Hemodynamic and clinical response to enalapril, a long-acting converting-enzyme inhibitor, in patients with congestive heart failure

T. Barry Levine, M.D., Maria Teresa Olivari, M.D., Victoria Garberg, R.N., Scott W. Sharkey, M.D., and Jay N. Cohn, M.D.

ABSTRACT  Enalapril, a new oral angiotensin converting–enzyme inhibitor, was administered to nine patients with severe congestive heart failure. Short-term hemodynamic response was noted within 2 hr and persisted for up to 24 hr. At peak effect mean arterial pressure fell from 83.4 ± 10(SD) to 72.1 ± 16.2 mm Hg (p < .01), right atrial pressure from 13.6 ± 6.0 to 10.4 ± 7.5 mm Hg (p < .01), pulmonary arterial pressure from 38.9 ± 4.8 to 31.9 ± 4.8 mm Hg (p < .01), pulmonary capillary wedge pressure from 28.2 ± 3.5 to 22.1 ± 5.1 mm Hg (p < .01), and total pulmonary resistance from 875 ± 304 to 697 ± 291 dynes-sec-cm⁻² (p < .05). Cardiac index was not changed, but there was a significant redistribution of regional blood flow with an increase of renal blood flow after enalapril. Plasma renin activity rose significantly from 6.2 to 28.6 ng/ml/hr, whereas plasma norepinephrine did not change after enalapril. Seven patients were treated with enalapril for 4 weeks. Five patients reported symptomatic improvement. Five of six patients tested had an increase in both exercise time (NS) and maximum oxygen consumption (NS). Repeat hemodynamic evaluation in six patients after long-term enalapril therapy showed a persistent effect with significant reductions in right atrial pressure from 13.8 ± 7.2 to 7.1 ± 4.7 mm Hg and in mean arterial pressure from 82.5 ± 10.4 to 76.6 ± 5.3 mm Hg and a significant increase in cardiac index from 2.1 ± 0.5 to 2.5 ± 0.5 l/min/m² (all p < .05). Long-term therapy was well tolerated, even by two patients who had developed toxic side effects to another converting–enzyme inhibitor, captopril. Enalapril is therefore a long-acting oral converting–enzyme inhibitor with an acute vasodilatory effect that appears to be well tolerated during long-term administration in patients with congestive heart failure.


THE CONVERTING-ENZYME INHIBITOR captopril has been demonstrated to improve left ventricular performance and relieve symptoms in patients with chronic congestive heart failure.1–3 Although the short-term hemodynamic response to captopril in these patients appears to be related to the degree of activity of the renin-angiotensin system as measured by plasma renin activity (PRA), long-term therapeutic benefits have been observed even in patients who do not have elevated PRA.4 These observations have raised a question as to whether all of the benefits of captopril therapy in patients with congestive heart failure can be attributed to its converting–enzyme inhibition.

A new converting–enzyme inhibitor of an entirely different structure has recently been introduced into clinical study. This drug, enalapril, appears to produce a prolonged inhibition of converting–enzyme activity and provides the opportunity to study the effect of converting–enzyme inhibition in patients with heart failure with the use of a different compound. In addition, some of the side effects that have been observed in response to captopril have been attributed to the chemical structure of the compound, which includes a sulfhydryl group. Since enalapril does not have such a structural component it is possible that this drug might be tolerated by patients who develop side effects to captopril. Furthermore, study of the onset and duration of action of enalapril is important in developing a dosing regimen for this converting–enzyme inhibitor.

In this study we have examined the short- and long-term responses to enalapril in a group of patients with chronic congestive heart failure. The results suggest that enalapril has a slower onset and longer duration of action than captopril, although the hemodynamic re-
sponses to the drugs are similar. The drug appears to be well tolerated by patients who have developed side effects during captopril therapy.

Methods

Nine patients with chronic congestive heart failure were studied (Table 1). The six men and three women ranged in age from 31 to 67 years. The cause of the heart failure was ischemia in five patients and primary congestive cardiomyopathy in four. All patients had been symptomatic for at least 3 months before study. By New York Heart Association classification, four patients were functional class III and five patients were functional class IV. No patient was studied within 3 months of a myocardial infarction, nor was angina a significant complaint of any patient. All patients were screened to ensure that congestive heart failure was their only major medical problem. At the time of study, treatment with digitalis and diuretics was maintained on a stabilized dosage regimen. The study protocol had been approved by the University of Minnesota Committee on the Use of Human Subjects in Research and informed consent was obtained from each patient before they entered the study.

