Differential long-term intrarenal and neurohumoral effects of captopril and prazosin in patients with chronic congestive heart failure: importance of initial plasma renin activity

BERTRAND METTAUER, M.D., JEAN-LUCIEN ROULEAU, M.D., F.R.C.P. (C)
DANIEL BICHET, M.D., F.R.C.P. (C), CLAUDE KORTAS, M.D., CHRISTIANE MANZINI, R.T.,
GERARD TREMBLAY, M.D., F.R.C.P. (C), AND KANU CHATTERJEE, M.B., F.R.C.P.

ABSTRACT  Fifty patients with congestive heart failure received, by infusion, 15 ml/kg body weight water load, and systemic hemodynamic, renal function, and neurohumoral parameters values were measured before, 2 days, and 1 month after randomly allocating patients to prazosin or captopril therapy. Both prazosin and captopril caused similar and persistent hemodynamic changes, but important differences existed between their renal and neurohumoral effects. After 1 month of continuous therapy, captopril increased creatinine clearance from 71 to 84 ml/min/1.73\textsuperscript{2} (p < .05), increased the water load excreted in 5 hr from 50% to 71% (p < .005), and increased 5 hr sodium excreted from 6.8 to 14.7 meq (p < .005). Captopril also caused a decrease in plasma norepinephrine from 568 to 448 pg/ml (p < .005), in plasma epinephrine from 94 to 73 pg/ml (p < .05), and in plasma aldosterone from 57 to 28 ng/dl (p < .005), without changing plasma vasopressin. These beneficial effects were greater after 1 month of therapy than after 2 days. The only beneficial effect of prazosin was to increase water excretion from 49% to 59% (p < .05). The long-term response to captopril was similar in patients with higher (> 2.5 ng/ml/hr) and lower renin levels. However, in patients with lower renin levels, prazosin decreased pulmonary capillary wedge pressure (24.8 to 21.8 mm Hg, p < .05), decreased plasma arginine vasopressin (1.16 to 0.75 pg/ml, p < .05), increased water excretion (62% to 85%, p < .005), and decreased plasma epinephrine (81 to 46 pg/ml, p < .05), while in patients with higher renin levels none of these beneficial effects were noted. We conclude (1) that captopril produces long-term beneficial renal and neurohumoral effects that prazosin does not despite similar hemodynamic changes with the two drugs, (2) that these effects are at least partially dependent on the initial neurohumoral and hemodynamic status of the patient, and (3) that through hemodynamic improvement vasodilators may chronically interrupt vasopressin overstimulation.


FOR OVER 10 years, vasodilators have been shown to have beneficial effects in patients with congestive heart failure.\textsuperscript{1-2} After short-term clinical and hemodynamic improvement, however, tolerance to the initial beneficial effects of these drugs has become apparent in some patients.\textsuperscript{1,2} To better understand the reasons why some patients develop tachyphylaxis and others do not, the compensatory neurohumoral changes accompanying heart failure and the short-term effects of therapy on them have recently been studied.\textsuperscript{3-6} However, the long-term effects of vasodilators on these compensatory mechanisms have not been extensively studied, despite their possible relationship to the pathophysiologic mechanisms of tachyphylaxis.

In the present study, we measured the short- and long-term hemodynamic, renal, and neurohumoral effects of two commonly used vasodilators, one that has extensive renal and neurohumoral effects (captopril) and one that does not (prazosin). We found that although captopril and prazosin had similar short- and
long-term hemodynamic effects, they led to very different long-term renal and neurohumoral changes, and that these differences were partly dependent on the initial neurohumoral and hemodynamic status of the patients.

