inferior segments, and the regional area stiffness constant decreased in the anterior segments but not in the inferior segments. There were no changes in heart rate, cardiac output, or right atrial pressure, excluding alterations in right ventricular/pericardial constraint. In contrast, in the patients with dilated cardiomyopathy the decrease in LV end-diastolic pressure from 22±2 to 18±2 mm Hg (P<.05) was accompanied by a significant fall in right atrial pressure (9±1 to 6±1 mm Hg), implicating alterations in pericardial constraint. The patients with dilated cardiomyopathy showed no improvement in regional diastolic relaxation, filling, or distensibility.

Conclusions Intracoronary enalaprilat at a dosage that did not cause systemic neurohormonal activation improved LV diastolic chamber distensibility and regional relaxation and filling in patients with LV hypertrophy due to aortic stenosis. In contrast, these effects of intracoronary enalaprilat on diastolic function were not observed in patients with dilated cardiomyopathy who did not have concentric hypertrophy. These observations support the hypothesis that the cardiac renin-angiotensin system is activated in patients with concentric pressure-overload hypertrophy and that this activation may contribute to impaired diastolic function. (Circulation. 1994;90:2761-2771.)

Key Words • angiotensin • enzymes • diastole • hemodynamics • hypertrophy • aortic valve • stenosis

Left ventricular hypertrophy (LVH) is characterized by impaired chamber distensibility, relaxation, and early diastolic filling.1 This may be related in part to an enhanced activation of angiotensin II in the heart by cardiac angiotensin-converting enzyme (ACE). The renin-angiotensin system has been implicated as a modulator of cardiac hypertrophy;2 the inhibition of ACE has been shown to prevent the development of LVH in rats3-5 and to reduce its extent in humans with pressure-overload hypertrophy.6,7 Cardiac ACE activity and mRNA levels are elevated in the hypertrophied ventricles of a rat model of aortic stenosis, and the increased rate of angiotensin II production is associated with severe and reversible impairment of diastolic function in the hypertrophied hearts.8 In human isolated trabecular muscle, angiotensin II has a direct effect on excitation-contraction coupling.9 Foul et al10 studied the effects of infusion of intracoronary...
enalaprilat in patients with advanced dilated cardiomyopathy. They found that while ejection fraction fell slightly, left ventricular (LV) end-diastolic pressure (LVEDP) also fell, suggesting that intracardiac inhibition of ACE had a favorable effect on LV diastolic distensibility.

We evaluated the effects of the specific local inhibition of cardiac activation of angiotensin II by conversion of angiotensin I on LV diastolic dysfunction in patients with pressure-overload LVH due to aortic stenosis and in patients with dilated cardiomyopathy without concentric hypertrophy. We tested the hypothesis that the intracoronary administration of the ACE inhibitor enalaprilat would result in improvement in the impaired LV diastolic distensibility, relaxation, and filling that is characteristic of patients with aortic stenosis with severe LVH. In addition, we used a regional enalaprilat infusion technique, which allowed us to assess changes in regional diastolic myocardial function in the infused segments compared with function in the noninfused myocardium in the same patient.

Methods

Patient Selection

Thirteen men and seven women with compensated aortic stenosis (age, 70±8 years [mean±SD]; mean gradient, 57±4 mm Hg; valve area, 0.7±0.1 cm²; wall thickness, 14.3±0.5 mm) were administered intracoronary enalaprilat. Eight other patients with aortic stenosis—3 men and 5 women (mean age, 71±3 years; mean gradient, 62.7±7 mm Hg; valve area, 0.7±0.1 cm²; wall thickness, 13.2±0.5 mm)—were administered vehicle. Four men and six women with dilated cardiomyopathy (mean age, 59±9 years; wall thickness, 10.1±0.5 mm) were administered intracoronary enalaprilat. Studies were performed at the University of Louvain (Brussels, Belgium: 22 patients), Beth Israel Hospital (Boston, Mass: 12 patients), and University Hospital (Zurich, Switzerland: 4 patients). All patients were in normal sinus rhythm without left bundle branch block. No patient had significant coronary artery disease (ie, all coronary arteries had <50% diameter stenosis), nor had any patient received an ACE inhibitor during the 2 preceding weeks. Patients with aortic insufficiency or mitral valvular abnormalities were excluded. All patients with aortic stenosis had diastolic LV wall thickness >12 mm as assessed by echocardiography. The mean LV ejection fractions in patients with aortic stenosis and patients with dilated cardiomyopathy were 52±4% and 35±10%, respectively. All patients gave informed consent according to institutional ethical guidelines for human studies.

Cardiac Catheterization Procedure

β-Blockers and calcium channel blockers were discontinued 48 hours before the procedure, and patients had fasted for at least 12 hours. Patients were premedicated with diazepam 10 mg PO and diphenhydramine 50 mg PO. The presence of coronary artery disease was excluded by coronary angiography using nonionic contrast. Right heart catheterization was performed with a 7F balloon-flotation catheter via the femoral approach. LV pressure was measured with an 8F high-fidelity micromanometer catheter (Millar Instruments). A 5F coronary artery infusion catheter was engaged in the left main coronary artery and its position confirmed by nonionic contrast injection.