Patients were hospitalized for a stabilization period of at least 3 days, during which time all previous vasodilator therapy was stopped. A baseline exercise tolerance test in which a bicycle ergometer with progressive 25 W workloads was used was performed by each patient. In addition to total exercise time, peak O₂ consumption (VO₂) was calculated by monitoring expired air volume and O₂ concentration with a Beckman O₂ analyzer. To ensure that each patient achieved close to his or her aerobic capacity, expired CO₂ concentration was also recorded so that the respiratory quotient could be monitored on-line during exercise. An increase in respiratory quotient of greater than 0.1 was taken as evidence that anaerobic threshold had been achieved. Patients were studied in a fasting state and digitalis and diuretics were withheld for at least 18 hr before testing. Right heart catheterization was performed percutaneously by inserting via a median basilic vein a No. 7F thermocoupled, flow-directed catheter. An arterial cannula was inserted into the brachial artery. The electrocardiographic and pressure measurements were continuously monitored throughout the study.

After a 1 hr rest period with the catheters in place, control measurements were obtained. The hemodynamic measurements were done in duplicate within ½ hr and did not vary by more than 10%. Heart rate, right atrial pressure (RA), pulmonary arterial pressure (PA), pulmonary capillary wedge pressure (PCW), and arterial pressure (AP) were recorded. Cardiac output (CO) by thermodilution was determined in triplicate with an Edwards 9150 thermodilution computer. PRA (by radioimmunoassay; RENAK Kits, Roche Laboratories) and plasma norepinephrine (PNE; by radioenzymatic assay; CAT-A-KIT, Upjohn Company) were also measured. Control measurements of regional blood flow were also taken at this time. Forearm blood flow was measured by double-cuff venous occlusion plethysmography with a mercury-in-silicone rubber strain gauge. Hepatic blood flow was estimated by the rate of indocyanine green dye disappearance. After administering a 25 mg bolus of dye, central venous blood sampling was performed at 3 min intervals for 15 min. Renal blood flow was estimated by the rate of para-aminohippuric acid (PAH) clearance after 3 ml of a standard 20% PAH solution was injected followed by central venous blood sampling at 10, 15, 20, 25, and 30 min. The estimation of regional organ flow is expressed as K, a value derived from the ratio of a constant (the natural log ½) and the half-life of the indicator substance. K is directly proportional to flow if it is assumed that neither the plasma volume nor cellular extraction of the indicator substance is altered by the administration of enalapril.

After control measurements were obtained, a single dose of enalapril (5, 10, or 20 mg) was given orally and the short-term hemodynamic response was monitored for the next 24 hr. At peak hemodynamic effect PRA, PNE, and regional blood flow measurements were repeated. Mean intravascular pressures were obtained by electronic integration. Systemic vascular resistance (SVR) and total pul-

TABLE 1

Summary of clinical data from nine patients with congestive heart failure

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>BSA (m²)</th>
<th>Diagnosis</th>
<th>NYHA class</th>
<th>Previous therapy</th>
<th>PRA (ng/ml/hr)</th>
<th>PNE (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>F</td>
<td>1.68</td>
<td>IHD</td>
<td>IV</td>
<td>Digitalis, furosemide, spironolactone, prazosin</td>
<td>9.1</td>
<td>1839</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>M</td>
<td>1.98</td>
<td>IHD</td>
<td>III</td>
<td>Digitalis, furosemide</td>
<td>3.2</td>
<td>236</td>
</tr>
<tr>
<td>3</td>
<td>52</td>
<td>M</td>
<td>1.80</td>
<td>IHD</td>
<td>IV</td>
<td>Digitalis, furosemide, spironolactone, prazosin</td>
<td>5.7</td>
<td>813</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>M</td>
<td>1.74</td>
<td>CM</td>
<td>IV</td>
<td>Digitalis, furosemide, minoxidil, ISDN, captopril</td>
<td>9.6</td>
<td>553</td>
</tr>
<tr>
<td>5</td>
<td>43</td>
<td>M</td>
<td>1.96</td>
<td>CM</td>
<td>IV</td>
<td>Digitalis, furosemide, spironolactone, metolazone, prazosin</td>
<td>6.2</td>
<td>1352</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>M</td>
<td>1.98</td>
<td>CM</td>
<td>IV</td>
<td>Digitalis, furosemide, captopril</td>
<td>7.4</td>
<td>818</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>F</td>
<td>1.60</td>
<td>IHD</td>
<td>III</td>
<td>Digitalis, furosemide, HCTZ, spironolactone, ISDN</td>
<td>10.0</td>
<td>731</td>
</tr>
<tr>
<td>8</td>
<td>52</td>
<td>M</td>
<td>2.02</td>
<td>CM</td>
<td>III</td>
<td>Digitalis, furosemide, ISDN, prazosin</td>
<td>2.0</td>
<td>239</td>
</tr>
<tr>
<td>9</td>
<td>67</td>
<td>F</td>
<td>1.56</td>
<td>IHD</td>
<td>III</td>
<td>Digitalis, furosemide hydralazine, ISDN</td>
<td>4.3</td>
<td>177</td>
</tr>
</tbody>
</table>

