Hemodynamic and Volume Changes Associated with Captopril

Robert C. Tarazi, M.D., Emmanuel L. Bravo, M.D., Fetnat M. Fouad, M.D., Per Omvik, M.D. and Robert J. Cody, Jr., M.D.

SUMMARY The effects of captopril on hemodynamic, volume, and neurohumoral indices were investigated in 33 patients with essential hypertension or renal arterial disease. Changes associated with treatment were studied under two conditions: immediately (4 to 1 hour) after administration of the drug, or after 5 to 7 days of therapy. Blood pressure (BP) reduction in both conditions was due to a reduction in total peripheral resistance (TPR) \( r = 0.714, p < 0.001 \) for \( \Delta MAP / TPR \); there was no significant change in either cardiac output or heart rate. The immediate BP and TPR responses were significantly related to pretreatment plasma renin activity (PRA) \( r = 0.737, p < 0.001 \), but this correlation was much weaker \( r = 0.392, p > 0.50 \) after maintained treatment. Response to therapy could not be predicted from either hemodynamic or volume characteristics of the patients \( r = 0.265, \text{NS for} \Delta MAP / \text{TBV} \) and \(-0.262, \text{NS for} \Delta MAP / \text{cardiac output} \). There was no significant change in body weight during treatment, while plasma volume increased slightly \( (+7\% \pm 2.8 \text{SE}, p < 0.05) \) but only in those patients who maintained a good BP response to captopril. Simultaneously, plasma aldosterone (PA) levels were reduced in relation to pretreatment level \( r = 0.955, p < 0.001 \). Thus, whereas the hemodynamic pattern of response to captopril remained unchanged during therapy, its relationship to pretreatment PRA became progressively weaker. The clinical antihypertensive effectiveness of captopril was therefore not related to either humoral, hemodynamic, or volume characteristics of this group of patients. The unusual pattern of lack of significant plasma volume expansion during therapy might be related in part to sustained reduction of plasma aldosterone levels. (Hypertension 2: 576-585, 1980)

Key Words • captopril • essential hypertension • hemodynamics • kidney disease • aldosterone • converting enzyme inhibitor • renovascular hypertension

An orally active converting enzyme inhibitor, captopril, was recently introduced as an antihypertensive agent; it rapidly proved to be quite effective in both man and experimental animals, both in renovascular and spontaneous hypertension. As has often been the case with other antihypertensive agents, the antihypertensive effectiveness of captopril was well documented before its exact mechanism(s) of action was elucidated. A lively controversy still persists regarding the dependence of its blood pressure (BP) lowering effect on interference with the renin-angiotensin system. In this context, a discussion of possible mechanisms of action would not be complete if restricted to consideration of BP levels alone. Important hemodynamic effects can occur with some agents in the apparent absence of any change in arterial pressure.

We summarize, therefore, our experience with the volume and hemodynamic changes associated with the use of captopril in hypertensive patients. We have correlated the changes observed with alterations in plasma renin activity (PRA) and aldosterone levels as well as with the degree of BP control.

Material and Methods

Patient Population

The patients were mostly from the patient population followed by the Research Division of the Cleveland Clinic Foundation; a few were referred to the Research Division because of resistance to other antihypertensive therapy. The purpose and details of the trial and studies were explained, and all gave their informed consent to the new treatment and special investigations, which had also been approved by the Institutional Review Committee.

The patients investigated have been described in detail in previous publications. All had extensive
laboratory investigations including renal arteriography; tests for primary aldosteronism or pheochromocytoma were performed when warranted. The immediate effects (1/2 to 1 1/2 hours) of captopril were studied in 23 untreated patients, 14 of whom had essential hypertension and seven, documented renal arterial disease; of the remaining two, one had chronic glomerulonephritis and one persistent hypertension despite unilateral nephrectomy for atherosclerotic renal arterial disease and a patent vessel to the remaining kidney. In all, plasma volume and plasma renin activity (PRA) were determined before the administration of captopril; BP and heart rate were monitored constantly before and after the effective dose of captopril, which was determined for each patient the day before the test. In addition, hemodynamic studies were obtained in 13.