Protocol

Fig 1 is a diagram of the study protocol. All patients underwent coronary angiography. Group I patients were studied either at the University of Louvain or at University Hospital (13 aortic stenosis—enalaprilat, 6 aortic stenosis–vehicle, 7 dilated cardiomyopathy—enalaprilat). A delay of at least 15 minutes was allowed for dissipation of contrast effects. Just before the end of this delay (T₁), baseline hemodynamics (heart rate, aortic pressure, right atrial pressure, pulmonary arterial pressure, and LV micromanometer pressure), oxygen consumption, arterial–mixed venous oxygen difference, and blood samples for neurohormonal analysis were obtained from all patients. Group I patients then underwent contrast ventriculography with nonionic contrast injected through the Millar catheter at a rate of 10 mL/s with simultaneous micromanometer measurement of LV pressure. Group 2 patients were studied at Beth Israel Hospital (7 aortic stenosis—enalaprilat, 2 aortic stenosis–vehicle, 3 dilated cardiomyopathy–enalaprilat), and did not undergo contrast ventriculography. Instead, simultaneous LV micromanometer pressures and M-mode, Doppler, and two-dimensional echocardiography were obtained just before the end of the 15-minute delay (T₁). Then enalaprilat (0.05 mg/min at an infusion rate of 1 mL/min) or vehicle (1 mL/min) was infused into the left main coronary artery for 15 minutes. Measurements of heart rate, pulmonary arterial pressure, aortic pressure, and LV pressure were monitored at 3-minute intervals. At the end of the second 15-minute period (T₂), all measurements performed at the end of the first, as well as contrast left ventriculography (in Group I) and M-mode, two-dimensional, and Doppler echocardiography (in Group 2), were repeated. Enalaprilat and its vehicle were supplied by Merck and Co, Inc.

Data Analysis

Cardiac output was determined by the method of Fick.¹¹ The time constant of LV pressure decay (τ) was determined from analysis of LV micromanometer pressure tracings of five consecutive beats during quiet respiration. LV pressure was digitized at 5-millisecond intervals during the isovolumic relaxation period, defined as the interval from the time of peak negative first derivative of pressure to the time when LV pressure decreased to 5 mm Hg above end-diastolic pressure. A modified exponential fit with asymptote pressure yields excellent agreement (r² > 0.99) with the true data. τ was estimated by the derivative method by computing the linear
regression of the negative rate of rise of LV pressure \((-dP/dt)\) against pressure with the use of the digitized data points from the period of isovolumic relaxation.\(^{14}\)

For angiographic evaluation of LV volumes, ventricular silhouettes were digitized frame by frame on a video screen (cine frame rate, 50 frames per second). Premature and post premature beats were excluded from analysis. A computer system (APU Phillips, Phillips Electronic Instruments Co) was used to derive the correction factor for x-ray magnification and calculated volumes every 20 milliseconds by applying Simpson's rule.\(^{15}\) Wall thickness at the LV equator was traced on the last unmasked diastolic frame and was computed for the subsequent frames assuming a constant LV mass. Midwall circumferential stress was calculated with the formula of Minsky.\(^{16}\) Mean systolic wall stress was obtained by averaging data from the start to the end of ejection. Volume data were normalized using body surface area. Peak filling or ejection rates were calculated using a data-smoothing program.\(^{17}\)

Regional LV properties were analyzed in the subset of patients studied at the University of Louvain using the same method.\(^{18,19}\) To quantify regional wall motion during diastole, the LV silhouette in the right anterior oblique projection was divided into eight segments, four anterior and four inferior, with the long axis as the reference system (Fig 2A). Because displacement of a reference point used to calculate regional area could create artifactual changes in regional wall motion, we did not analyze the apical segments (segments 4 and 5), where ventricular motion was greatest. The beginning of the isovolumic relaxation period was defined as peak \(-dP/dt\), and the end of the isovolumic relaxation period was defined as 80 milliseconds after peak \(-dP/dt\). The percentage regional area change during the isovolumic relaxation period for each segment was calculated by dividing the absolute change in area during the isovolumic relaxation period by the end-diastolic area (Fig 2B). Regional nonuniformity of LV wall motion during the isovolumic relaxation period was indicated by the SD of the percentage change in area during the isovolumic relaxation period for the six segments for each patient. For each segment, regional peak filling rate was automatically obtained by determining the rate of maximal wall expansion (mm²/s) in a time window starting 60 milliseconds after the maximal systolic pressure-volume ratio and ending 100 milliseconds before the next R wave.

\[
P = \alpha e^{\Delta A} + \gamma
\]

where \(P=\) pressure (mm Hg), \(A=\) regional area (mm²), \(\beta=\) regional area stiffness constant \((10^{-3} \text{ mm}^2)\), \(\alpha=\) material constant (mm Hg), and \(\gamma=\) asymptote (mm Hg), to the LV pressure and regional area data from minimum diastolic pressure to end diastole for each segment.