BSA = body surface area; IHD = ischemic heart disease; CM = cardiomyopathy; ISDN = isosorbide dinitrate.
monary resistance (TPR) were expressed as dynes-sec-cm\(^{-5}\). These were calculated as:

\[
SVR = \frac{\text{MAP-RA}}{\text{CO}} \times 80
\]

\[
TPR = \frac{\text{PA}}{\text{CO}} \times 80
\]

Seven of the patients studied over the short term were treated with enalapril for 4 weeks at a daily dose ranging from 5 to 20 mg. Digitalis and diuretic therapies were maintained at constant dosages during this period. After 4 weeks of therapy, exercise testing was repeated and six of the patients underwent a second hemodynamic study 24 hr after the last dose of enalapril.

Analysis of variance for repeated measurements was used to analyze the short-term hemodynamic response to enalapril over time. Student’s paired \(t\) test was used to compare control with peak response to the drug for changes in PRA, PNE, hepatic blood flow, forearm blood flow, and renal blood flow. Likewise, short- and long-term responses were compared by use of Student’s paired \(t\) test.

### TABLE 2
Short-term hemodynamic response to enalapril in nine patients with congestive heart failure

| Patient No. | Control | D\(_6\) | D\(_{24}\) | Control | D\(_6\) | D\(_{24}\) | Control | D\(_6\) | D\(_{24}\) | Control | D\(_6\) | D\(_{24}\) | Control | D\(_6\) | D\(_{24}\) | Control | D\(_6\) | D\(_{24}\) | Control | D\(_6\) | D\(_{24}\) |
|-------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| HR (beats/min) | 123 | 126 | 126 | 54 | 59 | 60 | 96 | 102 | 87 | 105 | 75 | 103 | 78 | 75 | 70 | 87 | 80 | 75 | 75 | 87 |
| RA (mm Hg) | 17 | 17 | 14 | 11 | 10 | 6 | 10 | 8 | 5 | 22 | 21 | 28 | 20 | 22 | 17 | 43 | 41 | 35 | 36 | 40 |
| PA (mm Hg) | 37 | 33 | 36 | 35 | 32 | 35 | 45 | 37 | 31 | 30 | 27 | 22 | 28 | 29 | 26 | 43 | 41 | 35 | 36 | 40 |
| PCW (mm Hg) | 28 | 27 | 30 | 24 | 23 | 22 | 32 | 26 | 25 | 20 | 24 | 17 | 20 | 29 | 26 | 17 | 32 | 30 | 24 | 31 |
| MAP (mm Hg) | 80 | 75 | 80 | 78 | 75 | 78 | 80 | 65 | 63 | 60 | 60 | 95 | 60 | 103 | 98 | 85 | 90 | 85 | 80 | 90 |
| CI (l/min/m\(^2\)) | 1.6 | 2.0 | 1.6 | 1.9 | 2.1 | 1.4 | 1.9 | 2.4 | 2.2 | 2.0 | 3.0 | 3.3 | 1.9 | 3.5 | 3.4 | 1.7 | 1.6 | 1.7 | 3.1 | 3.4 |
| SVR (dynes-sec-cm\(^{-5}\)) | 1916 | 1365 | 1941 | 1437 | 1232 | 1894 | 1709 | 1076 | 1197 | 810 | 625 | 1159 | 823 | 1084 | 1110 | 1900 | 2156 | 1784 | 1557 |
| TPR (dynes-sec-cm\(^{-5}\)) | 1122 | 777 | 1058 | 751 | 607 | 976 | 1099 | 698 | 640 | 561 | 446 | 681 | 607 | 477 | 436 | 1198 | 1343 | 1140 | 416 | 959 |

