Acute Hemodynamic Effects of Captopril in Children With a Congestive or Restrictive Cardiomyopathy

A. Resai Bengur, MD; Robert H. Beekman, MD; Albert P. Rocchini, MD; Dennis C. Crowley, MD; M. Anthony Schork, PhD; and Amnon Rosenthal, MD

The acute hemodynamic effects of captopril were evaluated at cardiac catheterization in 16 children (age, 0.3–18 years) with cardiomyopathy. Twelve children had congestive cardiomyopathy, whereas four had restrictive cardiomyopathy. Hemodynamic measurements were obtained 30 and 60 minutes after the oral administration of captopril (0.5 mg/kg). Blood pressures were measured in the aorta, pulmonary artery, right atrium, and pulmonary capillary wedge position; cardiac outputs were measured by the thermodilution technique. Hemodynamic data could not be obtained after the administration of captopril in one child with congestive cardiomyopathy because of an immediate, severe hypotensive response. In 11 of 12 children with congestive cardiomyopathy, cardiac index increased by 22%, from 2.3 to 2.8 l/min/m² (p<0.05), and stroke volume increased by 22%, from 23 to 28 ml/m² (p<0.05). Systemic vascular resistance decreased from 32 to 21 units·m⁻² (p<0.01), but the mean aortic pressure did not change significantly. In contrast, four children with restrictive cardiomyopathy had no change in cardiac output after captopril, but there was a trend toward significant arterial hypotension (mean aortic pressure decreased from 78 to 59 mm Hg). Thus, captopril acutely reduced systemic vascular resistance and increased both cardiac output and stroke volume in children with congestive cardiomyopathy. In children with restrictive cardiomyopathy, however, captopril did not affect cardiac output, but it did decrease aortic pressure. These data indicate that captopril may benefit children with a congestive cardiomyopathy but that captopril probably should not be used in children with restrictive disease. (Circulation 1991;83:523–527)

Captopril, an oral angiotensin converting enzyme inhibitor, is of value in the management of children and adults with congestive heart failure.1–11 It decreases both left ventricular afterload and preload and is, therefore, beneficial in treating patients with congestive heart failure that is refractory to conventional inotropic and diuretic therapy.7–11 Captopril exerts beneficial hemodynamic effects in adults with ischemic cardiomyopathy12–21 and in children with heart failure due to left-to-right shunt lesions.6,22–24 Although studies in children have assessed the hemodynamic effects of vasodilator therapy in left-to-right shunt lesions or primary myo-cardial disease,5,6,25–30 the hemodynamic effects of captopril in children with congestive or restrictive cardiomyopathy have not been systematically evaluated. Therefore, the purpose of this study was to

See p 707

assess, at cardiac catheterization, the acute hemodynamic effects of oral administration of captopril in children with congestive heart failure due to congestive or restrictive cardiomyopathy.

Methods

Patient Population

Sixteen children, 12 with congestive and four with restrictive cardiomyopathy, were studied at cardiac catheterization. The patients ranged in age from 3 months to 18 years. The distinction between congestive and restrictive cardiomyopathy was based on measurements of the left ventricular end-diastolic volume, left ventricular ejection fraction, and ventricular filling pressures.31 Patients were classified as
having congestive cardiomyopathy when left ventricular end-diastolic volume exceeded 80 ml/m² and left ventricular ejection fraction was less than 50%, with normal to slightly increased filling pressures. Patients were classified as having restrictive cardiomyopathy when left ventricular end-diastolic volume was normal (<80 ml/m²) with preserved systolic function (ejection fraction, >50%), increased left ventricular end-diastolic pressure, and a left ventricular diastolic pressure tracing with a typical dip-plateau pattern.

All patients had clinical signs and symptoms of congestive heart failure and were treated with digoxin and diuretic therapy. Three patients in the congestive group and two patients in the restrictive group had mild-to-moderate mitral regurgitation. Several patients had mild tricuspid regurgitation detected by Doppler echocardiography (six patients in the congestive group and two patients in the restrictive group), but none had clinically apparent tricuspid regurgitation. The etiology of the cardiomyopathy in patients with congestive cardiomyopathy included idiopathic cardiomyopathy (n=8), familial disease (n=1), acute myocarditis (n=1), adriamycin cardiotoxicity (n=1), and right ventricular dysfunction after the Mustard operation for transposition of the great arteries (n=1). The group with restrictive cardiomyopathy included three patients with idiopathic disease and one patient who had received chest radiation therapy. This patient developed restrictive myocardial disease after having constrictive pericarditis and a pericardiectomy.