For echocardiographic evaluation of LV volumes and function, standard views were used, and recordings were made when visualization of the endocardium and epicardium of each of the cardiac chambers was optimal. The echocardiogram of one patient could not be analyzed because of poor visualization of endocardium. Using the apical four-chamber view, end-diastolic and end-systolic endocardial surfaces of the left ventricle were traced on stop-frame images using a video screen and light pen interfaced with a computerized graphic analyzer (Freeland Cardiac Workstation). Ventricular end-diastolic (smallest ventricular cavity area) and end-diastolic (R-wave peak) cavity areas were calculated using the single-plane Simpson's rule method\(^{20}\) and averaged over three to five consecutive cardiac cycles. LV endocardium and epicardium and length were digitized from the twodimensional echocardiographic parasternal short-axis view at the high chordal level and apical four-chamber views, respectively, for calculation of circumferential and meridional wall stress according to previously published formulas.\(^{21}\) End-systolic wall stress, end-diastolic wall stress, and peak systolic stress were calculated using the appropriate high-fidelity LV pressure and either end-diastolic or end-systolic (for both peak and end-systolic stress) measurements.\(^{21}\) Continuous digitization of septal and posterior wall endocardial borders of two-dimensional guided M-mode echoes of the left ventricle at the high chordal level and of simultaneously recorded high-fidelity LV pressure was used to construct pressure-dimension loops. Digitization was done at 6- to 12-millisecond intervals, depending on heart rate. Pre- and postintervention curves were displayed on the same graph to visually compare diastolic pressure-dimension relations to assess changes in LV diastolic distensibility.

Two-dimensional guided pulsed Doppler recordings were made of mitral inflow velocity from the apical four-chamber view with the cursor positioned at the midpoint of the annulus, parallel to assumed flow. Three to six consecutive flow-velocity profiles were digitized and averaged. Measurements included peak velocity of LV inflow in early diastole and accompanying atrial systole, their ratio (E to A ratio), the area under the early and atrial velocity curves, and total flow velocity area. Atrial filling fraction was calculated.
TABLE 1.  Hemodynamics at Baseline and in Response to Administration of Intracoronary Enalaprilat and Vehicle

<table>
<thead>
<tr>
<th></th>
<th>Aortic Stenosis (n=20)</th>
<th>Dilated Cardiomyopathy (n=8)</th>
<th>Aortic Stenosis (n=8)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Enalapril</td>
<td>Baseline</td>
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<tr>
<td>Heart rate, bpm</td>
<td>73±3</td>
<td>73±3</td>
<td>77±6</td>
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<tr>
<td>Right atrial pressure, mm Hg</td>
<td>7±1</td>
<td>7±1</td>
<td>9±1</td>
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<tr>
<td>Mean arterial pressure, mm Hg</td>
<td>96±3</td>
<td>90±3*</td>
<td>105±5</td>
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<td>Systemic vascular resistance, dyne·s·cm⁻²</td>
<td>1626±128</td>
<td>1458±102*</td>
<td>1611±163</td>
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<tr>
<td>Mean pulmonary arterial pressure, mm Hg</td>
<td>23±3</td>
<td>22±3</td>
<td>22±1</td>
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<tr>
<td>LV systolic pressure, mm Hg</td>
<td>212±7</td>
<td>205±7†</td>
<td>148±4</td>
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<td>LV end-diastolic pressure, mm Hg</td>
<td>24±2</td>
<td>19±2</td>
<td>22±2</td>
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<tr>
<td>Arteriovenous oxygen difference, mL/L</td>
<td>45±2</td>
<td>46±2</td>
<td>44±2</td>
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<tr>
<td>Cardiac output, L/min</td>
<td>4.8±0.4</td>
<td>4.9±0.3</td>
<td>5.0±0.4</td>
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<tr>
<td>Peak +dP/dt, mm Hg/s</td>
<td>1761±104</td>
<td>1740±89</td>
<td>1034±64</td>
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<tr>
<td>Peak –dP/dt, mm Hg/s</td>
<td>1811±95</td>
<td>1760±85</td>
<td>1100±72</td>
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<tr>
<td>Isovolumic relaxation constant, ms</td>
<td>58±4</td>
<td>53±3</td>
<td>101±7</td>
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</table>

bpm indicates beats per minute; LV, left ventricular.

*P = .03 for enalaprilat administration compared with baseline; †P = .001; ‡P = .01; ‖P = .005; ‡‖P = .0005; ††P = .006. Values are reported as mean±SEM.

