Direct myocardial and coronary effects of enalaprilat in patients with dilated cardiomyopathy: assessment by a bilateral intracoronary infusion technique

JEAN-MARC FOULT, M.D., OSCAR TAVOLARO, M.D., ISABELLE ANTONY, M.D., AND ALAIN NITENBERG, M.D.

ABSTRACT Angiotensin II elicits contractile responses in the coronary arteries and myocardial tissue, which suggests that blockade of the renin-angiotensin system by specific agents should lead to both coronary vasodilation and an alteration of left ventricular inotropism. The present work was designed to delineate —independently from its systemic effects —the intrinsic actions of an angiotensin converting—enzyme inhibitor on the coronary circulation and left ventricular function. To minimize peripheral effects, a bilateral intracoronary infusion of enalaprilat (0.05 mg·min⁻¹·m⁻², 1 ml·min⁻¹ in each coronary artery) was performed in 16 patients with dilated cardiomyopathy. All patients had normal coronary arteriograms. In 12 patients (group I) the intracoronary infusion of enalaprilat resulted in minimal peripheral changes, with a 5% reduction in the mean aortic pressure (p < .05) and no significant alteration in indexes of preload, i.e., left ventricular end-diastolic pressure and volume, or of afterload, i.e., left ventricular end-systolic stress and systemic resistances. Myocardial oxygen consumption was also unaffected by the intracoronary infusion of enalaprilat. Coronary vasodilation was demonstrated by a significant elevation of coronary sinus blood flow (+19%, from 181 ± 73 to 214 ± 79 ml·min⁻¹, p < .001) and a reduction of coronary resistance (−18%, from 0.51 ± 0.17 to 0.41 ± 0.15 mm Hg·ml⁻¹·min, p < .001), with a parallel increase in coronary sinus oxygen content and pressure (both p < .05). Oxygen extraction by the myocardium was reduced (p < .01). The intracoronary infusion of enalaprilat resulted, on the other hand, in a significant deterioration of all indexes of left ventricular function: cardiac index (−9%, from 2.59 ± 0.61 to 2.36 ± 0.64 liters·min⁻¹·m⁻², p < .01), ejection fraction (−12%, from 0.32 ± 0.11 to 0.28 ± 0.10, p < .02), and end-systolic stress/end-systolic volume ratio (−8%, from 2.37 ± 0.51 to 2.19 ± 0.60 g·cm⁻²·ml⁻¹, p < .01). In 4 patients (group II) with similar baseline characteristics, intracoronary enalaprilat induced the same hemodynamic alterations, with return to basal values after cessation of the intracoronary infusion and no significant alteration of plasma renin activity and plasma aldosterone. This study demonstrates that, when its peripheral effects are avoided by a bilateral intracoronary infusion technique, enalaprilat produces both a selective vasodilation of the coronary arteries and a negative inotropic effect on left ventricular contractility in patients with dilated cardiomyopathy.


ALTHOUGH NUMEROUS trials have established the value of angiotensin converting—enzyme inhibitors in the treatment of severe chronic congestive heart failure,¹⁻³ little information is available on the specific actions of these drugs on the coronary vessels and myocardial contractility in humans. Angiotensin II induces a contractile response in both coronary vascular smooth muscle and myocardium. These positive inotropic and vascular contractile actions of angiotensin II have been demonstrated in various species.⁴⁻⁶ Inhibition of the renin-angiotensin system by specific agents is therefore expected to result in both negative inotropic effects and vasodilation of the coronary arteries. Instead, the majority of patients receiving captopril or enalapril exhibit an elevation of left ventricular ejection fraction and cardiac index.⁷⁻¹⁴ Similarly, most studies of coronary blood flow after angiotensin converting—enzyme inhibition have demonstrated either no change or a reduction of coronary flow,¹⁵⁻²¹ suggesting that these drugs had little effect — if any — on the coronary vasculature. Such a discrepancy between the experimental properties of angiotensin II and the clin-
ically observed effects of converting–enzyme inhibitors could result from the marked systemic vasodilator actions of captopril\textsuperscript{22} and enalapril\textsuperscript{23} when they are administered by the oral or intravenous route. Indexes of left ventricular function and coronary blood flow are both highly sensitive to the loading conditions of the heart in the sense that a reduction in afterload may result by itself in an improvement in variables of left ventricular function and a reduction in coronary blood flow.\textsuperscript{24}

