Intracoronary Angiotensin-Converting Enzyme Inhibition Improves Diastolic Function in Patients With Hypertensive Left Ventricular Hypertrophy

Howard L. Haber, MD; Eric R. Powers, MD; Lawrence W. Gimple, MD; Clarence C. Wu, MSE; Komathi Subbiah, ME; William H. Johnson, RN; Marc D. Feldman, MD

Background There is increasing recognition of myocardial angiotensin-converting enzyme, which is induced with the development of left ventricular hypertrophy (LVH). The potential physiological significance of subsequent increased angiotensin I to II conversion in the presence of LVH is unclear but has been postulated to cause abnormal Ca\(^{2+}\) handling and secondary diastolic dysfunction. Accordingly, we hypothesized that acute angiotensin-converting enzyme inhibition would result in decreased production of angiotensin II and improved active (Ca\(^{2+}\)-dependent) relaxation in patients with hypertensive LVH.

Methods and Results Intracoronary (IC) enalaprilat was administered to 25 patients with and without LVH secondary to essential hypertension. Indexes of diastolic and systolic LV function were determined from pressure (micromanometer)–volume (conductance) analysis at steady state and with occlusion of the inferior vena cava. Patients were divided into those receiving high (5.0 mg, n=15) and low-dose (1.5 mg, n=10) IC enalaprilat during a 30-minute infusion at 1 mL/min. The high-dose patients were further divided along the median normalized LV wall thickness of 0.671 cm/m\(^2\). The time constant of isovolumic relaxation (\(\tau\)) was prolonged at baseline in patients receiving high-dose enalaprilat with wall thickness >0.671 cm/m\(^2\) (\(\tau_{1}\), 56±2 versus 44±2 and 45±2 milliseconds, respectively, \(P<.01\) by ANOVA) and shortened only in this patient group (\(\tau_{1}\), 49±3 versus 46±2 and 43±2 milliseconds, respectively, \(P<.01\) versus baseline and other groups by ANOVA). The improvement in \(\tau_{1}\) was directly proportional to the degree of LVH (\(r=.92, P<.001\)). Although there was a decrease in LV end-diastolic pressure (23±2 to 15±1 mm Hg, \(P<.01\)) and volume (86±8 to 67±9 mL/m\(^2\), \(P<.05\)) in those patients with a reduction in \(\tau_{1}\), this is due to movement down a similar diastolic pressure-volume relation with no change in chamber elastic stiffness (0.023±0.002 to 0.025±0.004 mL/m\(^{-1}\), \(P=NS\)).

Conclusions Intracoronary enalaprilat resulted in an improvement in active (Ca\(^{2+}\)-dependent) relaxation in those patients with more severe hypertensive LVH. The improvement in active relaxation was directly proportional to the severity of LVH. These results support the hypothesis that the cardiac renin-angiotensin system is an important determinant of active diastolic function in hypertensive LVH. (Circulation. 1994;89:2616-2625.)

Key Words • hypertrophy • diastole • angiotensin • enzymes • enalaprilat

Angiotensin-converting enzyme inhibitors have gained widespread use in the therapy of chronic hypertension and secondary left ventricular hypertrophy (LVH). This is due in part to the recognition of the role of the circulating renin-angiotensin system in the pathophysiology of essential hypertension and LVH.\(^1\) More recently, the existence of a physiologically active cardiac renin-angiotensin system has been demonstrated, with evidence of local synthesis of angiotensinogen, renin, angiotensin-converting enzyme, and angiotensin-converting enzyme mRNA in the heart.\(^2\)-\(^9\) Nevertheless, the local physiological effects of angiotensin II on cardiac function remain to be clarified.