**Methods**

Fifty patients with severe chronic congestive heart failure were chosen for the study. There were 12 women and 38 men, with a mean age of 62 ± 9 years. All patients were New York Heart Association class III or IV, and the cause of heart failure was ischemic in 42 and cardiomyopathic in eight. Before entry into this study, all patients were found to be resistant to the standard therapy of digoxin and diuretics. After obtaining informed consent (this study was approved by the ethics committee of l'Hôpital du Sacré-Coeur of Montréal), all patients were hospitalized for at least 1 week before the study and fed diets containing 2 g of sodium/day with fluid intake restricted to a maximum of 1500 ml/day. Once the patients were considered optimally controlled on digoxin and diuretics, and once their weight varied less than 0.5 kg over 3 consecutive days, they were considered ready to enter the study, and were transferred to the coronary care unit of l'Hôpital du Sacré-Coeur in Montréal. Digoxin and diuretics were discontinued for 24 hr before each water load procedure. No patients received vasodilators before the study.

**Water loads and hemodynamics measurements.** The evening before the study, a No. 7F triple-lumen, flow-directed, balloon-tipped thermodilution catheter (Edwards Laboratories, Santa Anna, CA) was introduced transcutaneously through the internal jugular vein of each patient by the Seldinger technique and advanced to a pulmonary wedge position according to pressure tracings. Pulmonary arterial, right atrial, and pulmonary capillary wedge pressures (PCWP) were monitored by a Gould-Statham P231 I'd transducer and were recorded on an Electronics for Medicine VR-6 Photographic Recorder. Cardiac output was measured by means of the computerized thermodilution technique with iced 5% dextrose in water. Systemic arterial blood pressure was obtained through an intra-arterial catheter. After an overnight fast, baseline hemodynamic, renal, and neurohumoral measurements were obtained (day 0). A 15 ml/kg body weight water load consisting of 5% glucose in water was then administered intravenously over 45 to 90 min and renal water excretion was monitored over the next 5 hr, as previously described. Blood was drawn every hour through the arterial line for measurements of electrolytes, osmolality, blood urea nitrogen, glucose, creatinine, protein, and albumin. Samples were also taken for measurements of plasma arginine-vasopressin, plasma renin activity, plasma aldosterone, plasma norepinephrine, and plasma epinephrine. Urine was obtained by spontaneous voiding every hour. The volume of each collected urine sample was recorded and urine was analyzed for electrolytes, osmolality, urea nitrogen, and creatinine.

Derived hemodynamic values were calculated as follows:

\[
\text{Cardiac index (1/min/m}^2) = \frac{\text{Cardiac output}}{\text{Body surface area}}
\]

\[
\text{Stroke work index (g.m/m}^2) = \frac{\text{(Mean arterial pressure-PCWP)} \times \text{stroke volume \times 0.0136}}{\text{Body surface area}}
\]

\[
\text{Systemic vascular resistance (dyn·sec·cm}^{-5}) = \frac{80 \times (\text{Mean arterial pressure - right atrial pressure})}{\text{Cardiac output}}
\]

**Vasodilator therapy.** Vasodilator therapy was administered in the following manner. Patients were randomly allocated to the captopril or prazosin group. Prazosin (0.5, 1, 2, and 5 mg) or captopril (6.25, 12.5, and 25 mg) was given in increasing doses every 6 hr until one of the following end points was reached: (1) a decrease in mean arterial pressure of between 10 and 20 mm Hg, (2) a decrease in systolic arterial pressure to a value below 100 mm Hg, or (3) a maximal dose of 5 mg of prazosin or a maximal dose of 25 mg captopril. Twenty-six patients received captopril and 24 patients received prazosin. The median dose of prazosin necessary was 2 mg and the median dose of captopril necessary was of 12.5 mg. Intravenous furosemide was given after the end of the first water load study and again 24 hr before the second water load as necessary to maintain urine output within 500 ml of intake in order to keep total body water constant between the control and the day 2 studies.

