Captopril in Primary Pulmonary Hypertension

CARL V. LEIER, M.D., DENNIS BAMBA CH, M.D., STEVE NELSON, M.D.,
JAMES B. HER MILLER, M.D., PATRICIA HUSS, R.N., RAYMOND D. MAGORIEN, M.D.,
AND DONALD V. UNVERF ERTH, M.D.

SUMMARY Seven women with primary pulmonary hypertension underwent hemodynamic evaluation, at rest and during exercise, before and after the oral administration of captopril. Dose-response curves were generated for the 25-, 50- and 100-mg doses. Captopril significantly reduced systemic blood pressure and systemic vascular resistance; these effects persisted at submaximal levels of exercise. Captopril did not alter pulmonary artery pressure or resistance, cardiac output or stroke volume at rest or during exercise. Exercise tolerance did not improve. Four of the patients also received captopril chronically for 12 weeks at doses of 75 and 100 mg every 8 hours. Resting and exercise hemodynamic evaluation was repeated at the end of the 12-week period. Except for a persistent reduction in mean systemic blood pressure at rest, chronic captopril administration did not elicit hemodynamic changes. Measured exercise duration did not change during continuous captopril treatment, although one patient reported mild subjective improvement in activity tolerance.

In primary pulmonary hypertension, captopril exerts its major effect on systemic vasculature, with little or no effect on the pulmonary circuit. While an occasional patient may experience some clinical improvement with captopril therapy, the majority of adult patients with severe primary pulmonary hypertension will not benefit from its chronic administration.

THE CURRENT treatment regimens of primary pulmonary hypertension are generally inadequate. Numerous reports have shown favorable clinical and hemodynamic responses in an individual or a small group of patients to phenolamine, isoproterenol, diazoxide or hydralazine. However, no one vasodilator is of major benefit in the majority of patients.

Captopril is a relatively new drug whose effects are mediated primarily through the inhibition of angiotensin I-angiotensin II-converting enzyme. This drug decreases systemic blood pressure in patients with systemic hypertension and reduces systemic and pulmonary vascular resistances in patients with cardiogenic heart failure. Although the mechanisms of primary pulmonary hypertension are not known, most of the body's converting enzyme is in the lungs.

This study was performed to determine if captopril can elicit favorable hemodynamic effects, particularly in the pulmonary vasculature, in patients with primary pulmonary hypertension and to investigate (albeit indirectly) the role of angiotensin and converting enzyme in this disease.

Methods

Patients

Seven adult female patients, mean age 40 years (range 24–54 years), with primary pulmonary hypertension were studied. The mean duration of symptoms was 37 months. At the time of entry into the study, patients 1, 4, 5, 6 and 7 were limited by dyspnea or fatigue with mild exertion, patient 3 by dyspnea on mild exertion and moderate peripheral edema, and patient 2 by fatigue and angina with mild exertion. Patients 1, 2 and 4 had one or more syncopal or near-syncopeal episodes in the year before the study. None of the patients had a history of taking birth control pills or any other hormonal preparation. All patients had evidence of elevated pulmonary artery and right heart pressures and right ventricular hypertrophy on physical examination. Features of right atrial and ventricular enlargement were present on the ECG and the chest roentgenograms of each patient. Cardiac catheterization, selective pulmonary angiography and left ventricular and coronary cineangiography were performed within 2 months of this study. Patients with secondary forms of pulmonary hypertension or an additional cardiac abnormality were excluded from study. The hemodynamic data obtained during diagnostic catheterization were comparable to those presented in this report. Patients 1, 4, 6 and 7 were receiving oral diuretics (0.125–0.25 mg/day) and patients 3, 6 and 7 were taking furosemide (20–40 mg/day). These drugs and doses were continued throughout the study period, with p.m. dosing to avoid the potential hemodynamic effects of peak absorption.

Procedures and Measurements

Each patient gave written, informed consent before the study. The patients underwent bicycle ergometry 1 day before study to familiarize them with this technique. A flow-directed, triple-lumen catheter was introduced percutaneously into the left subclavian vein and positioned in the pulmonary artery. This catheter, interphased with an Electronics for Medicine M 2101 pressure amplification and recording system, provided measurements of pulmonary artery, pulmonary capillary wedge (pulmonary arterial occlusive) and right atrial pressures. Cardiac output was determined in triplicate by thermodilution using an Instrumentation Laboratories 601 computer and 602 recorder. Systemic blood pressure was measured by cuff and a mercury
column sphygmomanometer. A Quinton model 845 bicycle ergometer was used for exercise testing.