The effects of the cardiac renin-angiotensin system on ventricular function may be important in the pathophysiology and hemodynamic consequences of LVH. The binding of angiotensin II to its cardiac receptor activates phospholipase C, resulting in an increased cellular content of inositol phosphates and changes in the mobilization and reuptake of cytosolic free [Ca\(^{2+}\)].\(^10\) Since cardiac hypertrophy is associated with abnormalities in Ca\(^{2+}\) extrusion by the sarcolemma and reuptake by the sarcoplasmic reticulum, these increases in cytosolic free [Ca\(^{2+}\)] due to angiotensin II could impair myocardial relaxation during diastole.\(^11\)-\(^14\) In an isovolumic perfused rat heart model of pressure-overload hypertrophy from aortic banding, angiotensin I administration caused an increased LV end-diastolic pressure in hypertrophied hearts compared with controls.\(^7\) In a similar model, the administration of the angiotensin-converting enzyme inhibitor enalaprilat attenuated the increase in LV end-diastolic pressure of hypertrophied hearts in response to low-flow ischemia.\(^15\) The clinical significance of these molecular and hemodynamic ab-

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From the Department of Internal Medicine, Cardiovascular Division, University of Virginia Health Sciences Center, Charlottesville.
Correspondence to Marc D. Feldman, MD, Director, Cardiac Catheterization Laboratory, University of Pittsburgh Medical Center, 200 Lothrop St, Pittsburgh, PA 15213.
normalities in human LVH is unknown. We hypothesized that angiotensin-converting enzyme inhibition would acutely improve active (Ca²⁺-dependent) relaxation in patients with LVH caused by systemic hypertension. Furthermore, we hypothesized that the severity of LVH would be related to the extent of induction of cardiac angiotensin-converting enzyme and, hence, to the degree in improvement in active relaxation with acute angiotensin-converting enzyme inhibition. To test these hypotheses, we administered intracoronary (IC) enalaprilat to 25 patients with and without LVH secondary to systemic hypertension and measured indexes of LV diastolic and systolic function.

Methods

Patient Selection Criteria

Patients scheduled for elective cardiac catheterization at the University of Virginia were eligible for enrollment. Twenty-five patients referred for cardiac catheterization for the evaluation of dyspnea and chest pain syndromes with a clinical history of hypertension of at least 1 year were enrolled in this study. No patient in this group had any history of myocardial infarction or any segmental wall motion abnormality during left ventriculography. Patients were excluded from study if they had any exposure to angiotensin-converting enzyme inhibitors within 6 weeks. Other exclusions included atrial fibrillation or significant valvular disease. All medications were withheld for at least 16 hours before the cardiac catheterization. Written informed consent was obtained from each patient, and the protocol was approved by the Human Investigation Committee at the University of Virginia.

Data Acquisition

For echocardiographic LV wall thickness, standard M-mode and two-dimensional images were obtained within 24 hours of cardiac catheterization. Measurements of the interventricular septum and LV posterior wall from the M-mode parasternal long-axis view were made with a quantitative image processing system (IMAGEPRO). These values were averaged and normalized to the body surface area.

Conductance Catheter Technique

A detailed description of the principles and technique of the conductance catheter are described elsewhere.16,17 The present study used an 8F conductance catheter (Webster Laboratories) and a 2F micromanometer catheter (Millar Instruments) fully extended within its lumen. The catheters were positioned under fluoroscopic guidance along the long axis of the left ventricle (LV) and connected to a signal-conditioner/processor (Sigma SDF, Cardiodynamic) operating at 20 kHz. The system uses a dual excitation algorithm via two pairs of stimulating electrodes positioned at the apex and base of the ventricle. Resistances measured across intervening electrode pairs are inversely related to segmental volumes, and individual segment volumes are summed to yield total chamber volume. Real-time pressure-volume loops were displayed on a PC-based data acquisition and analysis system (Halcom Inc). Pressure and volume data were acquired at 200 samples per second.

Protocol

Patients underwent routine right and left heart catheterization, coronary angiography, and left ventriculography. Nonionic contrast was used (Isovue, Squibb Diagnostics) to minimize the negative inotropic effects of contrast media. After the diagnostic study, the 8F conductance and 2F micromanometer catheters were advanced into the LV cavity as described previously. Subsequently, a 7F 40-mm balloon occlusion catheter (Cordis Corp) was placed in the right atrium to perform inferior vena caval occlusion. Baseline hemodynamic parameters recorded at least 30 minutes after the diagnostic cardiac catheterization included heart rate, mean right atrial pressure, pulmonary capillary wedge pressure (PCWP), LV pressure (LVP), thermodilution cardiac output, and stroke volume. Subsequently, inferior vena caval occlusion was performed, and pressure-volume loops were recorded on a beat-by-beat basis for up to 50 seconds.