The longer term studies of hemodynamic and volume changes with maintained therapy (average 5 ± 0.3 days) were obtained in 29 patients. Hemodynamic investigations were performed in eight, volume determinations were obtained in all 29; of these, 19 had essential hypertension and 10 had documented renal arterial disease. Results in 17 of these 29 patients have been reported before, along with the protocol to which all patients were subjected. Briefly stated, they were given an isocaloric diet containing 10 mEq of potassium/day supplemented by 90 mEq Na given as sodium chloride tablets; following an equilibration period of at least 3 days on that diet control determinations were obtained and captopril started with incremental doses until a fall of at least 10 mm Hg mean arterial pressure (MAP) was achieved or the maximum allowable dosage reached. Antihypertensive medications were discontinued in all but six patients for at least 2 weeks before the study; in those six patients, diuretics could not be stopped because of severity of hypertension or history of past cardiac decompensation. The dose of the diuretic agent was kept constant throughout the study as captopril was added in the same way as for other patients. Calculation of data with and without these patients did not alter the conclusions. Hemodynamic and volume studies were obtained as described below.

Hemodynamic Studies

Cardiac output studies were determined in most patients by thermal dilution and in the minority by dye (indocyanine green) dilution; both methods have been described in detail previously. Correlation of both methods as performed in our laboratory was very close (r = 0.92 and 0.87 in two separate series). However, none of the comparisons reported below involved a crossing over of methods; the same method was used consistently for the same patient and each subject served as his or her own control.

All patients were studied in the morning after at least 30-45 minutes of supine rest. Blood samples were first obtained for determination of PRA and plasma aldosterone (PA); plasma volume was then measured by radioiodinated (125I) serum albumin with a 10-minute equilibration period; total blood volume was calculated from the plasma volume and simultaneously determined corrected packed cell volume. Results were calculated in ml/cm height in order to minimize effect of age and overweight; normal values (± 1 sd) in our laboratory average 15.3 ± 1.68 ml/cm for women and 18.4 ± 1.95 ml/cm for men. Because of significant sex differences, values were expressed as % at normal (N) in order to include both men and women in subsequent analyses. Cardiac output was then determined at least in triplicate; in the case of dye dilution curves, blood withdrawn for each curve was reinfused before the next determination. Thermodilution curves were obtained from injection of 10 ml of 5% dextrose solution of 0°C. Measured values included heart rate (bpm), cardiac output (liter/min), systemic blood pressure (mm Hg), pulmonary artery pressure (mm Hg), and pulmonary wedge pressure (mm Hg). Derived hemodynamic indices (stroke volume, MAP, and vascular resistance) were calculated by standard methods.

Extracellular Fluid Volume (ECF)

Extracellular fluid volume (ECF) was determined in eight patients with oral radiosulphate. The method has been described in detail previously; 100 μCi of Na2 35SO4 were given orally on an empty stomach, and plasma samples were obtained at half-hourly intervals from 2 1/2 to 4 hours after ingestion of the dose. Calculation of ECF was based on standard principles

\[ ECF = \frac{D \times C \times W}{C \times \text{cpm/ml}} \]

where D is the administered dose in counts per minute (cpm), C is the plasma concentration at zero time, W is the water content of serum, and k is a constant (0.224) representing the Gibbs-Donnan and other correction factors for sample size and efficiency of counting. The ECF volume is closely related to body weight (r = 0.86, p < 0.001), and normal values in our laboratory average 18.9% body weight ± 2.4 (sp); repeated determinations in hypertensive patients on constant sodium intake showed a coefficient of variation of only 4.5% between two measurements.

Analytical Procedures

The PRA was determined by radioimmunoassay of generated angiotensin I and results expressed in ng/ml/hr; normal values for a daily intake of 100 mEq Na range from 0.4-2.6. The PA, also determined by radioimmunoassay in our laboratory, average 10 ± 4 ng/dl under the same conditions (100 mEq Na/day).

Statistical Analysis

Statistical analysis and significance of results were calculated by standard methods to determine unpaired and paired t tests as well as correlation coefficients. Values reported are averages ± SEM.
Results

Hemodynamic Effects

Reduction of arterial pressure by captopril occurred through decreased total peripheral resistance both in the early and delayed studies. Whether determined ½ hour after oral administration of the drug or 3 to 7 days later, cardiac output was not significantly changed whereas total peripheral resistance was significantly reduced in close correlation with the change in MAP (table 1 and fig. 1).