Neurohormonal Analysis

Blood samples for neurohormonal analysis were collected into chilled tubes containing reduced glutathione and ethylene bis, EGTA (for norepinephrine and epinephrine) or EDTA (for plasma renin activity, atrial natriuretic peptide, and aldosterone), centrifuged at 3000g for 20 minutes to separate the plasma, and stored at −70°C. Plasma norepinephrine and epinephrine were determined by a radioenzymatic assay using the enzyme catechol-O-methyltransferase as previously described.23 Plasma renin activity was determined by radioimmunoassay.23 ACE activity was measured using a radioimmetric assay (Ventrex Laboratories) that is a modification of the method of Friedland and Silverstein24; it uses radiolabeled [1H]Hip-Gly-Gly-b, which is converted by ACE to [1H]hippuric acid. Atrial natriuretic peptide was measured by radioimmunoassay after extraction from acidified plasma.24 Aldosterone was assayed by a standard radioimmunoassay using a specific monoclonal antibody.28

Data are presented as mean±SEM. Baseline and 15-minute infusion data were compared using a paired Student’s t test, for both enalaprilat and vehicle.

Results

In the group of 8 patients with aortic stenosis administered intracoronary vehicle, there were no significant hemodynamic changes (Table 1).

Aortic Stenosis

Hemodynamic Response to Intracoronary Enalaprilat

In patients with aortic stenosis who were administered enalaprilat, LVEDP was elevated (24±2 mm Hg, compared with normal values of ≤12 mm Hg27) and isovolumic relaxation was prolonged (58±4 milliseconds compared with normal values of 30 to 54 milliseconds14) at baseline (Table 1). Cardiac output and LV ejection fraction were normal. During the infusion of intracoronary enalaprilat, there was no significant change in right atrial pressure. Indexes of afterload (systemic vascular resistance, end-systolic wall stress) decreased modestly but significantly. LVEDP declined significantly, and the decrease tended to be greatest for patients with the most elevated pressure (Fig 3A). There was no significant change in LV end-diastolic volume index by either ventriculography or echocardiography (Table 2) to account for the change in LVEDP.

Global LV Diastolic Function

Global indexes of LV relaxation and filling did not change. τ was prolonged at 58±4 milliseconds and showed a trend toward improvement, with the greatest improvement seen in those with the most prolonged values (Fig 4). In patients in whom baseline τ was >60 milliseconds, τ decreased from 77±3 to 63±3 milliseconds (P = .04) compared with those with τ <60 milliseconds (47±3 to 48±3 milliseconds, P = .NS). There was no change in the global LV peak filling rate, time to peak filling rate, or the E to A ratio.

To assess the effect of regional enalaprilat infusion on global LV distensibility, relations of LV diastolic pressure to LV volume and LV dimension were analyzed (Fig 5). Despite the fact that only the anterior region of the LV myocardium was exposed to the enalaprilat infusion, downward shifts in the global relations between LV diastolic pressure and volume and LV diastolic pressure and dimension were observed in 11 of 19 patients who were administered the drug. Overall, significant downward shifts in the relations between LV diastolic pressure and volume and LV diastolic pressure and dimension were observed with ventriculography and echocardiography, respectively.

Regional LV Diastolic Function

The regional area change during isovolumic relaxation increased significantly in the anterior segments but decreased in the inferior segments (Fig 6, Table 3), indicating the occurrence of enhanced segmental early relaxation during the isovolumic relaxation period in the region of myocardium that was perfused with intracoronary enalaprilat. Because total LV volume must remain constant during the isovolumic relaxation period,
Linear regression analyses showed that there was no significant correlation between changes in global or regional relaxation parameters and any index of systolic load, including LV systolic pressure, end-systolic wall stress, and systemic vascular resistance.

Infusion of vehicle had no significant effect on regional area change during isovolumic relaxation (anterior, 1.1±1.4% to -0.4±2.3% of end-diastolic area; inferior, -0.1±3.3% to 1.5±2.7% of end-diastolic area; NS) or change in regional peak filling rate (anterior change, -86±97 mm²·s⁻¹·m⁻²; inferior change, -340±160 mm²·s⁻¹·m⁻²; NS).

**Dilated Cardiomyopathy**

**Hemodynamic Response to Intracoronary Enalaprilat**

As with the aortic stenosis group (Table 1), LVEDP was elevated (22±1 mm Hg) and r was markedly prolonged (101±7 milliseconds) at baseline in the patients with dilated cardiomyopathy who were administered enalaprilat. Intracoronary enalaprilat did not change LV systolic pressure but caused a significant fall in LVEDP (from 22±2 to 18±2 mm Hg). In contrast to the aortic stenosis group, pulmonary arterial pressure and right atrial pressure also fell significantly in the dilated cardiomyopathy group, implicating changes in right ventricular pressure and relaxation of pericardial constraint as a cause for the changes in LV diastolic function. Fig 7 shows that the percentage change in LVEDP correlated closely with the percentage change in right atrial pressure for the dilated cardiomyopathy group (r=.7) but not the aortic stenosis group (r=-.1).