A 6F Judkins left coronary catheter was inserted into the left main coronary artery for the purpose of IC drug administration. Patients received a 30-minute IC infusion of enalaprilat (flow rate, 1 mL/min) for a total dose of 1.5 mg in the first 10 patients and a total dose of 5 mg in the remaining 15 patients. Hemodynamic measurements were then repeated and pressure-volume loops recorded after inferior vena caval occlusion as described. Left ventriculography was repeated for recalibration of the conductance volume signal.

Data Analysis

Data obtained from the conductance and micromanometer catheters were analyzed off-line by computer (Halcom Inc). The pressure and volume recordings were smoothed with a three-point, nonweighted moving average filter before hemodynamic parameters were determined. Absolute volume measurements from the conductance catheter were calibrated with corrections for offset and gain before and after the administration of IC enalaprilat. The gain correction was calculated as the ratio between thermodilution stroke volume and conductance stroke volume. The offset correction was computed as the product of the gain correction and the conductance end-diastolic volume, subtracted by the right anterior oblique left ventriculographic end-diastolic volume (determined with the Kennedy-Dodge regression).18 The time-variant ventricular volume was then calculated as the gain correction multiplied by the conductance ventricular volume, subtracted by the offset correction. The series of pressure-volume loops used to generate the end-systolic and end-diastolic pressure-volume relations commenced with the beat preceding a visual fall in volume and ended either at nadir volume or with baroreflex activation (defined as a 5% increase in heart rate on three consecutive beats). All premature and supraventricular beats were excluded from the analysis. The following variables were determined.

LV Afterload: Effective Arterial Elastance (Eₐ)

Eₐ was calculated from the ratio of end-systolic pressure (Pₑₛ) and stroke volume (SV), or Eₐ=Pₑₛ/SV, as previously defined.19,20

Diastolic Parameters

1. Time constant of isovolumic LVP relaxation, Tauₑ, was calculated from the ln(LVP)-versus-time relation, as derived by Weiss et al,21 which assumes that during isovolumic relaxation, LVP decayed in a monoeponential manner to zero. Tau measures the active diastolic properties of the LV and represents the time constant for calcium dissociation from the myofilaments.22-24 The goodness of fit for the calculation of Tauₑ in the present study was r²=0.999.

2. Time constant of isovolumic LVP relaxation, Tau₀, was calculated from the dp/dt-versus-pressure relation, as derived by Raff and Glantz.25 The goodness of fit for the calculation of Tau₀ in the present study was r²=0.973.

3. Peak LV filling rate (dV/dt max). The peak LV filling rate was calculated from the maximum value of the first derivative of the calibrated conductance volume signal.

4. Minimum LVP (LVPₘᵢₙₐᵣₑ). The minimum LVP was determined during early diastole.

5. Early diastolic transmitral gradient (PCWP-LVPₘᵢₙₐᵣₑ). The early diastolic transmitral gradient was approximated by subtracting the minimum early LVP from the maximum PCWP obtained from the peak of the "v" wave.
6. Chamber elastic stiffness (B). The diastolic pressure-volume relation was derived from the last 50% of diastolic filling ending immediately before atrial systole. A single point within this interval was selected for the baseline pressure-volume loop and each subsequent pressure-volume loop obtained during a load change with inferior vena caval occlusion. These points were fixed at a set interval before end diastole. The diastolic pressure-volume relation was obtained by connecting these points. Chamber elastic stiffness was calculated by fitting these diastolic pressure-volume points to an elastic model, $P = P_0 + a(e^{Bv} - 1)$, with a Marquardt nonlinear least-squares algorithm, where B is passive chamber elastic stiffness (milliliter$^{-1}$), $P_0$ is the baseline pressure (mm Hg), and a is a constant. Thus, chamber elastic stiffness is a measure of the passive late diastolic properties of the LV.