There was no significant change in heart rate in either the early or later studies despite the significant reduction of arterial pressure in both. Following acute administration of captopril, heart rate in the 23 patients increased slightly by 3.9 ± 1.4 beats/min (0.05 > p < 0.10). The increase in the 13 who had hemodynamic investigations reached borderline significance (+5 ± 2.2, p < 0.05); however, the scatter of heart rate variations was large and no significant correlation was found between changes in MAP and in heart rate (r = 0.20, NS).

Pulmonary hemodynamic indices showed no significant change during captopril therapy, either acutely* or following 1 week of treatment (table 2).

Volume Effects

After 3-8 days (average, 5.03) of treatment with captopril, body weight showed no significant change (−0.42 ± 0.24 kg [SE], p > 0.05) despite a significant reduction in MAP by 13.1 ± 2.5 mm Hg, p < 0.001. Concomitantly, plasma volume increased slightly (+3.7% ± 1.71%), a change of only borderline statistical significance (p < 0.05). Extracellular fluid volume was slightly reduced in the eight patients in whom serial determinations were obtained (table 3). There was no difference, however, between those whose arterial pressure was lowered by captopril and nonresponders to the drug.

The interpretation of average values for 29 patients, including both responders and nonresponders to captopril, would be difficult because of the wide variation in BP response within this group. The data were therefore analyzed in two ways. The first approach involved comparing variations in body weight and plasma volume during treatment between responders and nonresponders. Blood pressure response was defined, as previously, by 1) responders whose MAP was reduced by > 10 mm Hg and treatment BP was ≤ 150/95; 2) partial responders whose MAP was reduced by > 10 mm Hg but whose average daily BP was still ≥ 150/95; and 3) nonresponders whose MAP was not significantly changed (± 10 mm Hg). The second approach was designed to avoid these somewhat arbitrary classifications; changes in body weight and plasma volume during treatment were correlated with concomitant changes in arterial pressure in the whole group of patients.

There was no significant change in body weight in any of the three groups of patients (table 4). Plasma volume was not significantly altered in either nonresponders or patients showing partial response whereas there was a 7.01% ± 2.8% increase in "good responders" (p < 0.05). This statistical significance must, however, be evaluated in context of the inherent variability in plasma volume determinations; a change of 5-7% in plasma volume (table 4) would not be significant in that regard. Only in six of the 29 patients did plasma volume increase by > 10%.

The biological significance of these results was further called in question by the absence of any significant correlation between changes in MAP and alterations in either body weight (r = 0.22, NS) or plasma volume (r = 0.22, NS) (fig. 2). This was also true if values for responders were calculated alone (r = −0.245, NS).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Captopril</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mm Hg)</td>
<td>14.5 ± 2.2</td>
<td>14.4 ± 2.5</td>
<td>0.6 NS</td>
</tr>
<tr>
<td>PWP (mm Hg)</td>
<td>7.6 ± 1.8</td>
<td>6.2 ± 1.8</td>
<td>0.7 NS</td>
</tr>
<tr>
<td>CO (liter/m)</td>
<td>4.8 ± 0.3</td>
<td>5.3 ± 0.4</td>
<td>0.2 &lt;0.05</td>
</tr>
<tr>
<td>PVR (units)</td>
<td>2.5 ± 0.4</td>
<td>2.7 ± 0.5</td>
<td>0.2 NS</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Captopril</th>
<th>Significance</th>
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</thead>
<tbody>
<tr>
<td>MPAP (mm Hg)</td>
<td>14.5 ± 2.2</td>
<td>14.4 ± 2.5</td>
<td>0.6 NS</td>
</tr>
<tr>
<td>PWP (mm Hg)</td>
<td>7.6 ± 1.8</td>
<td>6.2 ± 1.8</td>
<td>0.7 NS</td>
</tr>
<tr>
<td>CO (liter/m)</td>
<td>4.8 ± 0.3</td>
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</tr>
<tr>
<td>PVR (units)</td>
<td>2.5 ± 0.4</td>
<td>2.7 ± 0.5</td>
<td>0.2 NS</td>
</tr>
</tbody>
</table>

Data from two independent series (Fouad et al. ref 9, and Cody et al. ref 8) both show essentially the same pattern of unchanged heart rate (HR) and cardiac output (CO) despite significant reduction in mean arterial pressure (MAP) and total peripheral resistance (TPR). Statistical significance (p) based on paired t test. (by permission from Circulation and Clin Sci Mol Med).
HEMODYNAMICS OF CAPTOPRIL/Tarazi et al.