Cardiac index, stroke volume index, pulmonary vascular resistance, systemic vascular resistance, and mean systemic blood pressure were calculated by standard formulas.

### Protocol

The hemodynamic response to oxygen and isoproterenol was assessed on day 1. After a 2-hour equilibration period, after the pulmonary artery catheter insertion, baseline hemodynamic measurements were made in duplicate (20-minute interval) and averaged. Oxygen was then administered by mask at $\geq 90\%$ inhalation concentration. Hemodynamic measurements were made after 30 minutes of oxygen. After these measurements, oxygen was discontinued and the patient was allowed to re-equilibrate over the next 2 hours. Baseline hemodynamic studies were repeated. Isoproterenol, 0.25 mg/kg, was administered sublingually, followed by hemodynamic measurements at 15, 30 and 60 minutes. Peak effects occurred at 30 minutes; the 30-minute values are presented in figure 1 to show the hemodynamic responsiveness to isoproterenol.

All studies involving captopril were performed in the postabsorptive state between 0700 and 1400 hours. Baseline resting hemodynamic measurements were made in duplicate (20–30-minute interval) and averaged. After baseline measurements, captopril was administered: 25 mg orally on day 2, 50 mg on day 3 and 100 mg on day 4. Resting hemodynamic measurements were made 30, 60, 90, 120, 180, 240, 300 and 360 minutes after each dose.

Exercise studies were performed on day 5. Upright (sitting) hemodynamic measurements were made at rest, at 180-second intervals during exercise and at maximal exercise. Exercise was started at a work load of 50 kg-m/min advanced to 100 kg-m/min at 180 seconds, and subsequently increased by 100-kg-m/min increments at 180-second intervals. Maximal exercise duration was taken as the time the exercise was discontinued because of severe dyspnea or fatigue. The ergometry study was performed before captopril and 1½–2 hours afterwards. The captopril dose selected for evaluation during exercise was the dose that elicited the maximal responses in hemodynamic measurements made at rest (days 2, 3, and 4) with the fewest undesirable effects (hypotension, near-syncope, chest pain, nausea and vomiting). This dose was 100 mg in four patients, 75 mg in one patient and 25 mg in one. One patient performed less than 60 seconds of exercise and was excluded from the exercise phase of study.

Patients 1, 3, 5 and 6 agreed to participate in the chronic administration phase of study. They continued taking captopril for 3 months: three patients took 100 mg and one patient 75 mg every 8 hours. The patients were rehospitalized at the end of the 3-month period. Dosing was not interrupted. Resting and exercise hemodynamic measurements were made before and 1½–2 hours after the 0800 dose of captopril.

### Statistical Analysis

Statistical analysis included repeated measures and one-way and two-way analyses of variance with appropriate aftertests. The $t$ test for paired data was used to analyze the effects of oxygen and isoproterenol. Values are mean ± sd.

### Results

The study population had severe pulmonary hypertension, with average systolic, diastolic and mean pulmonary arterial pressures of $97 \pm 15, 47 \pm 13$ and $63 \pm 12$ mm Hg, respectively, and a mean pulmonary vascular resistance of $1750 \pm 650$ dyn-sec-cm$^{-5}$. The mean pulmonary arterial pressure/mean systemic blood pressure and the pulmonary vascular resistance/systemic vascular resistance ratios averaged 0.61. The mean cardiac index was low, $1.95 \pm 0.75$, with a depressed mean stroke volume index of $24 \pm 12$ ml/beats/min$^2$. Individual patient data are presented in table 1. Hemodynamic values did not change with oxygen inhalation (fig. 1). Isoproterenol did effect a 20% reduction in pulmonary vascular resistance, a