**Systolic Parameters**

1. LV stroke work index (SWI). SWI was calculated from the integrated area circumscribed by each pressure-volume loop normalized by body surface area.

2. Preload recruitable stroke work ($M_\text{sw}$). LV stroke work was plotted against LV end-diastolic volume for each of the pressure-volume loops generated after inferior vena caval occlusion. $M_\text{sw}$ represents the slope of this relation by linear regression.25

3. End-systolic elastance ($E_{es}$). The end-systolic pressure-volume point of each loop was selected as the data point with the maximum ($P_0(V-V_0)$). A least-squares linear regression of those points was applied, generating slope ($E_{es}$) and intercept ($V_0$) estimates. With this estimate of intercept, points of maximal ($P_0(V-V_0)$) for each cycle were obtained, and a subsequent regression was used to determine new estimates for $E_{es}$ and $V_0$. This process was repeated until there was no change in either parameter with subsequent iterations (Fig 1).27

**Statistical Analysis**

Data were compiled and analyzed on a minicomputer (VAX 8200, Digital Equipment Corp) using RS/1 (Bolt, Beraneck and Newman). Continuous variables were expressed as mean±SEM, and differences between groups were estimated by either a t test with pooled variance or a one-way ANOVA. Categorical data were expressed as proportions, and differences between groups were estimated by the Fisher exact test or $\chi^2$. Differences between groups were considered significant at a value of $P<0.05$ (two-tailed with Bonferroni correction).

**Results**

**Clinical Patient Characteristics**

The characteristics of the 25 patients enrolled in this study are shown in Table 1. Patients given the 1.5-mg dose of IC enalaprilat (n=10) composed a younger group of predominantly male patients without severe LVH. Patients in the 5-mg IC enalaprilat group (n=15) composed an older group of predominantly female patients with a spectrum of LVH. The median...
normalized LV thickness in the 5-mg dose group was 0.671 cm/m². Patients in the 5-mg dose group were divided into groups with and without severe LVH on the basis of this median value. Although all patients were referred for cardiac catheterization because of dyspnea and chest pain syndromes, only four patients (16%) had epicardial coronary artery disease. The distribution of coronary stenoses in these four patients was isolated right coronary artery disease, two-vessel coronary artery disease involving the diagonal and obtuse marginal branches in one and the left anterior descending and right coronary arteries in another, and three-vessel coronary disease in the last. Finally, 23 patients (92%) had never been exposed to an angiotensin-converting enzyme inhibitor before this study. The remaining two patients (8%) had not taken an angiotensin-converting enzyme inhibitor for at least 6 weeks before study.

**Effect of Intracoronary Angiotensin-Converting Enzyme Inhibition on Chronotropy and Load**

The effects of IC enalaprilat on heart rate, preload, and afterload in patients who received the 1.5-mg dose and those with and without severe LVH who received the 5.0-mg dose are shown in Table 2. At baseline, load and heart rate were similar in all three groups of patients. LV preload (LV end-diastolic volume index) fell only in patients given high-dose IC enalaprilat. Among those patients who received the high dose, the greatest preload reduction was observed in those with

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>LV Thickness/BSA, cm/m²</th>
<th>1.5-mg Dose</th>
<th>5.0-mg Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.671  (n=10)</td>
<td>&lt;0.671  (n=7)</td>
<td>&gt;0.671  (n=8)</td>
</tr>
<tr>
<td>Age, y</td>
<td>48±2*</td>
<td>59±3</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>7 (70)</td>
<td>1 (14)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td>59±3</td>
<td>64±2</td>
</tr>
<tr>
<td>LV thickness, cm/m²</td>
<td>0.57±0.02</td>
<td>0.61±0.02</td>
</tr>
<tr>
<td>Coronary disease, n (%)</td>
<td>2 (20)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; BSA, body surface area; and LVEF, angiographic left ventricular ejection fraction.

*P<.01 vs other groups (ANOVA).