To delineate the specific effects of a soluble solution of enalapril (enalaprilat, MK 422, Merck Sharp & Dohme — Chibret Laboratories) on both left ventricular performance and coronary circulation of patients with dilated cardiomyopathy, a bilateral intracoronary infusion technique was used, thereby minimizing the peripheral action of the drug. This approach allowed for a specific determination of the direct myocardial and coronary effects of enalaprilat, and avoided problems inherent in evaluating agents with both systemic and cardiac actions.

**Methods**

**Patient selection.** Sixteen patients — 10 men and six women (mean age 50 ± 10 years) — with dilated cardiomyopathy as documented by echocardiography and previous episodes of congestive heart failure were investigated. All these patients were in sinus rhythm and had angiographically normal coronary arteries, and no cause could be found for their ventricular dysfunction.

**Catheterization procedure.** Cardiac catheterization was performed after the patients gave informed consent; all cardiac drugs were discontinued 48 hr before the study, and all patients were in the fasting state for at least 12 hr before the procedure. No premedication was administered and local anesthesia was achieved with 1% lidocaine. In 12 patients (group I) a No. 7F high-fidelity double-tipped micromanometer catheter (PC-770, Millar Instruments) was placed into the left ventricle through a femoral artery and positioned to record left ventricular and aortic pressures simultaneously. Two No. 5F sheaths were placed into the other femoral artery for left ventriculography and coronary arteriography catheters. A No. 7F Swan-Ganz thermodilution catheter (Edwards Laboratory) was placed into the pulmonary artery via a femoral vein for determination of cardiac output (Cardiac output computer 9520 A, Edwards Laboratory). A No. 7F coronary sinus thermodilution catheter (Wilson Webster Laboratories) was inserted into the left subclavian vein and positioned into the coronary sinus for measurement of coronary sinus blood flow; the position of the catheter was controlled by fluoroscopy before each measurement of coronary sinus blood flow to place the proximal thermistor in front of the posterior interventricular vein leading to the coronary sinus.

In four patients (group II) a different protocol without measurement of coronary sinus blood flow was followed.

**Protocol.** In group I patients, four periods (t\textsubscript{1}, t\textsubscript{2}, t\textsubscript{3}, and t\textsubscript{4}) were observed for completion of the protocol (figure 1). At t\textsubscript{1}, left ventricular angiography (1 ml·kg\textsuperscript{-1} body weight ioxaglate meglumine), with simultaneous recording of left ventricular and aortic pressures, and coronary arteriography were performed. A 30 min delay was then observed to eliminate the effects of contrast material.\textsuperscript{25} At t\textsubscript{2}, measurements of heart rate, left ventricular, aortic, and right atrial pressures; cardiac output; and coronary sinus blood flow were performed. Arterial, pulmonary arterial and sinus blood samples were obtained. Enalaprilat was then directly and simultaneously infused into the right and left main coronary arteries with the use of saline as a vehicle (0.05 mg·min\textsuperscript{-1}, 1 ml·min\textsuperscript{-1} in each coronary artery). At t\textsubscript{3}, all measurements performed at t\textsubscript{2} were repeated 15 min after initiation of the intracoronary infusion of enalaprilat. At t\textsubscript{4}, a second left ventricular angiogram was obtained in the same 30 degree right anterior oblique incidence as that used at t\textsubscript{1}, the right coronary catheter being removed for that purpose, and heart rate, left ventricular, and aortic pressures were recorded.

