Clinical Investigation and Reports

Effects of Cardiac Versus Circulatory Angiotensin-Converting Enzyme Inhibition on Left Ventricular Diastolic Function and Coronary Blood Flow in Hypertrophic Obstructive Cardiomyopathy

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Background—Left ventricular (LV) diastolic function and coronary flow are impaired in hypertrophic obstructive cardiomyopathy (HOCM). This study was designed to evaluate the impact of cardiac and circulatory ACE inhibition on such derangements.

Methods and Results—Twenty patients with HOCM underwent cardiac ACE inhibition with intracoronary (IC) enalaprilat (0.05 mg/min infused into the left anterior descending coronary artery for 15 minutes) followed by circulatory ACE inhibition with 25 mg sublingual (SL) captopril. Contrast ventriculography, pressure, and coronary flow measurements were performed at baseline, after IC enalaprilat infusion, and 45 minutes after SL captopril. Heart rate was not affected by the respective interventions (75±11 versus 76±13 versus 75±10 bpm; P=NS), whereas mean aortic pressure dropped slightly after IC enalaprilat and significantly after SL captopril (90±8 versus 85±10 versus 74±9 mm Hg; P<.05). Compared with baseline, IC enalaprilat resulted in a decrease in LV end-diastolic pressure (17.6±5.9 versus 14.4±4.9 mm Hg; P<.05), time constant of isovolumic LV pressure relaxation (τi) (69±9 versus 52±10 ms; P<.05), and outflow gradient (45.2±6.9 versus 24.4±3.7 mm Hg; P<.05) and in an increase in coronary blood flow (107±10 versus 127±12 mL/min; P<.05) and coronary flow reserve (2.2±0.4 versus 2.6±0.3; P<.05). After SL captopril, τi was prolonged (60±13 ms; P<.05 versus IC enalaprilat), and LV outflow gradient, coronary blood flow, and coronary flow reserve values returned to baseline (45.5±5.3 mm Hg, 107±12 mL/min, and 2.2±0.5, respectively; P=NS versus baseline).

Conclusions—Activation of the cardiac renin-angiotensin system contributes to LV diastolic dysfunction as well as to the decreased coronary blood flow and coronary flow reserve in HOCM. Cardiac ACE inhibition restores and circulatory ACE inhibition aggravates the above derangements. (Circulation. 1998;97:1342-1347.)

Key Words: angiotensin II enzymes hypertrophy cardiomyopathy

Left ventricular hypertrophy, which is usually but not always asymmetrical, and abnormal orientation of cardiac fibers are the pathological hallmarks of HOCM.1-3 LV systolic and diastolic dysfunction with or without subaortic or midventricular obstruction and myocardial ischemia are prominent pathophysiological features of the disease.3-4

The RAS plays an important role in HOCM, regulating, in part, the expression of cardiac hypertrophy.3,6 Moreover, the presence of ACE genotype DD, which results in increased levels of ACE in the plasma and possibly the heart, is associated with an increased incidence of sudden cardiac death in HOCM.7

Inhibition of RAS is associated with a significant improvement in LV diastolic function in LV hypertrophy secondary to hypertension8 or aortic stenosis9 and favorably affects coronary hemodynamics in experimental animals10-12 and in humans.13-16 Despite these potentially beneficial effects of RAS inhibition, there has been limited use of ACE inhibitors or angiotensin receptor blockers in the treatment of HOCM.17 This is most likely because of concerns that the LV unloading after circulatory RAS inhibition may aggravate the LV outflow gradient in patients with subaortic obstruction.18

The purpose of the present study, enrolling patients with HOCM and mild LV outflow obstruction, was to investigate the effects of selective cardiac ACE inhibition with intracoronary enalaprilat on LV diastolic function and coronary blood flow and the extent to which these effects are modified after circulatory ACE inhibition with sublingual captopril.