### Table 2. Effect of Intracoronary Enalaprilat on Chronotropy and Load

<table>
<thead>
<tr>
<th>LV Thickness/BSA, cm/m²</th>
<th>1.5-mg Dose</th>
<th>5.0-mg Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.671  (n=10)</td>
<td>&lt;0.671  (n=7)</td>
<td>&gt;0.671  (n=8)</td>
</tr>
<tr>
<td>HR, bpm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>74±4</td>
<td>84±4</td>
</tr>
<tr>
<td>Post</td>
<td>74±4</td>
<td>84±4</td>
</tr>
<tr>
<td>EDVI, mL/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>81±3</td>
<td>74±4</td>
</tr>
<tr>
<td>Post</td>
<td>80±3</td>
<td>65±2*</td>
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<tr>
<td>SVR, dynes · s/cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>...</td>
<td>1492±129</td>
</tr>
<tr>
<td>Post</td>
<td>...</td>
<td>1508±118</td>
</tr>
<tr>
<td>Eₐ, mm Hg/mL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>2.36±0.22</td>
<td>2.87±0.52</td>
</tr>
<tr>
<td>Post</td>
<td>2.24±0.24</td>
<td>2.68±0.42</td>
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<tr>
<td>PVR, dynes · s/cm²</td>
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<td></td>
</tr>
<tr>
<td>Pre</td>
<td>123±16</td>
<td>103±8</td>
</tr>
<tr>
<td>Post</td>
<td>132±14</td>
<td>111±8</td>
</tr>
</tbody>
</table>

LV indicates left ventricular; BSA, body surface area; HR, heart rate; bpm, beats per minute; EDVI, left ventricular end-diastolic volume index; SVR, systemic vascular resistance; Eₐ, effective arterial elastance; PVR, pulmonary vascular resistance; Pre, before enalaprilat; and Post, after enalaprilat.

*P<.05 Pre vs Post; †P<.05 change vs other groups (ANOVA).
severe LVH. Afterload and heart rate did not change after treatment with IC enalaprilat in any group of patients in the present study.

Effect of Intracoronary Angiotensin-Converting Enzyme Inhibition on Diastolic Function

The diastolic hemodynamic parameters of the patients given the 1.5-mg dose (n=10) and the patients given the 5.0-mg dose (n=15) of IC enalaprilat are shown in Table 3. At baseline, TauL was significantly prolonged in patients with severe LVH given high-dose enalaprilat (P=.003 by ANOVA). Furthermore, patients with severe LVH tended to have greater abnormalities in passive LV diastolic function, as measured by LV chamber stiffness (P=.058 by ANOVA). After IC enalaprilat, PCWP and LV end-diastolic pressure were reduced in patients with severe LVH given the 5.0-mg dose.

Active relaxation was improved with the 5.0-mg dose of IC enalaprilat in those with severe LVH, as indicated by improvements in the time constants of isovolumic relaxation ( TauL and TauG ) and minimum LVP ( LVPmin ). Conversely, the early transmitral gradient ( PCWP−LVPmin ) and the peak filling rate ( dV/dtmax ) were unchanged with IC enalaprilat despite an improvement in active relaxation in patients with severe LVH. Passive LV diastolic function (chamber elastic stiffness) was also unaffected by IC enalaprilat administration.
There is a linear relation between the improvement in active relaxation and increasing LV hypertrophy (r = .92; P < .001). BSA indicates body surface area.

The magnitude of the improvement in active relaxation with IC enalaprilat (reduction in Tau) was directly proportional to the degree of LVH in these patients (Fig 2, r = .92, P < .001). Similar results were found for Tau (r = .81, P < .001). The mean LV diastolic pressure-volume relations before and after IC enalaprilat for each of the three groups studied are shown in Fig 3. Visual assessment of these three sets of relations demonstrates no significant changes in chamber compliance. There was no significant change in the LV diastolic pressure-volume relation in the low-dose enalaprilat group. However, there were preload reductions at high dose, with movement down a similar diastolic pressure-volume relation.