### Table 1: Individual Hemodynamic Responses to Captopril in Doses of 25, 50 and 100 mg

<table>
<thead>
<tr>
<th>Pt</th>
<th>Pulmonary arterial pressure (mm Hg)</th>
<th>Pulmonary vascular resistance (dyn-sec-cm$^{-5}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cont 25 mg Cont 50 mg Cont 100 mg</td>
<td>Cont 25 mg Cont 50 mg Cont 100 mg</td>
</tr>
<tr>
<td>1</td>
<td>70 67 65 74 67</td>
<td>2960 2545 2870 3030 3442 2874</td>
</tr>
<tr>
<td>2</td>
<td>89 91 88 87 -- --</td>
<td>1420 1315 1730 1450 -- --</td>
</tr>
<tr>
<td>3</td>
<td>59 61 48 54 58</td>
<td>1900 1905 1600 1615 1708 2165</td>
</tr>
<tr>
<td>4</td>
<td>56 57 -- -- --</td>
<td>2050 2355 -- -- --</td>
</tr>
<tr>
<td>5</td>
<td>55 53 53 50 53 52</td>
<td>1230 1150 1210 1120 970 915</td>
</tr>
<tr>
<td>6</td>
<td>55 59 52 51 50 51</td>
<td>980 870 870 810 877 832</td>
</tr>
<tr>
<td>7</td>
<td>55 56 61 60 57 60</td>
<td>1593 1793 1960 1879 1854 2083</td>
</tr>
<tr>
<td>Mean</td>
<td>63 63 61 61 58 58</td>
<td>1733 1705 1707 1650 1770 1774</td>
</tr>
<tr>
<td>± sd</td>
<td>±13 ±13 ±15 ±14 ±10 ±6</td>
<td>±655 ±624 ±689 ±773 ±1030 ±878</td>
</tr>
</tbody>
</table>

The subjects were supine and at rest. The 1- and 2-hour postcaptopril data were averaged.

*p < 0.05 vs control.
TABLE 1. (Continued)

<table>
<thead>
<tr>
<th>Pulmonary vascular resistance/systemic vascular resistance (pulmonary arterial pressure/systemic blood pressure)</th>
<th>Cont 25 mg</th>
<th>Cont 50 mg</th>
<th>Cont 100 mg</th>
<th>Cont 25 mg</th>
<th>Cont 50 mg</th>
<th>Cont 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.64</td>
<td>0.68</td>
<td>0.64</td>
<td>0.68</td>
<td>0.60</td>
<td>0.60</td>
<td>0.60</td>
</tr>
<tr>
<td>0.86</td>
<td>0.86</td>
<td>0.86</td>
<td>0.86</td>
<td>0.86</td>
<td>0.86</td>
<td>0.86</td>
</tr>
<tr>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
<td>0.56</td>
</tr>
<tr>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
<td>0.64</td>
</tr>
<tr>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
<td>0.51</td>
</tr>
<tr>
<td>0.48</td>
<td>0.48</td>
<td>0.48</td>
<td>0.48</td>
<td>0.48</td>
<td>0.48</td>
<td>0.48</td>
</tr>
<tr>
<td>0.66</td>
<td>0.66</td>
<td>0.66</td>
<td>0.66</td>
<td>0.66</td>
<td>0.66</td>
<td>0.66</td>
</tr>
<tr>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
<td>0.62</td>
</tr>
<tr>
<td>±0.13</td>
<td>±0.13</td>
<td>±0.13</td>
<td>±0.13</td>
<td>±0.13</td>
<td>±0.13</td>
<td>±0.13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac index (l/min/m²)</th>
<th>Cont 25 mg</th>
<th>Cont 50 mg</th>
<th>Cont 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.20</td>
<td>1.35</td>
<td>1.10</td>
<td>1.10</td>
</tr>
<tr>
<td>3.69</td>
<td>4.04</td>
<td>3.00</td>
<td>3.55</td>
</tr>
<tr>
<td>1.58</td>
<td>1.60</td>
<td>1.52</td>
<td>1.51</td>
</tr>
<tr>
<td>1.58</td>
<td>1.41</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>1.98</td>
<td>2.01</td>
<td>1.94</td>
<td>2.10</td>
</tr>
<tr>
<td>2.29</td>
<td>2.66</td>
<td>2.39</td>
<td>2.56</td>
</tr>
<tr>
<td>1.50</td>
<td>1.53</td>
<td>2.46</td>
<td>2.29</td>
</tr>
<tr>
<td>2.00</td>
<td>2.08</td>
<td>1.92</td>
<td>2.06</td>
</tr>
<tr>
<td>±0.82</td>
<td>±0.98</td>
<td>±0.68</td>
<td>±0.89</td>
</tr>
</tbody>
</table>

25% reduction in systemic vascular resistance, and a 23% increase in cardiac index (all p < 0.05) (fig. 1). The increase in cardiac index was secondary to an elevation in heart rate. Stroke volume and pulmonary arterial and systemic blood pressures were not altered significantly by isoproterenol. Individual responses to isoproterenol were not predictive of subsequent individual responses to captopril.