Methods

Study Population

Twenty patients prospectively selected from patients undergoing cardiac catheterization for HOCM were studied. All had an asym-
metrically hypertrophic nondilated left ventricle (septal thickness >1.5 cm plus ratio of septal to posterior wall thickness >1.5) and a basal intraventricular pressure gradient >30 mm Hg recorded in the LV outflow tract. All patients were in sinus rhythm, and medications were discontinued 24 hours before the study. Patients with systemic or cardiac diseases that cause LV hypertrophy and those with angiographically documented coronary artery disease were excluded from the study. All patients gave informed consent according to the ethical guidelines for human studies of our institution.

Echocardiography

A Hewlett Packard Sonos 1500 system connected to a 2.5-MHz external transducer was used for M-mode and two-dimensional imaging as well as pulsed and color Doppler recordings. Each patient was examined in the left lateral decubitus position during shallow respiration. All recordings were made at the end-expiratory phase. Septal and posterior wall thicknesses were measured in diastole just before atrial systole. Two-dimensional guided pulsed Doppler recordings were made of mitral inflow velocity from the apical four-chamber view with the cursor positioned in the tips of the mitral valve leaflets. Measurements included peak flow velocity of early and late LV diastolic filling (E and A waves, respectively) and isovolumic relaxation time defined as the time interval from aortic valve closure to mitral valve opening. Doppler color flow imaging was used to diagnose and evaluate the severity of mitral regurgitation.

Study Protocol

The study protocol is shown in Fig 1. All patients underwent coronary angiography (T0). Fifteen minutes later (T15), when contrast effects had dissipated, baseline hemodynamics (heart rate, aortic pressure, right atrial pressure, pulmonary artery pressure, LV micro-manometer pressure, and cardiac output) and coronary blood flow measurements (Honeywell multichannel strip-chart recorder) were obtained, and left ventriculography was performed with nonionic contrast medium injected through the Millar catheter. Subsequently, enalaprilat (0.05 mg/min at an infusion rate of 1 mL/min) was infused into the LAD for 15 minutes. At the end of the second 15-minute period (T30), hemodynamic measurements, coronary blood flow measurements, and left ventriculography were repeated, and the patients were given 25 mg captopril sublingually. Forty-five minutes later (T45), hemodynamic measurements, coronary blood flow, and left ventriculography were repeated again.

Cardiac Catheterization

All patients were premedicated with diazepam 5 mg IM. Routine right and left heart catheterization, including coronary arteriography and left ventriculography, were performed as previously described.10 The left and right coronary arteries were imaged in multiple views, including craniocaudal projections. Coronary artery stenosis was considered significant if the lumen diameter was narrowed by >30%. LV pressure was measured with a 7F high-fidelity micromanometer catheter (Millar Instruments). LV volumes were evaluated in the right anterior oblique projection by the single-plane area-length method.20 All patients received 10 000 IU of intravenous heparin before coronary angiography and 5000 IU hourly during the procedure.

Intracoronary Doppler Flow Velocity Study

Coronary flow velocity was assessed with an intracoronary Doppler catheter, model DC-101, inserted through a 7F coronary guiding catheter and over a 0.010-in flexible angioplasty guidewire into the center of the proximal LAD in an area free of side branches or vessel overlap.21 Coronary flow velocity was recorded simultaneously with LV pressure obtained with a 7F Millar micromanometer catheter advanced into the LV apex via a left femoral sheath and arterial pressure obtained from the 7F coronary guiding catheter, which was connected to a fluid-filled pressure transducer zeroed at the midchest level. Doppler data were processed with a zero-cross velocimeter (Millar Instruments), from which mean and phasic coronary flow velocity signals were obtained. Before the Doppler catheter was placed in the guiding catheter, the mean and phasic Doppler flow velocity recordings were zeroed and calibrated from an internally set 0-to-100-cm/s signal for full-scale deflection. Before the study protocol was begun, the position of the Doppler velocity catheter and the range gate control of the 20-MHz pulsed Doppler meter were adjusted to optimize the audio coronary flow velocity signal and also to record an optimal signal for phasic coronary flow velocity wave form. Both phasic and mean Doppler coronary flow velocity and hemodynamic signals were displayed and recorded on a Honeywell strip-chart recorder. For data from the zero-cross velocimeter, the mean coronary flow velocity was measured from the tracings derived from the recorder in each study cycle (zero-cross frequency analysis). A bolus of 12 mg papaverine IC, injected through the guiding catheter, was used to measure coronary vasodilator reserve.