**LV Diastolic Function**

Global indexes of left ventricular relaxation and filling did not change (Table 2). The global LV pressure-volume relation did not shift downward as it did in the aortic stenosis group (Fig 8), indicating that the decrease in LVEDP that was observed resulted from a reduction in LV volume and movement along the same pressure-volume relation rather than from a downward shift in the curve. There was also no improvement in regional area change during isovolumic relaxation, regional peak filling rate, time to regional peak filling rate, or regional area stiffness constant (Table 3).

**Plasma Neurohormones**

There was no significant change in plasma renin activity, ACE activity, epinephrine, noradrenaline, aldosterone, or atrial natriuretic peptide in response to the intracoronary enalaprilat infusion in either the aortic stenosis or the dilated cardiomyopathy group (Table 4).

**Discussion**

The purpose of the present study was to assess whether the local inhibition of the cardiac renin-angiotensin system would result in improvement in abnormal LV diastolic properties in patients with severe concentric pressure-overload hypertrophy due to aortic stenosis. A novel observation of this study is that global LV distensibility improves with infusion of enalaprilat into the left coronary artery of patients with aortic stenosis. Improvement in global isovolumic relaxation was most pronounced in patients with the most prolonged base-


Table 2. Response to Intracoronary Enalaprilat in Aortic Stenosis and Dilated Cardiomyopathy Groups

<table>
<thead>
<tr>
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<th>Aortic Stenosis (n=13)</th>
<th>Dilated Cardiomyopathy (n=7)</th>
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<tr>
<td></td>
<td>Baseline</td>
<td>Enalaprilat</td>
</tr>
<tr>
<td>Angiographic volume analysis</td>
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<tr>
<td>LV end-systolic volume index, mL/m²</td>
<td>48±5</td>
<td>45±5*</td>
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<td>LV end-diastolic volume index, mL/m²</td>
<td>100±5</td>
<td>100±5</td>
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<tr>
<td>LV ejection fraction, %</td>
<td>52±4</td>
<td>55±4†</td>
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<tr>
<td>Peak ejection rate, mL/s</td>
<td>453±32</td>
<td>515±34</td>
</tr>
<tr>
<td>Peak filling rate, mL/s</td>
<td>465±54</td>
<td>503±53</td>
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<tr>
<td>Time to peak filling rate, ms</td>
<td>378±63</td>
<td>360±61</td>
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<tr>
<td>LV mean systolic wall stress, kdyne/cm²</td>
<td>330±21</td>
<td>306±24</td>
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<tr>
<td>LV end-systolic wall stress, kdyne/cm²</td>
<td>187±27</td>
<td>164±27‡</td>
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Echocardiographic volume analysis§

<table>
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<tr>
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<th>Baseline</th>
<th>Enalaprilat</th>
<th>Baseline</th>
<th>Enalaprilat</th>
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<tbody>
<tr>
<td>LV end-systolic volume index, mL/m²</td>
<td>37±9</td>
<td>34±7</td>
<td>54±15</td>
<td>61±14</td>
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<tr>
<td>LV end-diastolic volume index, mL/m²</td>
<td>72±13</td>
<td>65±11</td>
<td>106±37</td>
<td>114±40</td>
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<tr>
<td>LV ejection fraction, %</td>
<td>50±5</td>
<td>49±5</td>
<td>34±2</td>
<td>31±2</td>
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<tr>
<td>LV end-systolic CWS, kdyne/cm²</td>
<td>179±21</td>
<td>172±20</td>
<td>268±57</td>
<td>251±66</td>
</tr>
<tr>
<td>LV peak systolic MWS, kdyne/cm²</td>
<td>65±11</td>
<td>63±9</td>
<td>129±33</td>
<td>141±56</td>
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<td>LV end-systolic MWS, kdyne/cm²</td>
<td>60±8</td>
<td>54±8</td>
<td>116±25</td>
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<td>LV end-diastolic CWS, kdyne/cm²</td>
<td>62±15</td>
<td>39±8</td>
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<td>LV end-diastolic MWS, kdyne/cm²</td>
<td>28±8</td>
<td>17±4</td>
<td>51±22</td>
<td>20±5</td>
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<td>Peak velocity of rapid filling, cm/s</td>
<td>66±11</td>
<td>66±10</td>
<td>70±20</td>
<td>63±17</td>
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<tr>
<td>Atrial filling fraction, %</td>
<td>49±10</td>
<td>50±9</td>
<td>66±10</td>
<td>55±20</td>
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<tr>
<td>E to A ratio</td>
<td>1.1±0.4</td>
<td>1.0±0.3</td>
<td>0.8±0.3</td>
<td>1.0±0.4</td>
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</table>

§Data from one of the patients who underwent echocardiography could not be analyzed because of poor visualization of endocardium.

LV indicates left ventricular; CWS, circumferential wall stress; MWS, meridional wall stress; and E to A ratio, ratio of velocity of transmural flow during early diastole to that during atrial contraction.

*P=.06 for enalaprilat administration compared with baseline; †P=.04; ‡P=.02; ‖P=.03. Values are reported as mean±SEM. Improvement in the anterior segments of the left ventricle but not in the inferior segments, consistent with a regional improvement in diastolic function in the region perfused by the left coronary artery into which the ACE inhibitor was infused.