Study Protocol

The patients were studied in the catheterization laboratory after informed consent was obtained for the diagnostic study and vasodilator trial. A complete right and left heart catheterization was performed in all patients. Hemodynamic data were obtained in duplicate and before angiography, at baseline, and at 30 and 60 minutes after the administration of captopril (0.5 mg/kg p.o. or n.g.). At each time point, cardiac output was measured by the thermodilution technique in triplicate with a commercially available cardiac output computer (Arrow 7350, Reading, Pa.). Pressures were measured in the aorta, right atrium, pulmonary artery, and pulmonary capillary wedge positions with fluid-filled catheters and transducers (Sorenson, North Chicago) zeroed at the level of the midthorax. Oxygen saturations were measured in the aorta and pulmonary artery (OSM-3 Radiometer, Westlake, Ohio). Left ventricular volumes and ejection fraction were calculated with Simpson’s rule (Digisonics Analysis System 4.7, Houston) from a biplane cineangiogram obtained after the captopril trial.

Statistical Analysis

Hemodynamic data are presented as mean±SEM. For each cardiomyopathy group, values obtained at baseline and at 30 and 60 minutes after captopril administration were compared by a repeated measures analysis of variance. Multiple comparisons were then performed, using an experimentwise α error of 0.05 (Scheffe-type test), for all possible pairwise comparisons and also for the contrast between the baseline data and the average of the 30- and 60-minute data.32 The 30- and 60-minute values were not significantly different for any hemodynamic parameter (the greatest was F=0.84 for aortic mean pressure). To represent the steady-state response to captopril, the average of the 30- and 60-minute data and the significance of the contrast comparing them to baseline are presented below. All tests were two tailed, and a probability of 0.05 or less was defined as the level of significance.

Results

Baseline Hemodynamic Status

The children with congestive cardiomyopathy had a dilated left ventricle with depressed systolic function. The mean left ventricular end-diastolic volume was 241±55 ml/m², and the left ventricular ejection fraction was 26±3%. The left ventricular filling pressures in this group were elevated (pulmonary capillary wedge, 15±2 mm Hg), and the cardiac index was depressed (2.3±0.2 l/min/m²). In contrast, the four children with a restrictive cardiomyopathy had normal left ventricular end-diastolic volumes (56±6 ml/m²), with normal ejection fractions (60±3%) and elevated left ventricular filling pressures (pulmonary capillary wedge, 24±1 mm Hg). The baseline cardiac index was 2.8±0.5 in the restrictive group.

Hemodynamic Response to Captopril

Congestive group. In the children with congestive cardiomyopathy, captopril exerted a significant effect on cardiac index (T²=20.9, p=0.006), left ventricular stroke volume (T²=12.5, p=0.03), and systemic vascular resistance (T²=45, p=0.001). In 11 of 12 children with congestive cardiomyopathy (Table, Figure 1), captopril acutely increased cardiac index and stroke volume by 22%, from baseline to postcaptopril steady-state value (mean of 30- and 60-minute data). The cardiac index increased from 2.3±0.2 to 2.8±0.2 l/min/m² (p<0.05), and left ventricular stroke volume increased from 25±2 to 28±2 ml/beat/m² (p<0.05). Captopril also had a significant effect on systemic vascular resistance but not on arterial pressure. In these children, systemic resistance decreased by 34%, from 32.3±3 to 21.2 units·m⁻² (p<0.01), whereas aortic mean pressure did not decrease significantly (77±4 to 70±4 mm Hg). Captopril had no significant effect on heart rate, right or left ventricular filling pressures, pulmonary artery mean pressure, or pulmonary resistance. In one child with acute myocarditis (Table, patient 12), severe arterial hypertension and tachycardia occurred within 10 minutes of captopril administration. Volume expansion and pressure agents were required to stabilize the patient; therefore, hemodynamic data were not obtained 30 and 60 minutes after captopril administration.