Initial Administration

Captopril in oral doses of 25, 50 and 100 mg did not alter mean pulmonary arterial pressure or mean pulmonary vascular resistance over 6 hours after administration (table 1). Individual pulmonary hemodynamic responses to captopril varied, but the responses were not particularly striking for any patient (table 1). At these doses, captopril decreased systemic blood pressure and systemic vascular resistance significantly. The responses of systemic blood pressure and systemic vascular resistance to the three doses did not differ significantly from each other. The pulmonary vascular resistance/systemic vascular resistance and the pulmonary arterial pressure/systemic blood pressure ratios increased significantly after captopril (table 1) second-
TABLE 1. (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Cont 25 mg</th>
<th>Cont 50 mg</th>
<th>Cont 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke volume index (ml/beats/m2)</td>
<td>13.9</td>
<td>15.9</td>
<td>14.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>87</td>
<td>85</td>
<td>80</td>
</tr>
</tbody>
</table>

Dary to unaltered pulmonary parameters and consistent reductions of systemic vascular resistance and systemic blood pressure after captopril. Cardiac index and stroke volume index were not affected by the initial doses of captopril. Heart rate demonstrated a tendency to increase modestly.

Patient 4 developed symptomatic systemic hypotension with the 25-mg dose and was eliminated from the 50- and 100-mg dose studies. Patient 2 developed angina and gastrointestinal distress after the 50-mg dose, and was eliminated from the 100-mg dose study.

Exercise tolerance (mean exercise duration) did not improve after initial dose of captopril (fig. 2). The reduction in systemic blood pressure after captopril persisted at 3 minutes of exercise. At maximal exercise, only the systemic systolic pressure remained low.

![Figure 2](http://circ.ahajournals.org/) Baseline control and postcaptopril hemodynamic responses to exercise (bicycle ergometry). Upright measurements were made at rest, after 3 minutes of exercise and at maximal exercise (Max). Captopril decreased systemic blood pressure at rest and during submaximal exercise. No other hemodynamic effects were noted for captopril compared with control, and captopril did not acutely increase mean exercise duration.
er than that at control. The remaining hemodynamic measurements during exercise did not differ between control and initial-dose captopril.

**Chronic Administration**

Individual and group-mean resting and exercise hemodynamic data, obtained at baseline control, after initial-dose captopril and after 3 months of chronic dosage in the four patients (nos. 1, 3, 5 and 6) studied, are presented in figures 3 and 4. No changes occurred in the mean resting or exercise (3-minute and maximal) values of mean pulmonary arterial pressure, pulmonary vascular resistance, systemic vascular resistance, cardiac index, stroke volume index or heart rate after 3 months of captopril therapy. Resting mean systemic blood pressure remained decreased below control with chronic dosing. After 3 minutes of exercise, three patients demonstrated a decrease in mean systemic blood pressure (compared with baseline 3-minute exercise values) after initial-dose captopril, and this reduction was maintained after chronic administration, although it was of lesser magnitude in two. Mean systemic blood pressure during exercise increased after initial and chronic captopril dosing. Exercise tolerance (duration) did not change for the group (or any individual) after acute or chronic captopril administration compared to baseline control.

During chronic administration, patient 3 (represented by the closed circle in figures 3 and 4) noted mild improvement of symptoms and activity tolerance. She was the only patient to demonstrate a noteworthy reduction in mean pulmonary arterial pressure (resting and exercise) with acute or chronic captopril therapy; her resting and exercise pulmonary vascular resistance dropped modestly with acute captopril dosing; however, this variable returned to the baseline control value during chronic therapy. She was continued on captopril beyond the 3-month protocol, with questionable persistent clinical improvement. The remaining three patients did not have any change in symptoms or activity tolerance. Patients 3, 5 and 6 developed hoarseness and episodic nonproductive coughing during chronic captopril therapy; these symptoms abated when captopril was discontinued.