Effect of Intracoronary Angiotensin-Converting Enzyme Inhibition on Systolic Function

The systolic hemodynamic parameters of the patients given the 1.5-mg dose (n = 10) and the patients given the 5.0-mg dose (n = 15) of IC enalaprilat are shown in Table 4. At baseline, the three groups of patients were similar with respect to all systolic hemodynamic parameters. Among patients who received the 5.0-mg dose of IC enalaprilat, LV systolic pressure, SWI, and preload recruitable stroke work fell in the patients without severe LVH, whereas cardiac index and end-systolic elastance fell in the patients with severe LVH. Nevertheless, the effects of IC enalaprilat administration on all systolic hemodynamic parameters were similar in the three groups by ANOVA.

Discussion

The present study demonstrates the beneficial acute hemodynamic effects of local cardiac angiotensin-converting enzyme inhibition in patients with hypertensive LVH. Intracoronary enalaprilat administration resulted in an improvement in active (Ca\(^{2+}\)-dependent) relaxation in those with more severe LVH. Furthermore, this improvement in active relaxation was directly proportional to the severity of LVH in these patients. The greater the LVH, the greater the improvement in active (Ca\(^{2+}\)-dependent) relaxation. The reduction in PCWP in high-dose patients with severe LVH provided an additional hemodynamic benefit. This benefit, however, was not due to improvements in early diastolic filling or LV compliance, since the peak LV filling rate (dV/ dt\(_{max}\)) and chamber stiffness were unaffected by acute IC angiotensin-converting enzyme inhibition. LV filling pressures were reduced because of movement down a similar LV diastolic pressure-volume relation secondary to a reduction in preload rather than any intrinsic change in passive LV diastolic function.

The results of the present study support the hypothesis that the cardiac renin-angiotensin system is an important determinant of active diastolic function in hypertensive LVH. Angiotensin II administration has been shown to increase the L-type Ca\(^{2+}\) current independently of adenylyl cyclase, with a subsequent decrease in relaxation velocity, and affects the mobilization and reuptake of cytosolic free [Ca\(^{2+}\)] via phospholipase C activation and inositol phosphate second messengers. The reductions observed in Tau and LVP\(_{min}\) in LVH patients given the higher dose of angiotensin-converting enzyme inhibitor are consistent
with the premise that inhibition of cardiac angiotensin II production would result in improvement in active (Ca\(^{2+}\)-dependent) relaxation. Furthermore, the fact that the degree of improvement in Tau with IC angiotensin-converting enzyme inhibition is directly proportional to the severity of LVH provides physiological evidence that the cardiac renin-angiotensin system is induced to a greater extent with increasing LVH.\(^{2,7,9,15}\) These findings are even more impressive because the mode of administration of enalaprilat via the left coronary artery might be expected to cause regional asynchrony, which should retard active relaxation rather than improve it.

The reduction in preload after high-dose IC enalaprilat administration merits further comment. There were significant reductions in LV end-diastolic volume indexes seen in patients with and without severe LVH who received high-dose IC enalaprilat. It is unlikely that this observed preload reduction could have been due to volume depletion secondary to the nonionic contrast used during the diagnostic cardiac catheterization, because patients given the low dose of IC enalaprilat did not demonstrate any significant hemodynamic effects despite a similar experimental protocol (see Fig 3). This probably reflects a systemic concentration of enalaprilat despite its IC route of administration, with inhibition of bradykinin degradation in the venous system.\(^{29}\) Bradykinin has been shown to produce venodilation both because of direct effects\(^{30,31}\) and secondary to its effects on prostaglandins\(^{30,32}\) and endothelium-derived relaxing factor.\(^{30,33}\) This preload reduction may be responsible for the absence of improvement in the rate of early LV filling. An improvement in active diastolic function might be expected to improve the rate of early LV filling by increasing the early transmitral gradient.\(^{34,35}\) Although IC enalaprilat administration improved active diastolic function (Tau) in patients with LVH, the expected secondary improvement in peak early LV filling (dV/dt\(_{max}\)) did not occur. This may have been due to the accompanying preload reduction. Nevertheless, the reductions in LV filling pressures with angiotensin-converting enzyme inhibition provide additional hemodynamic benefit in patients with hypertensive LVH.