In group II patients, after left ventricular angiographic and coronary arteriographic examinations were performed, heart rate; mean right atrial, mean aortic, and left ventricular pressures; cardiac index; arteriovenous oxygen difference; plasma renin activity; and plasma aldosterone were measured at basal state (t\textsubscript{0}), after a 5 min bilateral intracoronary infusion of saline (1 ml·min\textsuperscript{-1} in each coronary artery) (t\textsubscript{1}), after a 15 min bilateral intracoronary infusion of enalaprilat (0.05 mg·min\textsuperscript{-1}, 1 ml·min\textsuperscript{-1} in each coronary artery) (t\textsubscript{2}), after another 2 to 4 min left intracoronary infusion of enalaprilat at the same dosage and removal of the right coronary catheter (t\textsubscript{3}), and finally after all intracoronary infusions had been discontinued for 10 min (t\textsubscript{4}).

**Data analysis and calculations.** Cardiac output and cardiac index (cardiac output/body surface area) were determined by the thermodilution method and coronary sinus blood flow was determined by the continuous thermodilution method\textsuperscript{26} (after a 1 ml·sec\textsuperscript{-1} infusion of saline solution). Heart rate, left ventricular end-diastolic pressure, left ventricular systolic pressure, mean aortic pressure, mean right atrial pressure, and systemic vascular resistances were calculated by means of a catheterization data analysis computer system (Hewlett-Packard 5600 M) that performed on-line analysis on 9 beats for averaging out respiratory variations. Left ventricular end-diastolic and end-systolic volumes as well as ejection fraction were calculated from a monoplane angiogram (100 frames·sec\textsuperscript{-1}) in a 30 degree right anterior oblique projection by means of the area-length method.\textsuperscript{27} Left ventricular mass was calculated according to the equation of Trenouth et al.,\textsuperscript{28} which was also used to calculate the equatorial end-systolic wall thickness. Average left ventricular end-systolic equatorial wall stress was calculated according to the equation of Falsetti et al.,\textsuperscript{29} by means of the left ventricular pressure corresponding to the left ventricular end-systolic volume (the left ventricular pressure and a frame marker were recorded during angiography). Finally, the end-systolic wall stress/end-systolic volume ratio was calculated. Left ventricular mean diastolic pressure was calculated by planimetry of the left ventricular diastolic pressure curve on three consecutive cycles. The coronary resistance (mm Hg·ml\textsuperscript{-1}·min) was calculated as
mean aortic pressure minus left ventricular mean diastolic pressure (mm Hg/coronary sinus blood flow (ml·min⁻¹)). Oxygen content of blood samples was determined by the galvanic cell method (Lex O₂, Con K, Waltham Instruments) and oxygen pressure was determined with a Clark PO₂ electrode (polarizing voltage between anode and cathode, ABL 30, Radiometer). Oxygen saturation was measured by a spectrophotometric method at 600 nm (OSM2, Radiometer). Myocardial oxygen consumption (ml·min⁻¹) was calculated as the arterial minus coronary sinus blood oxygen content difference (ml·100 ml⁻¹) times coronary sinus blood flow. Plasma renin activity and plasma aldosterone were assessed by a radioimmunoassay technique (International-CIS and Dode Baxter Travenol Diagnostics Inc., respectively).

Statistical analysis. The mean values and SD were calculated for each variable. In Group I, comparisons among data obtained at t₁, t₂, t₃, and t₄ were performed by means of the paired t test. In Group II, differences between postinjection data and basal state values were examined by analysis of variance. A difference of p < .05 was considered indicative of a significant difference.

Results

Group I patients. Angiographic data obtained at t₁ provided evidence of severe dilated cardiomyopathy in all patients, including increased left ventricular end-diastolic volume, reduced ejection fraction (see table 3), and lack of wall hypertrophy (left ventricular mass, 98 ± 18 g·m⁻²; left ventricular end-diastolic wall thickness, 7.6 ± 1.8 mm). Coronary arteriograms were normal in all patients.