In contrast, in patients with nonischemic dilated cardiomyopathy, intracoronary enalaprilat did not affect LV relaxation, distensibility, or stiffness. The fall in LVEDP in these patients was associated with altered right heart loading conditions. This suggests minimal contribution of intracardiac ACE to diastolic dysfunction in patients with dilated cardiomyopathy.

Role of Cardiac Angiotensin II in LVH

Whereas evidence for the local generation of the components of the renin-angiotensin system in a variety of tissues is clear,28-37 the physiological importance of a cardiac renin-angiotensin system is less well defined. Conversion of angiotensin I to angiotensin II in isolated perfused hearts has been established, and ACE inhibition blocks approximately 70% of this activity.8 Schunkert et al8 demonstrated that the fractional conversion of angiotensin I to angiotensin II was signifi-
Fig 5. Graphs of the relations between left ventricular (LV) diastolic pressure and LV volume and LV dimension in the aortic stenosis group, determined by ventriculography (n=13) (A) and echocardiography (n=6) (B), respectively. Measurements were performed simultaneously with LV micromanometer pressure measurements in all patients. Coordinates of pressure, volume, and dimension are averages at three diastolic points: early diastolic pressure nadir, mid diastole, and end diastole. In both groups there was a vertical downward shift with intracoronary enalaprilat indicating improved diastolic distensibility. P values indicate significance of the vertical downward shift for the relation (ANOVA for repeated measures). Bars indicate SEM.

Fig 6. Graph of the left ventricular (LV) regional area change during isovolumic relaxation in the aortic stenosis group. Because total LV volume must remain constant during the isovolumic relaxation period, the acceleration of regional isovolumic relaxation in the anterior segments perfused with enalaprilat was offset by a relative decrease in area in the inferior segments.

Isovolumic LV diastolic pressure in the nonhypertrophied control group, it caused a significant, dose-dependent increase in LV isovolumic diastolic pressure in the hypertrophied hearts with the high level of ACE expression. Furthermore, in recent studies the adverse effects of local cardiac angiotensin II activation on diastolic function in hypertrophied hearts were prevented by specific inhibition of ACE.

Global Versus Regional Analysis of Diastolic Function

The infusion of enalaprilat into the left coronary arteries of patients with aortic stenosis resulted in a fall in LVEDP and improvements in all measures of regional anterior wall diastolic function: regional isovolumic relaxation of the anterior wall, regional peak filling rate, time to regional peak filling rate, and β. Improvement in global parameters of diastolic function, however, was seen in the patients with the most prominent baseline elevation of LVEDP and prolongation of the isovolumic relaxation time constant, r. This is consistent with a recent preliminary observation that intracoronary enalaprilat had a negligible effect on diastolic function in patients with only mild dysfunction. It also suggests, as in animal models, that diastolic dysfunction is due in part to activation of the cardiac renin-angiotensin system in patients with higher diastolic pressures and more delayed relaxation.

The greater sensitivity of the regional analysis over the global analysis in our study was likely due to the acceleration of relaxation in the anterior wall, which would tend to improve both relaxation and filling but which leads to dysynchronous relaxation, which buffered the global improvement in relaxation and filling. The relative advantage of regional anterior diastolic relaxation was partially offset by the mechanical disadvantage of dysynchronous function. Global peak filling rate and regional dysynchrony of relaxation were inversely correlated (r = −.87); patients who developed the least dysynchrony exhibited the largest increase in global peak filling rate. While global measures of isovolumic relaxation and early diastolic filling did not show improvement, a measure of mid- and late-di-
astolic function, LV chamber distensibility, would not be expected to be as affected by dyssynchrony. Indeed, on both angiographic and echocardiographic analysis, the global LV pressure-volume relations exhibited downward shifts, demonstrating improved global LV distensibility (Fig 5).

We chose to determine LV volumes by echocardiography in addition to ventriculography to exclude the potential confounding effects of contrast injection. Because the same method was used in a given patient and all data collection was paired, possible differences between the two techniques could not influence our findings. Our regional analysis, however, relied on angiographic determinations alone. To minimize errors caused by manual tracing of the contours, a frame-by-frame analysis was used and regional motion was computed after data smoothing.20

We believe that our findings of improved regional diastolic function in the aortic stenosis group are strengthened by the presence of two control groups (the patients with aortic stenosis who received vehicle and those with dilated cardiomyopathy who received enalaprilat). First, no changes in global or regional diastolic function were observed in the control group of patients with aortic stenosis who received vehicle rather than enalaprilat. Second, in the dilated cardiomyopathy cohort, no changes in regional diastolic function were noted despite a fall in LVEDP that was due to alterations in right heart loading. While the ideal control group would consist of age-matched subjects without LVH, these subjects do not routinely undergo diagnostic catheterization in contemporary practice and are not available for study using intracoronary infusion techniques at our institutions.