Restrictive group. Hemodynamic data obtained in children (n=4) with restrictive cardiomyopathy are presented in the Table and in Figure 2. These data must be considered preliminary because statistical
inferences are unreliable with such a small sample size. In contrast to the children with congestive cardiomyopathy, children with restrictive cardiomyopathy showed no significant change in cardiac index or left ventricular stroke volume after captopril administration. There was a trend, however, for captopril to cause significant arterial hypotension in the children with restrictive cardiomyopathy. Mean aortic pressure decreased by 24% (78±7 to 59±3 mm Hg) and systemic resistance by 35% (26±5 to 17±2

**TABLE. Acute Hemodynamic Response to Captopril**

<table>
<thead>
<tr>
<th>Patient</th>
<th>HR (beats/min)</th>
<th>CI (l/min/m²)</th>
<th>SV (ml/beat/m²)</th>
<th>Rs (units/m²)</th>
<th>AO (mm Hg)</th>
<th>RA (mm Hg)</th>
<th>PCW (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
</tr>
<tr>
<td>Congestive cardiomyopathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>81</td>
<td>90</td>
<td>1.7</td>
<td>2.2</td>
<td>21</td>
<td>24</td>
<td>48</td>
</tr>
<tr>
<td>2</td>
<td>117</td>
<td>110</td>
<td>1.9</td>
<td>3</td>
<td>16</td>
<td>27</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>130</td>
<td>128</td>
<td>2</td>
<td>2.3</td>
<td>15</td>
<td>18</td>
<td>38</td>
</tr>
<tr>
<td>4</td>
<td>86</td>
<td>88</td>
<td>1.6</td>
<td>2.5</td>
<td>19</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>134</td>
<td>133</td>
<td>2.6</td>
<td>2.7</td>
<td>19</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>6</td>
<td>126</td>
<td>117</td>
<td>2.6</td>
<td>4</td>
<td>21</td>
<td>34</td>
<td>19</td>
</tr>
<tr>
<td>7</td>
<td>62</td>
<td>60</td>
<td>2</td>
<td>2.2</td>
<td>32</td>
<td>37</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>133</td>
<td>136</td>
<td>3.2</td>
<td>3.9</td>
<td>24</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>123</td>
<td>90</td>
<td>3.1</td>
<td>3.6</td>
<td>25</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>83</td>
<td>104</td>
<td>3.2</td>
<td>3.9</td>
<td>39</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>11</td>
<td>95</td>
<td>100</td>
<td>1.7</td>
<td>1.9</td>
<td>18</td>
<td>19</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>117</td>
<td>-</td>
<td>1.9</td>
<td>-</td>
<td>16</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>Mean</td>
<td>107</td>
<td>104</td>
<td>2.3</td>
<td>2.8</td>
<td>22</td>
<td>28</td>
<td>32</td>
</tr>
<tr>
<td>±SEM</td>
<td>7</td>
<td>6</td>
<td>0.2</td>
<td>0.2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Restrictive cardiomyopathy

<table>
<thead>
<tr>
<th>Patient</th>
<th>HR (beats/min)</th>
<th>CI (l/min/m²)</th>
<th>SV (ml/beat/m²)</th>
<th>Rs (units/m²)</th>
<th>AO (mm Hg)</th>
<th>RA (mm Hg)</th>
<th>PCW (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
<td>POST</td>
<td>PRE</td>
</tr>
<tr>
<td>1</td>
<td>103</td>
<td>98</td>
<td>2.8</td>
<td>3.3</td>
<td>27</td>
<td>34</td>
<td>26</td>
</tr>
<tr>
<td>2</td>
<td>102</td>
<td>92</td>
<td>1.7</td>
<td>1.7</td>
<td>17</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td>3</td>
<td>107</td>
<td>107</td>
<td>4</td>
<td>3.7</td>
<td>39</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>86</td>
<td>2.6</td>
<td>2.7</td>
<td>31</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Mean</td>
<td>99</td>
<td>94</td>
<td>2.8</td>
<td>2.9</td>
<td>28</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>±SEM</td>
<td>5</td>
<td>5</td>
<td>0.5</td>
<td>0.4</td>
<td>4</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>p</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

HR, heart rate; CI, cardiac index; SV, stroke volume; Rs, systemic vascular resistance; AO, aorta; RA, right atrial pressure; PCW, pulmonary capillary wedge pressure; PRE, precapritril baseline data; POST, average of 30- and 60-minute postcaptopril data; p, value of contrast between baseline data and average of data obtained 30 and 60 minutes after captopril administration; NS, nonsignificant at p<0.05.
units m⁻²). These changes might have been statistically significant with a larger patient group.