**Long-term study.** Once the short-term studies were completed the patients were transferred to a medical ward. To permit patients to receive the drug dosage used during the day 2 study four times a day, the dose of diuretics was adjusted before discharge of patients from the hospital. This was necessary because a number of patients had increased sodium and water excretion and therefore decreased body weight. In this way all patients were able to receive the same vasodilator dose during the short-term study, between studies (four times a day), and during the long-term study. Eight of the patients on prazosin received only 4 mg/day, 14 patients received 8 mg/day, and two patients received 20 mg/day. Of the patients receiving captopril, four received only 25 mg/day, while 22 received 50 mg/day. All patients remained on a 2 g sodium diet and a 1500 ml fluid restriction. No patient received vasodilators other than prazosin and captopril. All patients received furosemide before the control study and also between studies. Twenty of the 24 patients receiving prazosin also received 50 to 200 mg/day triamterene and 14 of the 26 patients receiving captopril also received 50 to 200 mg/day triamterene. The mean dose of triamterene given to patients receiving prazosin was of 138 ± 62 mg before the study and 143 ± 54 mg between the short- and long-term studies and the mean dose given to patients receiving captopril was of 154 ± 52 mg before the study and 119 ± 60 mg between the short- and long-term studies.

Four patients did not complete the long-term study: two died between studies and two refused to participate in the long-term study. Of the remaining 46 patients, 22 were receiving prazosin and 24 captopril. All patients were maintained over the long term on the same dosage of vasodilator used in the short-term study, but on a four-times-a-day basis. Between studies all patients were followed in the same manner by the same cardiologist. They were readmitted 4 weeks after the initial study and were maintained on a diet of 2 g of sodium/day and on a fluid restriction of 1500 to 1800/day. Twenty-four hours before the long-term study, digoxin and diuretics were withheld and the patients were transferred to the coronary care unit where a No. 7F triple-lumen, flow-directed, balloon-tipped thermodilution catheter and an arterial line were inserted percutaneously. Their regular dose of captopril or prazosin was continued until midnight before the study. After an overnight fast, baseline measurements were taken, the regular dose of captopril or prazosin was given, and the 15 ml/kg water load procedure was repeated.

**Arginine-vasopressin radioimmunoassay.** Plasma arginine-vasopressin was measured by a radioimmunoassay technique previously described. In brief, blood samples collected in chilled EDTA tubes were centrifuged at 4°C at 3000 rpm for 20 min and plasma for the determination of arginine-vasopressin was extracted by a modification of the acetone method described by Robertson et al. and by Durr et al. The tracer
used was vasopressin-8-arginine [125I]-moniodinated (New England Nuclear or Amersham). The antiserum (AS-2849) used, at a final dilution of 1/2.5 × 10^6 was generously provided by J. Durr and M. Lindheimer (Department of Obstetrics, Gynecology, and Medicine, University of Chicago). Sensitivity of the assay using this antiserum in our laboratory is 0.1 pg/assay tube and the 50% displacement is 1.2 pg/tube.

**Measurements of norepinephrine and epinephrine.** Arterial norepinephrine and epinephrine concentrations were measured by the radioenzymatic assay of Peuler and Johnson.12

**Measurements of plasma renin activity and plasma aldosterone by radioimmunoassay.**

**Plasma renin activity.** Blood samples were collected in chilled EDTA tubes, centrifuged at 4°C at 3000 rpm for 20 min, and kept at −20°C until assay. Incubation for generation of angiotensin I was carried out at pH 6.0 for 2 hr with 8-hydroxyquinoline. The antiserum used was highly specific. Tracer was [125I]-angiotensin I from New England Nuclear (Boston). Standard curves were prepared with synthetic angiotensin I (Sigma, St. Louis) in quantities that ranged from 10 to 500 pg per assay tube. Plasma renin activity was measured in nanograms of angiotensin I per milliliter of plasma per hour of incubation.13

**Aldosterone assay.** Plasma aldosterone was measured by a commercial kit (Abbott Diagnostics, Diagnostic Products, North Chicago).14 The antiserum used is highly specific and has virtually no cross reactivity with other steroids or lactone.