**Mechanisms for Improvement in Diastolic Function**

Although the mechanism by which intracoronary enalaprilat improved diastolic function in patients with pressure-overload hypertrophy is not known, we propose that the improved diastolic function was due to inhibition of intracardiac ACE, which led to a localized

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**TABLE 3. Regional Left Ventricular Diastolic Function**

<table>
<thead>
<tr>
<th></th>
<th>Anterior Segments</th>
<th>Inferior Segments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Enalaprilat</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>n=13</td>
<td></td>
</tr>
<tr>
<td>Regional area change during isovolumic relaxation, % of end-diastolic area</td>
<td>1.1±1.0</td>
<td>4.1±0.8*</td>
</tr>
<tr>
<td>Regional peak filling rate, mm² · s⁻¹ · m⁻²</td>
<td>612±67</td>
<td>688±79*</td>
</tr>
<tr>
<td>Time to regional peak filling rate, ms</td>
<td>587±13</td>
<td>558±11*</td>
</tr>
<tr>
<td>Regional area stiffness constant, 10⁻³×mm⁻²</td>
<td>10.1±1.4</td>
<td>7.0±0.9*</td>
</tr>
<tr>
<td>Dilated cardiomyopathy</td>
<td>n=7</td>
<td></td>
</tr>
<tr>
<td>Regional area change during isovolumic relaxation, % of end-diastolic area</td>
<td>4.2±1.0</td>
<td>4.0±1.2</td>
</tr>
<tr>
<td>Regional peak filling rate, mm² · s⁻¹ · m⁻²</td>
<td>394±86</td>
<td>284±62</td>
</tr>
<tr>
<td>Time to regional peak filling rate, ms</td>
<td>125±27</td>
<td>103±22</td>
</tr>
<tr>
<td>Regional area stiffness constant, 10⁻³×mm⁻²</td>
<td>7.6±3.1</td>
<td>6.7±3.1</td>
</tr>
</tbody>
</table>

*P<.05 for enalaprilat administration compared with baseline. Values are reported as mean±SEM.
reduction in angiotensin II. Reduction in angiotensin II could lead to improved diastolic function by means of several mechanisms, including alterations of calcium flux, myocardial blood flow, or catecholamine release in the heart. Hypertrophied cardiac myocytes manifest intrinsic prolongation of the calcium transient and impaired reserve for calcium uptake. Angiotensin II has been shown to potentiate the impaired relaxation of isolated cardiac myocytes from rats with pressure-overload hypertrophy. We speculate that the beneficial effect of intracoronary enalaprilat may be related to inhibition of the effects of angiotensin II on phosphoinositide second messengers, which may promote the release and delay the sequestration of calcium by the sarcoplasmic reticulum and increase myofilament calcium sensitivity. Altered calcium handling or a change in myofilament calcium sensitivity readily explains the effects of intracoronary enalaprilat on early diastolic relaxation; if a similar mechanism is to account for the observed improvement in diastolic LV distensibility, we must assume that persistent crossbridge activation affected passive diastolic tone during mid- and late diastole as during demand ischemia and not just during early isovolumic relaxation.

Infusion of intracoronary enalaprilat could also modify diastolic function by altering myocardial blood flow. Angiotensin II is a coronary vasoconstrictor; consequently, ACE inhibition may result in vasodilatation, particularly in hearts with an enhanced capacity for local angiotensin II generation. The modification of myocardial blood flow could be a direct result of angiotensin II inhibition or could be due to indirect effects of ACE inhibition on other modulators of coronary tone. While vasodilatation may be expected to increase vascular coronary turgor (the erectile effect) and decrease diastolic distensibility, the relief of subendocardial ischemia, which can accompany pressure-overload hypertrophy, would be expected to improve LV diastolic function. Isolated rat hearts with pressure-overload hypertrophy subjected to low-flow ischemia have an accentuated increase in LVEDP and slowing of relaxation compared with nonhypertrophied rat hearts. Enalaprilat has no effect on low-flow ischemia in nonhypertrophied control hearts but significantly attenuates the accentuated ischemic diastolic dysfunction in hypertrophied hearts, and this beneficial effect on ischemia cannot be explained by differences in coronary blood flow. Thus, it is possible that ACE inhibition, independent of coronary vasodilatation, may ameliorate the diastolic abnormalities attributable to subendocardial hypoperfusion in these hypertrophied hearts. The absence of effects of intracoronary enalaprilat on global or regional relaxation in dilated cardiomyopathy reinforces our arguments that indirect mechanisms such as a regional “garden hose” effect are not responsible for the changes observed in aortic stenosis. Moreover, we have previously injected 0.1 mg of nitroglycerin into the left main artery of a small number of patients with concentric hypertrophy and we did not observe an alteration in the time course of isovolumic relaxation or a change in synchrony of the anterior and posterior walls (H.P., M.F.R., unpublished data, 1982).

Lastly, it is possible that the mechanism by which intracoronary enalaprilat improves diastolic function is independent of the renin-angiotensin system; ACE is identical to kininase II, which metabolizes bradykinin. Blunted degradation of bradykinin could improve diastolic function through either direct coronary vasodilation or modulation of endothelial-myocardial coupling, which has been shown to affect relaxation in isolated papillary muscle preparations.