Discussion

During the past decade, vasodilator therapy has joined the traditional medical regimen of digoxin and diuretics in the medical management of many children with congestive heart failure.¹⁻⁶ The hemodynamic effects of vasodilator agents have been evaluated in children with primary myocardial disease,⁵,²⁻⁷⁻³⁰ or large left-to-right shunt lesions.⁶,²²⁻²⁶ Although the cardiovascular effects of captopril have been studied extensively in adults with congestive heart failure,¹²⁻²¹ captopril’s acute hemodynamic effects have not been studied in children with congestive cardiomyopathy. Furthermore, the effects of captopril in children or adults with restrictive cardiomyopathy have not been studied.

The present study documents that captopril acutely improves cardiovascular performance in children with congestive cardiomyopathy. This improvement was achieved by decreasing systemic vascular resistance by 34% and by increasing both cardiac index and left ventricular stroke volume by 22%. Arterial mean pressure did not change because the increase in cardiac output was sufficient to compensate for the decrease in systemic vascular resistance. Thus, captopril caused a significant reduction in afterload associated with a concomitant increase in left ventricular output in children with congestive cardiomyopathy. These findings are similar to those from previous studies showing that captopril acutely increases cardiac output by 18–30% in adults with congestive heart failure.¹⁶,¹⁹,²⁰ Unlike previous studies in adult patients,¹²⁻²¹ however, the present study shows that captopril had no significant effect on ventricular filling pressures. This unexpected finding can perhaps be explained by the fact that all children were receiving diuretics before catheterization and had fasted for 4–12 hours before the study; both are factors that decrease preload.

In the four children with restrictive cardiomyopathy, captopril caused no significant increase in cardiac index or left ventricular stroke volume. Arterial pressure tended to decrease substantially (Figure 2), an effect that probably would have been significant in a larger patient group. These hemodynamic responses to afterload reduction may reflect the fact that left ventricular systolic function is only mildly compromised in patients with restrictive cardiomyopathy.⁵¹ Stroke volume does not respond to a decrease in afterload sufficiently to compensate for the decrease in systemic vascular resistance, and arterial pressure, therefore, decreases. One may speculate that agents that diminish ventricular preload may further compromise stroke volume in a restrictive ventricle that is dependent on elevated filling pressures to maintain an adequate stroke volume.

Although 11 of 12 children with congestive cardiomyopathy responded favorably to captopril administration, one child in this group did not. This patient (Table, patient 12) was a 3-year-old boy with acute viral myocarditis and severe congestive heart failure. Within 10 minutes after captopril administration (0.5 mg/kg), mean arterial pressure decreased from 65 to 40 mm Hg (38%). Intravenous volume, calcium, and dopamine infusions were required to stabilize the patient. In this child, the left ventricular stroke volume response was not sufficient to compensate for the systemic vasodilation induced by captopril, and marked arterial hypotension occurred. Although captopril appears to have beneficial effects in most children with a congestive cardiomyopathy, the experience in this child emphasizes that captopril still must be used with caution in this patient population.

The acute hemodynamic findings of the present study indicate that captopril may have an important role in the treatment of many children with congestive cardiomyopathy. The reduction in afterload acutely improves cardiovascular performance in these patients, as manifested by a decrease in systemic vascular resistance and an associated 22%
increase in both cardiac index and stroke volume. Long-term clinical studies are needed to determine whether these acute hemodynamic changes are sustained and are translated into clinical improvement in children with congestive cardiomyopathy. Preliminary data in four children with restrictive cardiomyopathy suggest that captopril should not be used in this patient population. Restrictive cardiomyopathy is characterized by relatively normal left ventricular systolic function, with diastolic filling and stroke volume dependent on elevated filling pressures. The present study was unable to demonstrate any hemodynamic improvement in these patients after captopril administration.

References


Key Words: • captopril • heart failure • cardiomyopathy • children
Acute hemodynamic effects of captopril in children with a congestive or restrictive cardiomyopathy.

A R Bengur, R H Beekman, A P Rocchini, D C Crowley, M A Schork and A Rosenthal

_Circulation_. 1991;83:523-527
doi: 10.1161/01.CIR.83.2.523

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1991 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/83/2/523

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in _Circulation_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Circulation_ is online at:
http://circ.ahajournals.org//subscriptions/