**Discussion**

Captopril elicited little or no change in resting or exercise pulmonary arterial pressure or resistance in this group of adult patients with severe pulmonary
hypertension. Chronic administration did not improve pulmonary vascular hemodynamics over that of initial dosing. The systemic arterial vasculature in these patients responded to captopril; the response was manifested as a drop in systemic blood pressure and systemic resistance, at rest and during exercise, for both initial dosing and chronic administration. The reduction in systemic pressure and resistance was not accompanied by a significant increase in stroke volume or cardiac output. Apparently, afterload reduction did little to augment the function of the normal left ventricle, and because afterload reduction did not occur in the right heart–pulmonary vasculature, right ventricular systolic function was not improved. Mean heart rate increased modestly, probably secondary to the reduction in systemic blood pressure.

Several factors may explain why captopril has little or no effect on the pulmonary vasculature in patients with primary pulmonary hypertension. The degree of pulmonary hypertension in this population was moderately severe to severe. Although these patients showed some responsiveness to isoproterenol, the disease may have progressed to a state (irreversible vascular lesions) refractory to captopril. This study does not exclude the possibility that captopril may be effective in milder stages of primary pulmonary hypertension. However, most patients with primary pulmonary hypertension present in an advanced stage of this disease; so the notion that captopril may be effective only in milder forms is useful only if these patients can be diagnosed before entering into an advanced and irreversible form of pulmonary hypertension. Of the four patients who entered the chronic administration phase of study, two had severe pulmonary hypertension (mean pulmonary arterial pressure $\geq 70$ mm Hg) and two had a milder form (mean pressure $\leq 50$ mm Hg) (fig. 3). Captopril was not more effective in the two patients with lower initial pulmonary artery pressures (or pulmonary resistances) than in the two with markedly elevated pressures. In fact, the only patient who had a notable improvement in symptoms or hemodynamics with chronic captopril therapy had severe involvement.

Despite its high concentration in the lung, converting enzyme does not appear to be essential for maintaining high pulmonary arterial pressure or resistance in adult human subjects with primary pulmonary hypertension. Fyhrquist and colleagues$^{18}$ demonstrated
that chronic dosing with captopril increases lung and serum converting-enzyme activity in rats. Therefore, the potential beneficial effects of captopril may have been mitigated by the induction of converting enzyme. The role of angiotensin II itself in the regulation of pulmonary vascular tone in normal lung and in animal models of pulmonary hypertension is unclear. In this study population, captopril may have elicited little change in the pulmonary hemodynamics because angiotensin II plays a minor role in the development and maintenance of primary pulmonary hypertension in humans. The lungs of patients with pulmonary hypertension are less capable of extracting and metabolizing circulating catecholamines than are normal lungs. Thus, elevated catechols (evoked by the drop in systemic blood pressure after captopril), along with inadequate or deranged local catecholamine metabolism by the lung, may have negated beneficial pulmonary hemodynamic effects.

Captopril may act, in part, through other mechanisms of vasodilation, such as kininase II blockade (resultant increase in the circulating vasodilator bradykinin). Why these alternative mechanisms of action fail to elicit even a mild change in pulmonary hemodynamics in primary pulmonary hypertension is also unknown.

Although the effects of captopril in primary pulmonary hypertension were not particularly impressive, certain persons with this disease may derive some benefit. One of our seven patients is still taking captopril after the completion of the protocol because of continued mild subjective improvement. In general, however, efforts should probably be directed to evaluating other agents with greater potential for clinical and hemodynamic improvement.

Acknowledgment

The authors thank Max Bacher and Mitzi Prosser for their technical assistance and the Squibb Institute for Medical Research for supplying captopril. We also thank the nursing staff of the Coronary Care Unit of the Ohio State University Hospitals for their professional assistance in the care of these patients.

References


17. Applied Statistics. Dallas, TX, Texas Instruments, pp 4–20


Captopril in primary pulmonary hypertension.
C V Leier, D Bambach, S Nelson, J B Hermiller, P Huss, R D Magorien and D V Unverferth

Circulation. 1983;67:155-161
doi: 10.1161/01.CIR.67.1.155
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1983 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/67/1/155