Hemodynamic data (table 1). The comparison between data obtained at t₂ and t₃, i.e., before and during the intracoronary infusion of enalaprilat, indicated a moderate reduction in left ventricular systolic pressure (−5%, p < .05) and mean aortic pressure (−5%, p < .05). Cardiac index was reduced by 9% (p < .01) and the arteriovenous oxygen difference was enlarged (+9%, p < .01). There was no significant change in heart rate, left ventricular end-diastolic pressure, mean right atrial pressure, systemic vascular resistances, or rate-pressure product.

Coronary circulation (table 2). In all patients, the intracoronary infusion of enalaprilat resulted in a significant elevation of coronary sinus blood flow between t₂ and t₃ (+19%, p < .001), with a parallel reduction in coronary resistance noted in 11 of 12 patients (−18%, p < .001). Coronary sinus oxygen content and pressure were significantly increased, while oxygen extraction by the myocardium was reduced. Myocardial oxygen consumption was unchanged.

Left ventricular performance (table 3). The specific effects of enalaprilat on angiographically-derived indexes of left ventricular performance were assessed by comparison of the data obtained at t₁ and t₄. No significant change in left ventricular end-diastolic or end-systolic volumes was noted. Heart rate increased slightly between the two left ventricular angiograms (+6%, p < .05). There was a significant reduction in left ventricular ejection fraction (−12%, p < .02) and left ventricular end-systolic wall stress/end-systolic volume ratio (−8%, p < .01) (figure 2). Left ventricular end-diastolic pressure, left ventricular systolic pressure, and left ventricular end-systolic wall stress were not significantly different in t₁ and t₄.

Group II patients. In group II patients, basal coronary arteriograms were normal and left ventricular angiographic data were not different from those in group I patients for left ventricular mass (94 ± 16 g·m⁻²), end-diastolic wall thickness (7.3 ± 0.7 mm), end-diastolic volume (138 ± 24 ml·m⁻²), ejection fraction (32 ± 18%), end-systolic wall stress (370 ± 63 g·cm⁻²), and end-systolic stress/end-systolic volume ratio (2.49 ± 0.66 g·cm⁻²·ml⁻¹).

Serial data obtained in group II patients are presented in figure 3. Bilateral intracoronary infusion of saline, the vehicle for enalaprilat, resulted in no significant hemodynamic or hormonal change (t₁). At the end of the bilateral intracoronary infusion of enalaprilat, cardiac index was significantly reduced and arteriovenous oxygen difference was enlarged (t₂); other hemodynamic variables remained stable. These modifications were not affected by the removal of the right coronary catheter (t₃), but returned to basal values 10 min after discontinuation of the infusion of enalaprilat (t₄). Intracoronary enalaprilat resulted in no significant variation in plasma renin activity or plasma aldosterone.

Discussion

In the present study we sought to determine effects of the bilateral intracoronary infusion of enalaprilat in patients with dilated cardiomyopathy. This intracoronary infusion resulted in both significant coronary vaso-dilation and a myocardial negative inotropic effect that could not be explained by peripheral changes.

Previous studies of left ventricular performance after angiotensin converting-enzyme inhibition have consistently reported an improvement in the left ventricular ejection fraction or cardiac index in patients with heart failure. These results have been obtained after oral or intravenous administration of captopril or enalapril, with significant reductions in the mean aortic pressure and systemic resistances. Changes in indexes of left ventricular performance elicited by alterations in loading conditions are qualitatively similar to those that result from an improvement in inotropism. A reduction in afterload can by itself lead to an improvement in left ventricular variables of pump function, such as the ejection fraction and cardiac index. This
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TABLE 1
Mean ± SD hemodynamic data before (t2) and during the intracoronary infusion of enalaprilat (t3) in group I patients

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>HR (bpm) t2</th>
<th>LVSP (mm Hg) t2</th>
<th>LVEDP (mm Hg) t2</th>
<th>MAP (mm Hg) t2</th>
<th>RPP (mm Hg-bpm) t2</th>
<th>MRAP (mm Hg) t2</th>
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<tr>
<td>Mean</td>
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<td>118</td>
<td>20</td>
<td>94</td>
<td>10,974</td>
<td>5</td>
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SD ±16 ±15 ±20 ±20 ±8 ±7 ±16 ±16 ±2,630 ±2,486 ±5 ±4

p value NS <.05 NS <.05 NS NS

HR = heart rate; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; MAP = mean aortic pressure; RPP = rate-pressure product; MRAP = mean right atrial pressure; CI = cardiac index; SVR = systemic vascular resistances; A-VO2D = arteriovenous oxygen difference.