Data Analysis

Cardiac output was determined by the method of Fick.24 Systemic vascular resistance was calculated from the following formula: systemic vascular resistance=(mean aortic pressure−right atrial pressure)/cardiac output. p was determined from the dP/dt-versus-pressure relation, as derived by Raff and Glantz.25

The area under the coronary flow velocity curve was quantified by computerized planimetry. Systole was defined from the beginning of the LV pressure upstroke (or the R wave on the ECG) to the dicrotic notch of aortic pressure and diastole as the remainder of the cardiac cycle. Coronary flow reserve was defined as the ratio of mean coronary flow velocity at peak papaverine-induced hyperemia to mean resting coronary flow velocity.26 Coronary flow was taken as the product of the mean coronary flow velocity times the cross-sectional area of the proximal LAD. Cross-sectional area was determined at end diastole just distal to the Doppler velocity catheter tip from a single angiographic view, assuming a circular cross section, as follows: cross-sectional area = π×(vessel diameter/2)². Coronary arteriography to measure LAD...
diameter was performed after a single bolus injection of 8 mL of low-osmolarity contrast medium, at rest and at maximal hyperemia after intracoronary papaverine.

Statistical Analysis
Data are expressed as mean±SD. Intragroup comparisons of continuous variables were performed with repeated-measures ANOVA. When results of ANOVA were significant, the Scheffe test for multiple comparisons was used to isolate the individual significant differences. Factors predictive of the results were examined with linear regression analysis. A value of P<.05 was considered statistically significant.

Results
The demographic, clinical, and echocardiographic characteristics of the study population are shown in Table 1.

<p>| TABLE 1. Demographic, Clinical, and Echocardiographic Characteristics of the Study Patients |
|----------------------------------|---------------------------------|---------------------------------|-------------------------------|</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Intracoronary Enalaprilat</th>
<th>Sublingual Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>LV volume, cm³</td>
<td>1430±195</td>
<td>1316±179*</td>
<td>1174±170†</td>
</tr>
<tr>
<td>Peak systolic pressure, mm Hg</td>
<td>21±8</td>
<td>22±12</td>
<td>15±6†</td>
</tr>
<tr>
<td>Right atrial pressure, mm Hg</td>
<td>177±26</td>
<td>154±21*</td>
<td>167±23†</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>17.6±5.9</td>
<td>14.4±4.9*</td>
<td>14.3±4.8*</td>
</tr>
<tr>
<td>LV pressure, mm Hg</td>
<td>1655±284</td>
<td>1634±234</td>
<td>1631±264</td>
</tr>
<tr>
<td>t₀, ms</td>
<td>69±9</td>
<td>52±10*</td>
<td>60±13†</td>
</tr>
<tr>
<td>End diastolic pressure, mm Hg</td>
<td>34±18</td>
<td>35±21</td>
<td>31±16†</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>64±15</td>
<td>63±17</td>
<td>64±19</td>
</tr>
<tr>
<td>Mean pulmonary artery pressure,</td>
<td>4.7±0.5</td>
<td>4.8±0.6</td>
<td>4.7±0.6</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>1430±195</td>
<td>1316±179*</td>
<td>1174±170†</td>
</tr>
<tr>
<td>Mean aortic pressure, mm Hg</td>
<td>90±8</td>
<td>85±10*</td>
<td>74±9†</td>
</tr>
<tr>
<td>Systemic vascular resistance,</td>
<td>1430±195</td>
<td>1316±179*</td>
<td>1174±170†</td>
</tr>
<tr>
<td>mic relaxation, as indicated by</td>
<td>5.4±4.9*</td>
<td>4.7±0.6</td>
<td>4.3±0.7*</td>
</tr>
</tbody>
</table>
| dP/dt, LV end-systolic and end-diastolic volume, and ejection fraction were similar to baseline at the end of intracoronary enalaprilat infusion.