The present study demonstrated that although IC angiotensin-converting enzyme inhibition improved active relaxation, it did not affect the passive late diastolic properties of the LV as assessed either by a calculated LV chamber stiffness or the visual appearance of the LV diastolic pressure-volume relation. These results are contrary to those of others,\(^{7,8}\) who concluded in an

| Table 4. Effect of Intracoronary Enalaprilat on Systolic Function |
|------------------|------------------|------------------|
|                  | LV Thickness/BSA, cm/m\(^2\) |                  |
|                  | 1.5-mg Dose        | 5.0-mg Dose       |
|                  | <0.671 (n=10)     | <0.671 (n=7)     | >0.671 (n=8)     |
| LVSP, mm Hg      |                  |                  |
| Pre              | 159±9             | 173±10           | 179±12           |
| Post             | 156±7             | 159±10*          | 172±14           |
| CI, L·min\(^{-1}\)·m\(^{-2}\) |                  |                  |
| Pre              | 3.10±0.23         | 3.33±0.32        | 3.00±0.16        |
| Post             | 2.92±0.20         | 3.02±0.23        | 2.54±0.15†       |
| SVI, mL/m\(^2\)  |                  |                  |
| Pre              | 42±2              | 38±3             | 39±2             |
| Post             | 40±2*             | 36±2             | 35±2*            |
| ESVI, mL/m\(^2\) |                  |                  |
| Pre              | 39±3              | 36±4             | 42±9             |
| Post             | 40±3              | 29±2             | 39±7             |
| SWI, mm Hg·mL/m\(^2\) |                  |                  |
| Pre              | 4486±322          | 4747±428         | 4906±695         |
| Post             | 4175±318          | 4057±341†        | 4256±519         |
| E\(_{es}\), mm Hg/mL |                |                  |
| Pre              | 1.78±0.39         | 2.42±0.42        | 1.81±0.49        |
| Post             | 1.75±0.33         | 2.09±0.19        | 1.26±0.29*       |
| M\(_{sw}\), mm Hg |                  |                  |
| Pre              | 83±13             | 92±9             | 76±8             |
| Post             | 90±12             | 71±9*            | 76±7             |

LV indicates left ventricular; BSA, body surface area; LVSP, left ventricular systolic pressure; CI, cardiac index; SVI, stroke volume index; ESVI, left ventricular end-systolic volume index; SWI, left ventricular stroke work index; E\(_{es}\), end-systolic elastance; and M\(_{sw}\), preload recruitable stroke work. \*P<.05 Pre vs Post; †P<.01 Pre vs Post.
isolated perfused rat heart model that alterations of the cardiac renin-angiotensin system acutely changed diastolic compliance in hypertrophied hearts compared with controls. They further postulated that these effects on passive diastolic function must be secondary to changes in active Ca\textsuperscript{2+} handling mediated by the cardiac renin-angiotensin system. However, these changes were observed in an isovolumic preparation. The present study provides the first description of the effect of IC angiotensin-converting enzyme inhibition on passive LV diastolic function in ejecting hypertrophic ventricles. The observations of the present study appear to demonstrate an uncoupling of active and passive diastolic function in patients with abnormal active relaxation. Unfortunately, although measures of Tau may quantify the rate of LV relaxation, there are no direct measures of the extent of relaxation.\textsuperscript{56} Therefore, previous investigators have used the rate of relaxation as an indirect surrogate for the extent of relaxation and demonstrated that the end-diastolic pressure-volume relation of the normal filling canine LV was unaffected by changes in active relaxation provided that end diastole occurred more than 3.5 Tau,\textsuperscript{37} or 3.7 to 5.4 Tau after dP/dt\textsubscript{min}. By these criteria, one would not expect IC enalaprilat to alter the LV diastolic pressure-volume relation in patients with hypertrophy in the present study, since all should have had complete LV relaxation at baseline.