TABLE 2
Coronary hemodynamics and myocardial metabolism before (t2) and during the intracoronary infusion of enalaprilat (t3) in group I patients (mean ± SD)

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>CSBF (ml-min⁻¹) t2</th>
<th>CR (mm Hg·ml⁻¹·min⁻¹) t2</th>
<th>CSO2 (ml·100 ml⁻¹) t2</th>
<th>CSPO2 (kPa) t2</th>
<th>A-CSO2D (ml·100 ml⁻¹) t2</th>
<th>MVO2 (ml·min⁻¹) t2</th>
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<tbody>
<tr>
<td>1</td>
<td>108</td>
<td>0.69</td>
<td>5.7</td>
<td>3.00</td>
<td>10.8</td>
<td>11.66</td>
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<tr>
<td>2</td>
<td>192</td>
<td>0.44</td>
<td>7.0</td>
<td>2.10</td>
<td>13.0</td>
<td>24.96</td>
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<td>3</td>
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<td>0.40</td>
<td>7.0</td>
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<td>8.4</td>
<td>14.78</td>
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<tr>
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<td>190</td>
<td>0.25</td>
<td>7.0</td>
<td>3.10</td>
<td>13.9</td>
<td>26.41</td>
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<td>377</td>
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<td>7.0</td>
<td>2.95</td>
<td>8.3</td>
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<td>163</td>
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<td>19.40</td>
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<tr>
<td>7</td>
<td>177</td>
<td>0.66</td>
<td>5.2</td>
<td>2.30</td>
<td>12.3</td>
<td>21.77</td>
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<tr>
<td>8</td>
<td>109</td>
<td>0.61</td>
<td>4.8</td>
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</tr>
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</tr>
<tr>
<td>11</td>
<td>118</td>
<td>0.74</td>
<td>3.6</td>
<td>2.95</td>
<td>16.5</td>
<td>19.47</td>
</tr>
<tr>
<td>12</td>
<td>226</td>
<td>0.28</td>
<td>4.4</td>
<td>3.10</td>
<td>12.6</td>
<td>28.48</td>
</tr>
<tr>
<td>Mean</td>
<td>181</td>
<td>0.51</td>
<td>4.1</td>
<td>2.59</td>
<td>12.1</td>
<td>21.08</td>
</tr>
</tbody>
</table>

SD ±73 ±79 ±0.17 ±0.15 ±1.5 ±1.5 ±0.39 ±0.54 ±2.3 ±2.5 ±6.37 ±6.42

p value <.001 <.001 <.05 <.05 <.01 NS

CSBF = coronary sinus blood flow; CR = coronary resistance; CSO2 = coronary sinus blood oxygen content; CSPO2 = coronary sinus blood oxygen pressure; A-CSO2D = arterio-coronary sinus blood oxygen difference; MVO2 = myocardial oxygen consumption.
TABLE 1
(Continued)