Sublingual captopril resulted in no change in heart rate and in a significant decrease in right atrial pressure, mean aortic pressure, systemic vascular resistance, and mean pulmonary pressure compared with baseline or intracoronary enalaprilat (Table 2). Likewise, LV volumes became slightly but significantly lower compared with baseline or intracoronary enalaprilat, whereas the LV ejection fraction was similar to baseline or intracoronary enalaprilat. LV relaxation deteriorated compared with intracoronary enalaprilat, as indicated by the decrease in peak −dP/dt and the increase in t₀. The latter, however, remained lower compared with baseline. LV systolic pressure increased compared with intracoronary enalaprilat but remained lower compared with baseline, whereas the LV outflow gradient increased compared with intracoronary enalaprilat and returned to baseline (Fig 2). After sublingual captopril, the LV outflow gradient was lower in 13 patients, similar in 1 patient, and greater in 6 patients compared with baseline. The increase in LV outflow gradient was slight in 3 patients (2.3%, 2.5%, and 5%), modest in 1 (10%), and large in 2 (20% and 83%).

Results of cross-sectional area and coronary blood flow measurements in the LAD are shown in Table 3. Resting cross-sectional area and cross-sectional area at peak hyperemia were slightly but significantly increased after intracoronary enalaprilat or sublingual captopril. Likewise, cross-sectional area at baseline was not significantly different from that after intracoronary enalaprilat or sublingual captopril. Moreover, cross-sectional area at peak hyperemia was significantly greater than resting cross-sectional area at baseline and after intracoronary enalaprilat or sublingual captopril.

Intracoronary enalaprilat was associated with an increase in coronary flow, diastolic and systolic coronary flow, and...
coronary flow reserve and a decrease in systolic retrograde flow compared with baseline. Sublingual captopril resulted in a decrease in coronary flow, diastolic and systolic coronary flow, and coronary flow reserve and in an increase in systolic retrograde coronary flow compared with intracoronary enalaprilat. As a result, coronary blood flow measurements after sublingual captopril returned to baseline.

Figs 3 and 4 show that coronary artery flow and coronary flow reserve were inversely related to LV outflow gradient.

**Discussion**

The findings of the present study indicate that the cardiac RAS contributes to the LV diastolic dysfunction and impaired coronary flow observed in HOCM and that its selective inhibition with intracoronary enalaprilat is associated with an improvement in LV active relaxation, a decrease in LV outflow gradient, and an increase in resting coronary blood flow and coronary flow reserve. The salutary effects of cardiac RAS inhibition, however, are significantly attenuated after circulatory RAS inhibition with sublingual captopril, most likely because of the accompanying LV preload and afterload reduction. Thus, only differential inhibition of the cardiac but not the circulatory RAS might be beneficial in HOCM.

**RAS in HOCM**

A major component of the RAS is ACE, a ubiquitous enzyme acting not only on angiotensin I to convert it to angiotensin II, a trophic and mitogenic hormone, but also on other substances, including bradykinin, a potent vasodilator that stimulates the release of both vasodilating prostaglandins and endothelium-derived relaxing factor or nitric oxide from the endothelium. In contrast to normal subjects, there is activated expression of ACE mRNA in the left ventricle of patients with HOCM. Moreover, the ACE genotype DD, which results in increased levels of ACE in the plasma and possibly the heart, is common in patients from HOCM families with a high incidence of sudden cardiac death and is associated with severe LV hypertrophy. Thus, increased ACE activity is associated with a poor clinical outcome and severe LV hypertrophy in HOCM. The underlying molecular mechanism has not been delineated. ACE, by stimulating synthesis of angiotensin II, may act as a growth factor on cardiac myocytes, inducing cardiac hypertrophy independent from hemodynamic or neurohumoral effects.

**LV Diastolic Function and Outflow Gradient**

Cardiac ACE inhibition was associated with an acceleration of LV active relaxation (shortened \( \tau_R \) and increased peak \(-dP/dt\) compared with baseline), an increase in LV distensibility (decreased end-diastolic pressure with not significantly different end-diastolic volume compared with baseline), and a decrease in LV outflow gradient. The improvement in LV active relaxation after intracoronary enalaprilat was most likely due to a localized reduction in angiotensin II, which may adversely affect LV diastolic function by several mechanisms, including (1) activation of phospholipase C and generation of phosphoinositide second messengers, which modify mobilization of cytosolic calcium and myofilament calcium sensitivity, and (2) coronary vasoconstriction, leading to decreased coronary artery blood flow and subendocardial ischemia. However, the possibility that improved LV active relaxation was due to a decrease in bradykinin degradation mediated by intracoronary enalaprilat cannot be excluded.