Results

**Control measurements.** All patients had severe resting left ventricular dysfunction (table 2). RA and PCW were considerably elevated (mean 13.6 and 28.2 mm Hg, respectively) and cardiac index (CI) was reduced (mean 2.2 l/min/m\(^2\)). PRA averaged 6.2 ng/ml/hr and PNE averaged 716 pg/ml (normal 175 ± 30 pg/ml) (table 1).

**Short-term response to enalapril.** Enalapril appeared to have an onset of action within 2 hr after oral administration (figure 1) and persistent hemodynamic effects were seen 24 hr later (table 2). Mean AP (MAP), 83.4 ± 10.0 mm Hg at control, fell to 77.3 ± 13.1 mm Hg at 6 hr and 72.1 ± 16.2 mm Hg at 24 hr (p < .01). PCW also fell from 28.2 ± 3.5 mm Hg at control to 24.6 ± 4.2 mm Hg at 6 hr and to 22.1 ± 5.1 mm Hg at 24 hr (p < .01). Significant reductions in RA from

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D\(_6\) = 6 hr after enalapril; D\(_{24}\) = 24 hr after enalapril; HR = heart rate.
Long-term response. Seven patients were treated for 4 weeks with 5 to 20 mg enalapril given either once a day or in two equal doses daily. The dose was determined by the short-term response. Digitalis and diuretics were maintained at a constant dose and no other vasodilators were given.

Five of the patients were symptomatically improved while taking enalapril. This improvement took the form of having more energy to do things and being less tired at the end of a day. One patient stopped taking an afternoon nap that had been necessary before enalapril therapy. Three patients noted an improved sense of well-being on enalapril therapy. The drug was well tolerated with no side effects noted during long-term administration. Although exercise time and VO₂ increased in five of six patients tested (figure 4), neither achieved statistical significance. Repeat hemodynamic evaluation (24 hr after the last dose of drug) after 1 month of enalapril therapy carried out in six of these patients showed significant reductions in RA and MAP and a significant increase in CI over initial measurements before enalapril therapy (table 3).

Discussion

The short-term hemodynamic effects of enalapril were consistent with both arterial and venous dilation since there was a fall in MAP as well as in RA. Although this vasodilator activity is similar to that noted after captopril, the time course of effect was consider-
ably different. After enalapril, the onset of action was gradual and peak effect was often not seen until 24 hr after drug administration. In similar patients with severe heart failure, the onset of action of captopril was within 30 min and peak effect was 1 to 2 hr after drug. There was also more temporal dispersion in hemodynamic effect after enalapril. Arterial vasodilatation appeared to occur earlier than the venous effect. MAP was significantly reduced at 2 hr while RA was not significantly lower until 24 hr after drug administration (figure 1). CI did not change significantly after enalapril administration. The modest increase in CI seen here parallels the observations made of the short-term response to captopril. Finally, SVR did not change after enalapril. Again, this was due to marked interpatient variability. If maximum change in SVR had been used, irrespective of the time after drug, the fall in SVR would have been significant.

The neurohumoral response to enalapril is similar to the response to captopril. Enalapril, by inhibiting the converting enzyme, blocks the conversion of angiotensin I to angiotensin II. Lowered circulating angiotensin II levels reduce negative feedback suppression and account for a doubling of PRA. PNE tended to fall after enalapril, and a similar reduction is noted after captopril.