TABLE 3. Extracellular Fluid (ECF) and Plasma Volume (PV) Changes During 5-7 Days of Captopril Treatment in Eight Patients

<table>
<thead>
<tr>
<th>Pt</th>
<th>MAP (mm Hg)</th>
<th>Body wt (kg)</th>
<th>ECF (liter)</th>
<th>PV (%N)</th>
<th>(PV/IF) × 100</th>
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<tr>
<td></td>
<td>b</td>
<td>d</td>
<td>b</td>
<td>d</td>
<td>b</td>
</tr>
<tr>
<td>1</td>
<td>138</td>
<td>135</td>
<td>78.7</td>
<td>77.7</td>
<td>16.14</td>
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<tr>
<td>2</td>
<td>121</td>
<td>119</td>
<td>86.8</td>
<td>86.8</td>
<td>11.82</td>
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<tr>
<td>3</td>
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<td>119</td>
<td>71.7</td>
<td>71.4</td>
<td>9.92</td>
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<tr>
<td>4</td>
<td>147</td>
<td>137</td>
<td>92.6</td>
<td>90.9</td>
<td>18.87</td>
</tr>
<tr>
<td>5</td>
<td>111</td>
<td>91</td>
<td>46.7</td>
<td>47.1</td>
<td>8.39</td>
</tr>
<tr>
<td>6</td>
<td>140</td>
<td>130</td>
<td>70.4</td>
<td>69.4</td>
<td>12.94</td>
</tr>
<tr>
<td>7</td>
<td>118</td>
<td>121</td>
<td>78.1</td>
<td>77.5</td>
<td>13.40</td>
</tr>
<tr>
<td>8</td>
<td>123</td>
<td>124</td>
<td>99.4</td>
<td>97.9</td>
<td>12.43</td>
</tr>
<tr>
<td>X</td>
<td>127</td>
<td>122</td>
<td>77.0</td>
<td>76.3</td>
<td>12.99</td>
</tr>
</tbody>
</table>

RED | .27 | .25 | 0.32 | 3.40 | 17.1 |

p >0.10 | <0.05 | <0.05 | NS | NS |

In this small group of three responders (patients 4, 5, 6) and five nonresponders, body weight and ECF were slightly but significantly reduced (—0.71 kg and —0.88 liter respectively). No other change was statistically significant.

Correlates of BP Response

Humoral Effects

The immediate BP response to the first effective dose of captopril was closely related to pretreatment PRA; this was true whether the correlation was calculated on the basis of either arithmetic or log values of PRA (r = 0.742 and 0.737, p < 0.001 for both) (fig. 3). The slope of the regression line defining the relation between the two variables was not significantly different from the slope of the regression obtained in the same patients in response to [Sar¹, Thr⁴]AII, a specific angiotensin antagonist. This correlation did not hold, however, in the longer term study (r = 0.392, p > 0.50).

Plasma aldosterone concentration (PAC) did not predict BP response to the converting enzyme inhibitor but was definitely lowered by captopril therapy, from 40.3 ± 8.9 ng/dl to 22.0 ± 2.6 ng/dl. The fall in PAC barely reached statistical level because of unchanged values among those patients with initially normal levels. In fact, PAC reduction was closely related to the pretreatment levels (r = 0.955, p < 0.001). Before therapy, PRA and PAC were directly related to each other (r = 0.810, p < 0.001); with treatment, this relationship was lost (r = —0.075) as PRA increased and PAC fell. No instance of induced hypoaldosteronism was observed as PAC levels were normalized in those with initially high values.