While the mechanism by which intracoronary enalaprilat improved diastolic function in our patients with aortic stenosis is unclear, it is unlikely that the observed improvement in diastolic dysfunction was attributable to a systemic effect of the intracoronary enalaprilat. First, there were no significant measurable systemic neurohormonal changes. Second, in these patients but not in those with dilated cardiomyopathy, right atrial pressure did not change, which excludes alterations in right ventricular–pericardial constraint as a cause for changes in LV diastolic function and the downward shift in the LV pressure-volume relation. Third, although there was a small but significant decrease in LV systolic pressure, such systemic changes would be expected to promote global changes in ventricular relaxation, whereas the observed regional changes support a localized cardiac effect. Moreover, we have previously demonstrated that in patients with critical aortic stenosis, acute large changes in afterload due to nitroprusside administration did not result in demonstrable improvement in isovolumic relaxation or filling indexes. Similarly, patients with critical aortic stenosis who underwent afterload reduction by means of balloon aortic

<table>
<thead>
<tr>
<th></th>
<th>Aortic Stenosis</th>
<th>Dilated Cardiomyopathy</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Enalaprilat</td>
</tr>
<tr>
<td>Norepinephrine, pg/mL</td>
<td>433±61</td>
<td>387±32</td>
</tr>
<tr>
<td>Epinephrine, pg/mL</td>
<td>100±31</td>
<td>99±15</td>
</tr>
<tr>
<td>Plasma renin activity, ng · mL⁻¹ · h⁻¹</td>
<td>1.1±0.4</td>
<td>1.7±0.9</td>
</tr>
<tr>
<td>Aldosterone, ng/mL</td>
<td>8.0±1.8</td>
<td>7.5±1.8</td>
</tr>
<tr>
<td>Atrial natriuretic peptide, ng/mL</td>
<td>203±45</td>
<td>238±46</td>
</tr>
<tr>
<td>ACE activity, U/mL</td>
<td>63±3</td>
<td>62±3</td>
</tr>
</tbody>
</table>

ACE indicates angiotensin-converting enzyme.

There were no significant differences in plasma neurohormone level between baseline and enalaprilat administration. Differences between the aortic stenosis and dilated cardiomyopathy groups (unpaired Student's t tests) are also nonsignificant.
valvuloplasty did not have significant acute improvement in diastolic function.56

Our observations of improved diastolic function were confined to patients with severe concentric LV hypertrophy due to aortic stenosis. Our data suggest that the contribution of the local renin-angiotensin system to diastolic dysfunction differs between concentric pressure-overload hypertrophy and eccentric hypertrophy characteristic of dilated cardiomyopathy. Foulk et al10 administered a bilateral intracoronary infusion of enalaprilat (0.05 mg/min into both the right and left coronary arteries) to 16 patients with severe dilated cardiomyopathy and observed a small reduction in LVEDP and no effect on systemic neurohormones. Right heart filling pressures were not measured in that study. Our patients with dilated cardiomyopathy demonstrated a fall in LVEDP that was closely correlated with a significant decrease in right atrial pressure.

Limitations
First, the intracoronary infusion of enalaprilat into the left coronary artery was regional. We did not attempt bilateral coronary artery infusions. Although all patients who underwent regional analysis had right dominant coronary circulation, there may have been variation in the amount of inferior wall myocardium perfused with enalaprilat because of variation in the relative degree of dominance. For this reason, we did not analyze the most apical segments of the left ventricle where the right and left coronary beds may overlap. Second, our patients were predominantly elderly. Much basic investigation supports the involvement of the renin-angiotensin system in the pathogenesis of the diastolic abnormalities associated with hypertrophy in young animals; the interplay of aging and activation of the cardiac renin-angiotensin system is unknown. Third, although we did not observe systemic changes in neurohormonal activation, direct assessment of systemic angiotensin I and angiotensin II levels would have been a more sensitive measure of systemic blockade of the renin-angiotensin system.

Conclusions
Intracoronary enalaprilat improved diastolic LV chamber distensibility in patients with LVH due to aortic stenosis. Selective intracoronary enalaprilat improved regional relaxation, peak filling rate, and stiffness in the anterior segments of the left ventricles perfused with enalaprilat via the left coronary artery. These changes in global and regional diastolic function in response to intracoronary enalaprilat were not observed in patients with dilated cardiomyopathy. Thus, inhibition of cardiac ACE resulted in improved diastolic function in patients with LVH due to aortic stenosis but not in patients with dilated cardiomyopathy. These observations support the hypothesis that the cardiac renin-angiotensin system is activated in patients with pressure-overload hypertrophy, and that this activation may contribute to impaired diastolic function.

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References


Intracardiac angiotensin-converting enzyme inhibition improves diastolic function in patients with left ventricular hypertrophy due to aortic stenosis.


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