The improved LV distensibility was possibly secondary to the accelerated relaxation. The mechanism of decrease in LV outflow gradient was not assessed in this study. However, it is reasonable to assume that the regions perfused by intracoronary enalaprilat exhibited enhanced relaxation and increased

**Table 3. Cross-sectional Area and Blood Flow Measurements in the LAD**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Intracoronary Enalapril</th>
<th>Sublingual Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resting cross-sectional area, mm²</td>
<td>12.38±0.9</td>
<td>12.44±0.1*</td>
<td>12.45±0.3†</td>
</tr>
<tr>
<td>Cross-sectional area at peak hyperemia, mm²</td>
<td>12.42±2.7</td>
<td>12.52±2.8*</td>
<td>12.51±3†</td>
</tr>
<tr>
<td>Coronary flow, mL/min</td>
<td>107±10</td>
<td>127±12*</td>
<td>107±12</td>
</tr>
<tr>
<td>Diastolic coronary flow, mL/min</td>
<td>98±10</td>
<td>108±9*</td>
<td>97±13</td>
</tr>
<tr>
<td>Systolic retrograde coronary flow, mL/min</td>
<td>5±2</td>
<td>2±1</td>
<td>5±3</td>
</tr>
<tr>
<td>Systolic coronary flow, mL/min</td>
<td>9±6</td>
<td>19±5*</td>
<td>9±7</td>
</tr>
<tr>
<td>Coronary flow reserve</td>
<td>2.2±0.4</td>
<td>2.6±0.3*</td>
<td>2.2±0.5</td>
</tr>
</tbody>
</table>

*P<.05 vs baseline or sublingual captopril; †P<.05 vs baseline.

**Figure 3.** Inverse relationship between LV outflow gradient and coronary blood flow.

**Figure 4.** Inverse relationship between LV outflow gradient and coronary flow reserve.
Intracoronary enalaprilat was associated with a significant decrease in LV preload and afterload resulting in a decrease in LV cavity size and an increase in LV outflow gradient, which returned to baseline levels. LV relaxation deteriorated after sublingual captopril, as indicated by the increase in $\tau_0$ and the decrease in peak $-\Delta P/dt$ compared with intracoronary enalaprilat. This was most likely a result of the increased LV outflow gradient, which increased LV load during the first half of systole, and possibly of the decrease in LAD flow aggravating subendocardial ischemia. Likewise, LV distensibility deteriorated after sublingual captopril, and despite the reduction in LV end-diastolic volume as well as in right atrial and hence intrapericardial pressure compared with intracoronary enalaprilat, the LV end-diastolic pressure did not change significantly.

**LAD Blood Flow and Flow Reserve**

Intracoronary enalaprilat was associated with a significant increase in systolic and diastolic coronary blood flow and coronary flow reserve compared with baseline. These favorable effects, however, were abolished after sublingual captopril, and the values of all the above parameters returned to baseline.

The effect of ACE inhibition on coronary blood flow depends on the interaction between ventricular unloading and a variable reduction in coronary vasomotor tone. Intracoronary enalaprilat resulted in a significant decrease in LV end-diastolic pressure and outflow gradient, a slight reduction in mean aortic pressure, and a slight increase in LAD cross-sectional area in the present study. Thus, the observed increase in coronary blood flow and coronary flow reserve after intracoronary enalaprilat was most likely related to an increase in coronary perfusion pressure (mean aortic minus LV end-diastolic pressure) associated with a decrease in the outflow gradient and coronary vasodilatation. These are in accordance with previous reports. Sublingual captopril was associated with no significant change in LV end-diastolic pressure, an increase in LV outflow gradient, and a decrease in mean aortic pressure compared with intracoronary enalaprilat. Because LAD cross-sectional area was similar to that after intracoronary enalaprilat, the reduction in LAD blood flow and coronary flow reserve after sublingual captopril was due to a decrease in coronary artery perfusion pressure and an increase in LV outflow gradient. The pivotal role of the LV outflow gradient in the regulation of coronary artery flow in HOCM is further supported by the inverse relationship between LV outflow gradient and coronary flow as well as that between LV outflow gradient and coronary flow reserve observed in the present study. Similar findings have been reported recently.