<table>
<thead>
<tr>
<th>CI (1-min⁻¹-m⁻²)</th>
<th>SVR (mm Hg·min⁻¹·min)</th>
<th>A-VO₂D (ml·100 ml⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>t₁</td>
<td>t₂</td>
<td>t₃</td>
</tr>
</tbody>
</table>
| 3.05 | 3.23 | 16.2 | 13.4 | 4.4 | 3.2 | 1.69 | 2.09 | 2.03 | 3.10 | 1.60 | 3.10 | 1.92 | 1.59 | 30.9 | 32.8 | 7.6 | 8.0 | 2.52 | 2.18 | 18.1 | 17.8 | 6.8 | 7.5 | 3.48 | 2.94 | 18.3 | 20.0 | 3.3 | 3.9 | 1.89 | 1.77 | 20.5 | 23.1 | 5.4 | 6.0 | 2.25 | 2.39 | 29.2 | 25.8 | 5.4 | 5.4 | 2.95 | 2.71 | 16.0 | 16.7 | 4.0 | 4.5 | 3.59 | 3.16 | 22.6 | 26.2 | 5.5 | 6.5 | 2.26 | 3.01 | 19.7 | 21.6 | 5.7 | 7.6 | 2.59 | 2.36 | 20.6 | 22.0 | 5.5 | 6.0 |±0.61|±0.64|±5.6|±5.1|±1.4|±1.8|<.01|NS|<.05

TABLE 3
Left ventricular angiographic data before (t₁) and during the intra-coronary infusion of enalaprilat (t₄) in group I patients (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>t₁</th>
<th>t₄</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR (bpm)</td>
<td>87±14</td>
<td>92±16</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>EDV (ml·m⁻³)</td>
<td>154±41</td>
<td>150±41</td>
<td>NS</td>
</tr>
<tr>
<td>ESV (ml·m⁻³)</td>
<td>106±41</td>
<td>109±44</td>
<td>NS</td>
</tr>
<tr>
<td>SV (ml·m⁻³)</td>
<td>48±18</td>
<td>41±15</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>EF (%)</td>
<td>32±11</td>
<td>28±10</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>EDP (mm Hg)</td>
<td>19±7</td>
<td>17±7</td>
<td>NS</td>
</tr>
<tr>
<td>SP (mm Hg)</td>
<td>124±13</td>
<td>118±21</td>
<td>NS</td>
</tr>
<tr>
<td>ESS (g·cm⁻²)</td>
<td>394±57</td>
<td>374±65</td>
<td>NS</td>
</tr>
<tr>
<td>ESS/ESV (g·cm⁻²·ml⁻¹)</td>
<td>2.37±0.51</td>
<td>2.19±0.60</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

HR = heart rate; EDV = end-diastolic volume; ESV = end-systolic volume; SV = stroke volume; EF = ejection fraction; EDP = end-diastolic pressure; SP = systolic pressure; ESS = end-systolic stress; ESS/ESV = end-systolic stress/end-systolic volume ratio.

to an augmented cardiac index and ejection fraction. In addition, these unidirectional changes in favor of a depressant effect of enalaprilat on left ventricular function occurred without significant alteration of left ventricular preload, i.e., left ventricular end-diastolic pressure and volume. No significant variation in plasma renin activity or plasma aldosterone occurred after intracoronary enalaprilat in group II patients, providing an additional argument for the lack of systemic angiotensin converting enzyme inhibition in this study.

The modest decrease of left ventricular end-diastolic volume noted after intracoronary enalaprilat might have been produced by the resting position of the patients in the catheterisation laboratory. Although it cannot be ruled out, such an explanation is unlikely to account for our results, since cardiac index and heart rate of group II patients measured at the end of the protocol after a 45 min period in the supine position were identical to those measured initially.