Plasma norepinephrine levels were determined in 10 patients before and 3 days following captopril treatment; measurements were obtained in the morning after ½ hour of supine rest. No significant change was noted as plasma norepinephrine averaged 268 ± 19 ng/liter before treatment and 266 ± 36 3 days later.

FIGURE 1. Correlation between blood pressure response (ΔMAP) and change in total peripheral resistance (ΔTPR) in 13 patients given first [Sar¹, Thr⁴]AII (1000 µg i.v.) and then after return to control values, captopril orally (reproduced by permission from Fouad et al. Circulation, 1980). The closed circles represent response to the angiotensin antagonist, and the crosses represent the response to the converting enzyme inhibitor; in both cases ΔMAP was closely correlated with ΔTPR but not significantly with variations in cardiac output (a).
FIGURE 2. Correlation between mean arterial pressure response to captopril and concomitant changes in plasma volume (left panel) or body weight (right panel). Changes in plasma volume and body weight during treatment (both expressed as % of control) correlated significantly with each other \( r = 0.519, p < 0.005 \).

FIGURE 3. Correlation of acute response of mean arterial pressure \( (\Delta MAP) \) with plasma renin activity \( (PRA) \) in 23 patients given successively the angiotensin antagonist \([\text{Sar}^1, \text{Thr}^3]\)AI\(II (1.0 \mu g/Kg \text{ i.v.}) \) followed by captopril as described in the text. Both correlations were highly significant; the slopes of the regression lines were not significantly different from each other but the intercept was greater for \([\text{Sar}^1, \text{Thr}^3]\)AI\(II \) than for captopril \( (+8.47 \text{ vs } -10.17, p < 0.01) \). (Reproduced by permission from Fouad et al., Circulation, 1980).
Blood Volume

No relationship was found between BP response to captopril and pretreatment intravascular volume, either in the acute (r = 0.265, NS) or longer-term (r = 0.095, NS) studies.

Hemodynamic Characteristics

The BP response to captopril was not significantly related to pretreatment hemodynamic values; r value for \( \Delta \text{MAP} / \text{control cardiac output} \) was \(-0.262\) (NS). Fouad et al.\(^ 4 \) had also reported that BP response to [Sar\(^1\), Thr\(^8\)]AII was not related to cardiac output levels. In the eight patients studied after 5-7 days of therapy, BP response was also not related either to pretreatment cardiac output (\( r = 0.525, p > 0.10 \)) or TPR (\( r = 0.519, NS \)). The lack of statistical significance of these rather large r values (0.5) might be due to the small number of patients in that series. However, viewed in context of our acute hemodynamic studies and of the observations of Sullivan et al.,\(^ 17 \) the relationship of pretreatment hemodynamic characteristics of BP response to captopril did not appear to be of any real significance.

Discussion

This review of our experience\(^ 8, 9, 18 \) with captopril has outlined a complexity of effects, the pattern of which changed with maintenance of therapy. The basic hemodynamic mechanism of captopril's antihypertensive action seems well established from our results\(^ 8, 9 \) as well as those of others.\(^ 5, 17, 18 \) The reduction in arterial pressure was related in all reported studies to a lowering of TPR; this was observed within \( 1/2 \) to 1 1/2 hours from oral administration in men\(^ 6 \) as well as with maintained therapy for periods of 3 to 14 days.\(^ 6, 17 \) Similar results were observed in spontaneously hypertensive rats,\(^ 6 \) in rats with acute renovascular hypertension,\(^ 19 \) and even in normotensive dogs.\(^ 18 \)

Implications of Hemodynamic Results

The consistency of this hemodynamic pattern (reduction in TPR) in acute and in longer term studies contrasts with the variability of hemodynamic changes observed with \( \beta \)-adrenergic blockers,\(^ 5, 30 \) which were postulated by some to act primarily through interference with renin release.\(^ 21 \) Propranolol can induce several hemodynamic patterns from decreased output and unchanged arterial pressure to a lowering of TPR, depending on duration of therapy among many other factors.\(^ 22 \) In contrast, the antihypertensive effect of captopril was consistently found to be related both in the early phase of treatment and during its maintenance to a reduction in TPR. To the extent that hemodynamic changes reflect the factors involved in the action of a drug, the differences between propranolol and captopril suggest the interference of variables other than angiotensin activity in the antihypertensive action of one or both agents.