The major difference between enalapril and captopril appeared to be in the onset and duration of effect. Enalapril, as opposed to captopril, is absorbed in an inactive form and must be deesterified by the liver to its active metabolite. The marked variability noted in short-term response to enalapril could therefore in part reflect individual differences in hepatic blood flow or hepatocellular function. It has previously been reported that the short-term hemodynamic response to captopril correlated directly with the activation of the renin angiotensin system as measured by PRA. The absence of such a correlation in the present series may relate to the fact that none of these patients had PRA > 15 ng/ml/hr. Consequently, these patients might have been expected to have a less dramatic short-term response to a converting-enzyme inhibitor than patients with an activated renin-angiotensin system. After captopril the telescoped hemodynamic response does not allow dissection of any possible temporal difference between arterial and venous effects. After enalapril, however, MAP appeared to fall before RA, suggesting that the arteriolar vasodilation may be directly related to the reduction in angiotensin II, whereas venodilatation may be mediated through a secondary mechanism such as a reduction in sympathetic tone or increase in

---

**TABLE 3**

Hemodynamic response to long-term enalapril therapy in six patients with heart failure

<table>
<thead>
<tr>
<th></th>
<th>HR (beats/min)</th>
<th>RA (mm Hg)</th>
<th>PA (mm Hg)</th>
<th>PCW (mm Hg)</th>
<th>MAP (mm Hg)</th>
<th>CI (l/min/m²)</th>
<th>SVR (dynes-sec-cm⁻¹)</th>
<th>PVR (dynes-sec-cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>83.8 ± 16.3</td>
<td>13.8 ± 7.2</td>
<td>38.2 ± 5.6</td>
<td>28.0 ± 4.3</td>
<td>82.5 ± 10.4</td>
<td>2.1 ± 0.5</td>
<td>1543 ± 380</td>
<td>883 ± 316</td>
</tr>
<tr>
<td>Long-term therapy</td>
<td>78.4 ± 19.8</td>
<td>7.1 ± 4.7</td>
<td>34.5 ± 5.7</td>
<td>22.3 ± 1.6</td>
<td>76.6 ± 5.3</td>
<td>2.5 ± 0.5</td>
<td>1321 ± 332</td>
<td>670 ± 200</td>
</tr>
<tr>
<td>p value</td>
<td>NS</td>
<td>.05</td>
<td>NS</td>
<td>NS</td>
<td>.05</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

HR = heart rate.
vasodilator substances such as prostaglandins\textsuperscript{14, 15} or bradykinins.\textsuperscript{16}

Although CO did not increase significantly after the first dose of enalapril, a regional redistribution of blood flow was observed. The renal bed, which is extremely sensitive to the vasoconstrictive effect of angiotensin II, was preferentially dilated by enalapril, whereas the forearm vascular bed exhibited a slight but insignificant increase in flow. Flow in the hepatic bed, which is relatively insensitive to angiotensin II, was unchanged. This flow redistribution might be expected to maintain renal function and increase exercise capacity if this short-term response persists during long-term therapy.

Patients responded well to long-term enalapril therapy. The drug was given on a daily or twice-daily dosing schedule. Five of the seven patients reported symptomatic improvement (two were unchanged). In five of six patients tested, exercise time and VO\textsubscript{2} were increased (figure 4). Neither exercise time nor VO\textsubscript{2} were significantly increased for the group as a whole. Clinical improvement with long-term therapy did not correlate with short-term hemodynamic response to enalapril. Six patients underwent a repeat hemodynamic evaluation after 1 month on enalapril therapy (table 3) and persistent hemodynamic improvement was seen in the reduction in MAP and RA from control. Furthermore, although CI did not increase after initiation of drug therapy, it was significantly higher after long-term therapy. No side effects of the medication were noted. It is of interest that two of the patients (Nos. 4 and 6) had previously been treated with captopril, which had to be discontinued due to severe skin rash, and that both patients tolerated enalapril without recurrence of the rash. In this small group of patients it is not possible to determine whether enalapril is less toxic than captopril, but the data suggest that there is a different susceptibility to toxic side effects. Patients intolerant to captopril may tolerate enalapril.

Enalapril may thus serve as a useful alternative to captopril when vasodilator therapy with a converting enzyme inhibitor is indicated. Its long duration of action may be an advantage for long-term therapy, but the delayed and variable onset of effect may increase the complexity of monitoring the short-term response to the first dose of the drug before initiating long-term therapy. No severe hypotensive responses were observed in this series, but if there is greater activation of the renin-angiotensin system it may be necessary to monitor patients for 24 hr to determine the appropriate dose and frequency of administration of enalapril for heart failure.

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References

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