The direct effect of the renin-angiotensin system on LV systolic function in different species has been the subject of considerable interest. The positive inotropic effects of angiotensin II in cardiac tissues of most mammalian species have been well documented.\textsuperscript{40-44} These effects have been ascribed to specific receptors localized on cardiomyocytes\textsuperscript{45-46} and on intramyocardial sympathetic nerve terminals.\textsuperscript{47,48} These findings may be species specific, however, in view of the lack of a positive inotropic response to angiotensin II in myocardium from the guinea pig\textsuperscript{49} and the adult rat.\textsuperscript{50} Angiotensin II receptors have been identified in the myocardium and cardiac nerve terminals of human myocardium.\textsuperscript{51} More recently, the positive inotropic effects of angiotensin II on human cardiac muscle in vitro have been demonstrated.\textsuperscript{52} These results imply that IC administration of angiotensin-converting enzyme inhibitors to patients should exert a negative effect on myocardial contractility, which has been confirmed in patients with dilated cardiomyopathy.\textsuperscript{53} In the present study, IC administration of high-dose enalaprilat exerted at most a modest negative inotropic effect, unlike its more profound effects on active relaxation.

**Limitations of the Study**

There are several potential limitations to this study. The first involves the accuracy and linearity of the gain and offset calibration of the conductance volume signal.\textsuperscript{54,55} Although the gain calibration for the conductance volume signal is nonlinear over a large volume range, previous investigators have demonstrated that even during an acute load change, the calibrated conductance volume signal is accurate within the range of volume from end-diastolic volume to end-systolic volume of the baseline loop.\textsuperscript{56} Since IC enalaprilat did not reduce late diastolic volumes below that of the end-systolic volume of the baseline loop, the LV diastolic pressure-volume relation reported in the present study should be accurate. Another potential limitation is that the offset calibration caused by the parallel conductance of adjacent structures was assumed to be constant during the load change of inferior vena cava occlusion. This assumption should be valid, because previous investigators have demonstrated that the offset calibration of the conductance volume signal is relatively insensitive to changes in right ventricular volume\textsuperscript{16} or LV thickness and shape changes during the cardiac cycle.\textsuperscript{57} The possibility that the effect of enalaprilat on diastolic function may have been due to improvement in ischemia rather than via a direct myocardial effect merits further comment. Although LVH is associated with subendocardial ischemia during stress, it is unclear whether patients with LVH manifest chronic subendocardial ischemia while at rest. In a canine renal hypertension model of LVH, Mueller et al\textsuperscript{58} did not observe any abnormalities in endocardial perfusion or endocardial/epicardial flow compared with control animals. Although Rembert et al\textsuperscript{59} observed mild resting abnormalities in the resting endocardial/epicardial systolic (but not diastolic) flow ratio at rest in a canine coarctation banding model of LVH, they concluded that these animals were unlikely to have resting subendocardial ischemia because they were not in a state of maximal vasodilatation at rest, as evidenced by their more than twofold increase in flow with adenosine. Another limitation involves the use of the PCWP - LV\textsubscript{end-systole} difference to estimate the early transmural gradient during early diastole. The fluid-filled PCWP was obtained despite the abnormal frequency response and time delay through the pulmonary circulation. Although simultaneous left atrial - LV micromanometer pressure recording would have eliminated this technical limitation, it would have required an additional transseptal catheterization in an already heavily instrumented patient. The final limitation reflects infusion of enalaprilat only into the left coronary artery. We may have underestimated the benefit of angiotensin-converting enzyme inhibition on active relaxation, because this nonuniform mode of administration might be expected to cause regional asynchrony, which could retard active relaxation.

**Conclusions**

This study confirmed the hypothesis that angiotensin-converting enzyme inhibition acutely improves active (Ca\textsuperscript{2+}-dependent) relaxation in patients with LVH secondary to systemic hypertension. Furthermore, we confirmed a secondary hypothesis that the severity of hypertensive LVH would be related to the extent of induction of cardiac angiotensin-converting enzyme. The greater the LVH, the greater the improvement in active (Ca\textsuperscript{2+}-dependent) relaxation. As a result, this study represents the first demonstration of an acute direct benefit of an antihypertensive medication on hypertensive LV diastolic dysfunction.

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