In contrast with these differences, a comparison of captopril with [Sar\(^1\), Thr\(^8\)]AII seemed to indicate a close similarity between the hemodynamic effects of converting enzyme inhibition and those of this specific angiotensin antagonist. Fouad et al.\(^ 8 \) gave the two agents in close succession to the same group of hypertensive patients; in both conditions, BP response was related primarily to changes in TPR (fig. 1) while cardiac output was not changed significantly. However, another angiotensin antagonist (saralasin) was reported by many,\(^ 23-26 \) but not by all,\(^ 27 \) to lower cardiac output in most patients irrespective of their BP response. Other differences in cardiac\(^ 27 \) and catecholamine\(^ 28 \) effects have been reported between saralasin, [Sar\(^1\), Thr\(^8\)]AII and [Sar\(^1\), Ile\(^8\)]AII. This dissimilarity in cardiovascular effects among various angiotensin antagonists should caution against far-reaching conclusions based on similarity of hemodynamic patterns alone.\(^ 29 \)

The association of diminished TPR and arterial pressure with minimal changes in cardiac output may occur in several circumstances.\(^ 8, 30, 31 \) The most likely reason in our patients appeared to a combined effect of arteriolar and venous dilation.\(^ 8, 30 \) The pattern produced by captopril would thus be similar to that in hypertensive patients with compensated cardiac function in response to nitroprusside\(^ 36 \) or prazosin.\(^ 32 \) The suggestion that captopril may lead to venodilation was based on indirect evidence such as the lack of increase in cardiac output despite the significant reduction in

### Table 4. Blood Pressure, Body Weight, and Plasma Volume Changes During Captopril Treatment (\( \delta = 0 \) 3 Days)

<table>
<thead>
<tr>
<th>Group (n)</th>
<th>MAP (mm Hg)</th>
<th>Body wt (kg)</th>
<th>PV (%N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good (n = 12)</td>
<td>Control</td>
<td>124</td>
<td>2.3</td>
</tr>
<tr>
<td>( \Delta )</td>
<td>-21.4</td>
<td>1.7</td>
<td>-0.07</td>
</tr>
<tr>
<td>( p )</td>
<td>&lt;0.001</td>
<td>NS</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Partial (n = 7)</td>
<td>Control</td>
<td>147</td>
<td>5.0</td>
</tr>
<tr>
<td>( \Delta )</td>
<td>-19.8</td>
<td>4.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>( p )</td>
<td>&lt;0.001</td>
<td>&gt;0.05</td>
<td>NS</td>
</tr>
<tr>
<td>all (n = 19)</td>
<td>Control</td>
<td>133</td>
<td>3.4</td>
</tr>
<tr>
<td>( \Delta )</td>
<td>-20.8</td>
<td>1.8</td>
<td>-0.42</td>
</tr>
<tr>
<td>( p )</td>
<td>&lt;0.001</td>
<td>&gt;0.05</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Nonresponders (n = 10)</td>
<td>Control</td>
<td>130</td>
<td>4.2</td>
</tr>
<tr>
<td>( \Delta )</td>
<td>+2</td>
<td>2.5</td>
<td>-0.4</td>
</tr>
<tr>
<td>( p )</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

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TPR. Collier and Robinson have reported that intravenous converting enzyme inhibition (teprotide) results in dilatation of hand veins; more recently, captopril was shown to increase forearm venous distensibility in severely hypertensive patients. Also in favor of venodilation would be the slight but significant increase in plasma volume found in patients who responded to captopril with effective BP reduction (table 4). More direct evidence in favor of systemic venodilatation was reported in normotensive patients with heart failure; during treatment with captopril, the ratio of cardiopulmonary to total blood volume was reduced, suggesting peripheral redistribution of intravascular volume. However, the hemodynamic situation in heart failure is different from that in compensated hypertensive patients although both have elevated TPR and PRA. Further, the direct effect of angiotensin on systemic veins is still controversial. Whatever the case, the absence of a significant increase in venous return may help explain the lack of significant change in pulmonary arterial pressure. In contrast with its reduction of systemic vascular resistance, converting enzyme inhibition did not change pulmonary vascular resistance significantly.