The myocardial effects of this intracoronary infusion could have resulted in part from the vehicle used for enalaprilat, which was saline. However, this was probably not the case, since the intracoronary infusion of saline in group II patients resulted in no hemodynamic changes, whereas the intracoronary infusion of enalaprilat in the same patients produced significant variations in cardiac index and in arteriovenous oxygen difference. These findings are consistent with the high concentration of myocardial receptors to angiotensin II that has been demonstrated in various animal species,38-40 and with early experimental studies that indicate that blockade of the renin-angiotensin system can affect myocardial contractility.41 Thus, our data suggest that enalapril — when its intrinsic action on the myocardium is considered — exerts a negative effect on contractility. This effect is probably of modest magnitude, and most often cannot be observed on measurement of pump function indexes when the drug is administered orally or intravenously. In this situa-
The elevation of coronary blood flow obtained in this study after intracoronary enalaprilat could not be interpreted as an adaptative response to an enhanced myocardial metabolic demand, and must have resulted from an intrinsic coronary vasodilator effect. Since the negative inotropic effects of enalaprilat would be expected to lead to a reduction in coronary blood flow, the observed increase in this variable further supports a direct coronary vasodilative effect of this agent. Although angiotensin II is one of the most potent coronary vasoconstrictor agents, the majority of studies dedicated to the effects of angiotensin converting–enzyme inhibitors on the human coronary circulation have reported either no change, or a reduction in coronary sinus blood flow after teprotide or captopril, making the coronary vasoactive properties of converting–enzyme inhibition in man a matter of controversy.

In contrast to previous data obtained after oral or intravenous administration of angiotensin converting–enzyme inhibitors, the intracoronary infusion of enalaprilat given in our study resulted in a marked elevation in coronary sinus blood flow, paralleled by a similar reduction in coronary resistance. Difficulties in demonstrating the coronary vasodilator effects of captopril or teprotide can probably be explained by the simultaneous reductions in systemic resistances and myocardial oxygen consumption that are usually noted after oral or intravenous administration of these drugs. Since coronary blood flow is closely linked to the myocardial metabolic demand, a reduction in myocardial oxygen consumption will be followed by an appropriate decrease in coronary flow. No significant change in the major determinants of the myocardial metabolic demand were noted in this study: the end-systolic stress, rate-pressure product, and myocardial oxygen consumption remained stable throughout. The significant elevation of the oxygen content and pressure in the coronary sinus blood — together with a reduced coronary sinus oxygen extraction — further support a direct action of enalaprilat on the coronary vasculature. Another difference between this study and previous reports of angiotensin converting–enzyme inhibitors and coronary blood flow is that in a substantial proportion of patients who were studied after captopril, enalapril, or teprotide, heart failure was the result of coronary artery disease: the absence of an elevation in coronary blood flow in these patients with advanced ischemic cardiomyopathy could reflect a limited coronary reserve, with proximal atherosclerotic stenosis restraining an elevation of coronary blood flow. Our current assessment of the coronary vasodilator action

**FIGURE 3.** Hemodynamic data in group II patients (mean ± SD). HR = heart rate; CI = cardiac index; LVSP = left ventricular systolic pressure; LVEDP = left ventricular end-diastolic pressure; RAP = mean right atrial pressure; MAP = mean aortic pressure; SVR = systemic vascular resistances; AVO2D = arteriovenous oxygen difference; PRA = plasma renin activity; Ald = plasma aldosterone.

tion, the marked systemic actions of enalapril result in enhanced cardiac index or ejection fraction. The long-term clinical significance of enalapril's depressant effect on left ventricular contractility in patients with heart failure could not be assessed by our study. However, drugs currently reported to improve survival of patients with heart failure possess negative inotropic properties while agents with positive inotropic effects seem to have at best no, and sometimes a deleterious, effect on the long-term prognosis.
of enalaprilat in human heart failure is in agreement with early experimental observations by Cohen et al., who found that angiotensin injected directly into the coronary artery of anesthetized dogs increased coronary resistance, and with both initial and recent experimental reports demonstrating coronary vasodilation in dogs after blockade of the renin-angiotensin system by teprotide or enalapril.

In summary, specific effects of angiotensin converting–enzyme inhibitors on myocardial contractility and coronary circulation are masked when these drugs are administered orally or intravenously because of the reduction in ventricular loading. Indeed, useful information regarding the myocardial and coronary effects are provided when these drugs are administered by the intracoronary route. The present study demonstrates that a bilateral intracoronary infusion of enalaprilat results in both a negative inotropic effect on the left ventricle and selective vasodilation of the coronary arteries in patients with dilated cardiomyopathy.

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