**Clinical Implications**

The findings of the present study stress the involvement of the cardiac RAS in the development of LV diastolic dysfunction, LV subaortic obstruction, and decreased coronary flow reserve in HOCM. Thus, selective inhibition of the cardiac RAS either with ACE inhibitors or with angiotensin II receptor blockers might lead to symptom alleviation and decreased morbidity in this patient population. In a previous study, no significant differences in LV dimensions and exercise capacity were observed between patients with HOCM treated with captopril or enalapril and untreated patients. However, the number of enrolled patients was small (13 treated and 13 untreated patients), and the agents given differ dramatically in their cardioselectivity with regard to RAS inhibition. In doses equipotent for plasma ACE as assessed from the decrease in plasma ACE activity, enalapril shows only a 20% decrease in cardiac ACE activity lasting for ~1 hour compared with nearly complete blockade of cardiac ACE activity persisting for 24 to 48 hours after captopril.

Of utmost importance in the management of patients with HOCM with ACE inhibitors or angiotensin II receptor blockers is selective cardiac RAS blockade at doses that do not affect cardiac loading conditions. Despite the lack of clinical data regarding this issue, there are ample experimental data that this task can be accomplished. Ramipril and enalapril in doses that did not affect cardiac afterload did prevent the development and also caused regression of cardiac hypertrophy after abdominal aortic banding above the renal arteries. Moreover, cardiac hypertrophy induced by volume overload after aortocaval shunt was prevented by losartan, an angiotensin II receptor blocker, or with quinapril, an ACE inhibitor with high affinity for cardiac tissue ACE, but not with enalapril, an ACE inhibitor with low affinity for cardiac tissue ACE, and this effect appeared to be only in part related to the decrease in cardiac preload or afterload by losartan or quinapril.

**Study Limitations**

The first limitation involves enalaprilat infusion into the LAD. As a result of this nonuniform mode of administration, the benefit of ACE inhibition on active relaxation may have been underestimated because of regional asynchrony, which may retard active relaxation. A second limitation is lack of assessment of neurohormonal activation after intracoronary enalaprilat or sublingual captopril. However, no significant changes in plasma neurohormonal levels after intracoronary enalaprilat were observed in a recent report, and heart rate, a marker of sympathetic activity, remained stable during the study protocol. A third limitation reflects the fact that systemic angiotensin I and angiotensin II levels, which are the most sensitive markers of systemic RAS blockade, were not evaluated. A fourth limitation is lack of determination of the contribution of bradykinin, whose circulating and tissue levels are elevated by ACE inhibitors, to the observations of the present study. A fifth limitation is the use of two different ACE inhibitors for the two aspects of the study. Alternatively, oral or intravenous enalaprilat might have been given after intracoronary enalaprilat. However, the differences among ACE inhibitors are not as pronounced as those seen among calcium antagonists or $\beta$-blockers. Moreover, the late onset of action (1 to 2 hours) of oral enalapril would have resulted in an ethically unacceptable prolongation of the study protocol, and intravenous enalaprilat, which is not infrequently associated with severe hypotension, might have been deleterious for HOCM patients. Finally, the limitations regarding
the technique of coronary blood flow measurements used in the present study have been previously analyzed in detail.19,32

Conclusions
Cardiac RAS inhibition with intracoronary enalaprilat improves LV active relaxation, coronary blood flow, and coronary flow reserve and reduces LV outflow gradient in patients with HOCM. These salutary effects are significantly attenuated after LV unloading resulting from circulatory RAS inhibition with sublingual captopril. Thus, differential inhibition of the cardiac and not the circulatory RAS might be beneficial in this patient population. However, further clinical studies are necessary as to whether this is feasible with subpressor doses of ACE inhibitors or angiotensin II receptor blocker.

References
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