Effect on Heart Rate and Orthostatic Responses

Possibly linked to the absence of a significant increase in cardiac output was the lack of tachycardia despite the marked lowering of arterial pressure and peripheral resistance by captopril. Vasodilators that affect veins as well as arterioles have been reported to produce less reflex tachycardia than those predominantly affecting arterioles. Heart rate was not appreciably modified by captopril in most patients even following acute pressure reduction. This same observation, reported with longer term therapy, was also noted following intravenous administration of angiotensin antagonists and the intravenous converting enzyme inhibitor. Thus, the absence of reflex tachycardia appears as a feature common to different agents that interfere with the renin-angiotensin system at different levels, including those, like captopril, that do not seem to cross the blood-brain barrier to any significant degree. Captopril was reported to blunt baroreceptor reflex sensitivity in conscious normotensive rabbits, but this study was limited to demonstration of a reduction in heart rate response to arterial pressure variations; whether this result was due to a vagal or cardiac effect of captopril remains unclear. Experience with angiotensin antagonists both in man with saralasin and in dogs with [Sar1, Thr1]AII suggested that these antagonists might enhance parasympathetic activity. To suggest that converting enzyme inhibitors have the same effect would be pure speculation.

Whatever the reason for the reduced heart rate response to hypotension in the supine position, captopril did not interfere in our experience with homeostatic cardiovascular response to posture. Cody et al. have demonstrated that both heart rate and TPR responded adequately to head-up tilt in patients receiving captopril even when combined with diuretics or a low-sodium diet. The clinical implications of these results are particularly important in view of the frequent need for diuretics in captopril-treated patients. Experience with teprotide in normotensive volunteers had suggested that cardiovascular responses to posture during salt depletion were predominantly dependent on the effectiveness of the renin angiotensin system. However, orthostatic hypotension has not been a significant or frequent complication of captopril therapy either alone or in combination with diuretics or salt depletion. These discrepancies might be related to possible differences between teprotide and captopril; it is more likely that they reflect a variation with time during maintenance therapy, in the degree of interference with the renin angiotensin system by captopril.

Correlates of Hemodynamic Response to Captopril

The BP response to captopril did not seem related to either pretreatment hemodynamic indices or to magnitude of intravascular volume. Fouda et al. found no statistically significant difference in total blood volume between responders and nonresponders to captopril (86.6 ± 5.2 vs 92.8 ± 4.07 NS); the same patients also showed no correlation between control cardiac output or TPR levels and pressure response to the drug (r = -0.262 and -0.288 respectively, both NS).

In contrast, the acute response to captopril correlated significantly with control supine PRA (r = 0.737, p < 0.001). This correlation was closely similar to that found in the same patients between PRA and response to [Sar1, Thr1]AII (fig. 2). These findings, which are in agreement with those of Case et al., leave little doubt regarding the importance of the renin status of patients in determining their initial acute response to this oral converting enzyme inhibitor. However, when patients were tested a few days later, the relation between pretreatment PRA level and BP control by captopril became much more tenuous. The value of the correlation coefficient (r) was much lower and its statistical significance questionable; it alternatively passed or failed the 0.05 probability level depending on the number of patients examined. In an initial study of eight patients, r was -0.664 (p < 0.05); in a larger group of 17 patients, r fell to -0.392 (p > 0.05), while in a later review of 32 patients, r value attained 0.45 (p < 0.05). This variability in r values might be taken to indicate an unstable relationship of borderline significance; this assumption was substantiated by the finding of progressively weaker correlations between pretreatment PRA and BP response to captopril, as duration of therapy increased. In patients treated for a month, the r value had declined to 0.03. Thus, it would appear as if the initial BP response to captopril was in large part related to its interference with the renin angiotensin system. However, the
longer-term response, the response of most significance in the clinical management of most hypertensive patients, was not in our experience significantly dependent on or related to a high pretreatment PRA. The latter conclusion is in agreement with the findings of many other investigators; the contrast highlighted by our results between the acute and longer-term situation might help explain some of the discrepancies in reports about captopril.

Changes in Plasma and Extracellular Fluid Volume

In contrast with most antihypertensive agents, captopril did not lead to significant volume expansion in the majority of treated patients. Extracellular fluid (ECF) volume was not increased, and body weight did not change significantly during the period of observation. Plasma volume did show on the average a slight but statistically significant expansion in the 19 patients whose BP was lowered by captopril (+5.1% ± 2.11% se dif, p < 0.05) but not in the 10 non-responders (0.76 ± 2.85, NS). Whether this modest expansion could be interpreted as due to venodilation with intravascular redistribution of ECF is debatable. The ratio of plasma to interstitial fluid volume (PV/IF) showed some tendency to increase from 29.74% to 32.1% (se dif 17.1) but the change did not attain statistical significance. A small increase in plasma volume had been noted in the first small group of patients described by Cody et al. but not among the patients studied by Sullivan et al.. On the whole, the smallness of the changes described; the wide individual variations; and the lack of significant differences between various groups of responders, partial responders, and nonresponders, would all cast some doubt on the biological significance of this expansion for most patients. In only six of 19 patients did plasma volume increase by more than 10%.

Volume Changes and Late Resistance to Captopril Therapy

Of particular importance was the absence of any significant correlation between either change in body weight or alteration in plasma volume and the BP response to captopril (r = −0.091 and −0.224 respectively; NS for both). These negative findings contrast with the well-established tendency to volume expansion with most antihypertensive drugs (except for diuretics and beta-adrenergic blockers). This expansion has usually been held responsible for most instances of secondary resistance to therapy. The stability of body weight and plasma volume in most patients on captopril treatment might be related to its maintenance of PAC levels at near normal values. This reduction in PAC might be an index of continued interference by captopril in the production of angiotensin II, and could be an added factor in preventing sodium retention. Increased creatinine clearance and sodium excretion were recently reported with teprotide in essential hypertension. Studies of sodium balance during captopril treatment showed wide variations, however, and no relationship was found between natriuresis and BP response.

The lack of volume expansion in the present study cannot be related entirely to the relatively short period of observation because significant increase in plasma volume due to redistribution of ECF was demonstrated within a week of quinethidine treatment. However, Saragoca et al. found that, after 1 month follow-up of 32 patients treated with captopril, plasma volume tended to increase only in the group (12/32) that maintained a good BP response to captopril. Patients whose initial pressure responses gradually disappeared showed no evidence of volume expansion. This evolution of arterial pressure and plasma volume levels during captopril therapy was quite different from our experience with other antihypertensive agents, including propranolol. The lack of secondary resistance to beta-blockers was usually attributed by ourselves and others to absence of volume expansion. In contrast, secondary resistance to the antihypertensive effect of captopril did develop in the absence of evident volume expansion. This pattern of volume-pressure alterations during therapy is rather unusual, as extracellular and plasma volume expansion are considered of primary importance in loss of pressure response to antihypertensive agents. To our knowledge, only in the case of minoxidil, did fluid retention fail to interfere with BP control. However, the slight-to-moderate plasma volume increase encountered in some patients during captopril treatment resembled in no way, either in magnitude or universality, the marked fluid retention seen with minoxidil.

Secondary resistance to captopril was characterized in our experience by two seemingly contradictory features, absence of volume expansion and yet marked responsiveness to diuretics or salt depletion. Blood pressure responses to captopril were not related to changes in PRA consequent to converting enzyme inhibition. Possible explanations for these observations can only be speculative given the presently available data.

In summary, the spectrum of hemodynamic and volume changes encountered during captopril therapy appears much too complex, in our opinion, to be explained by one simple mechanism. The early BP response was related to a reduction in TPA. The alteration with time in the relationship of antihypertensive effectiveness to pretreatment PRA suggests that clinical use of the drug cannot be restricted to patients with high renin activity. It would also suggest that the long-term antihypertensive effect of captopril cannot be solely due to direct interference with generation of angiotensin II. Another important and not fully explained feature was the secondary resistance to maintained treatment in many patients. The mechanism(s) responsible for that secondary resistance are not clear; its pattern differed from that encountered with most other antihypertensive agents in that it was not related to volume expansion.
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