**Other analytic procedures and calculations.** Plasma osmolality (Posm) was determined in duplicate on 250 µl samples by freezing-point depression (Advanced Instrument Osmometer 3DII: Advanced Instruments, Inc., Nesham Heights, MA). Sensitivity of the instrument is ±1 mOsm and its coefficient of variation at 290 mOsm is 0.51%. Plasma for osmometry was always collected on heparin and recommendations from the literature were strictly followed.10 Plasma effective osmolality (Eosm, in mOsm/kg H2O) was calculated according to the formula:

$$Eosm = Posm - \left[ \frac{\text{Glucose (mg/dl)}}{18} + \frac{\text{BUN (mg/dl)}}{2.8} \right]$$

Osmolar clearance in ml/min was calculated according to the formula

$$\text{Osmolar clearance} = \frac{Uosm \times V}{\text{Posm}}$$

where Uosm = urinary osmolality (in mOsm/kg H2O); V = urinary flow rate (in ml/min); Posm = plasma osmolality (in mOsm/kg H2O).

**Statistical analysis.** For statistical analysis, the mean of the values (baseline, 1, 2, 3, 4, and 5 hr) from control, day 2, and the 1 month studies were compared by a two-factor repeated-measures analysis of variance followed by a Student-Newman-Keuls test. Control baseline values for any of the two groups were compared by a two-tailed unpaired t test. The changes in body weight, in plasma urea nitrogen, in plasma creatinine, and in mean furosemide dose between the times the control and 1 month values were obtained in patients on either drug were compared by a two-tailed paired t test.

**Results**

Only the 46 patients that underwent long-term study are considered in the results. Of the excluded patients, one belonged to each of the four subgroups described later so that any effects of their exclusion were distributed evenly. Values for all variables, hemodynamic, renal, neurohormonal, and others, are the means of the measurements at baseline, and 1, 2, 3, 4, and 5 hr during each water load procedure. The water load of 15 ml/kg had little hemodynamic effect; cardiac index did not change and pulmonary capillary wedge pressure increased an average of only 2 mm Hg at the end of the 1 hr water load. However, by 1 hr, the water load was sufficient to decrease plasma effective osmolality from 268 ± 7 to 257 ± 8 mOsm/kg H2O (p<.001), and to decrease plasma level of arginine-vasopressin from 2.8 ± 3.1 to 1.2 ± 1.3 pg/ml (p<.001). Normal individuals excrete at least 80% of a 15 ml/kg water load over the next 5 hr.

**Characteristics of the entire group.** As a whole, the patients chosen for the study had severe heart failure and compensatory neurohumoral stimulation (table 1). They had slight hyponatremia and renal impairment but had moderate urinary sodium and water excretion abnormalities.

**Patients with high renin vs those with lower renin.** Patients were classified according to control renin values. Patients with plasma renin activities of less than 2.5 ng/ml/hr were arbitrarily classified as having lower renin levels, while patients with values greater than 2.5 ng/ml/hr were classified as having higher renin levels.

Patients with higher renin tended to have more severe heart failure than those with lower renin (table 1): pulmonary capillary wedge pressure was higher while stroke work index, plasma osmolality, and plasma sodium concentration were lower in the latter group. Also, mean arterial pressure and cardiac index tended to be lower in patients with higher renin levels. As expected, plasma aldosterone was higher in the patients with higher renin levels.

**Captopril vs prazosin.** Captopril produced long-term hemodynamic improvement (table 2) and led to a decrease in neurohumoral overstimulation (figure 1). Cardiac index and stroke work index increased while right atrial pressure, pulmonary capillary wedge pressure, and systemic vascular resistance decreased. Plasma epinephrine, norepinephrine, and aldosterone decreased, but mean plasma arginine-vasopressin did not. As expected, plasma renin activity increased, but this increase was less after 1 month. The hemodynamic and neurohumoral changes caused by captopril led to improved renal function (figure 2). Water excretion, sodium excretion, creatinine clearance, and osmolar clearance all increased while minimal urine osmolality decreased.

Prazosin caused long-term hemodynamic improvement (table 2) but had no neurohumoral effects (figure 1) and few renal effects (figure 2). Cardiac index in-
TABLE 1
Hemodynamic, neurohumoral, and renal characteristics of patients with higher and lower renin levels

<table>
<thead>
<tr>
<th></th>
<th>Entire group (n = 46)</th>
<th>Higher renin group (n = 24)</th>
<th>Lower renin group (n = 22)</th>
<th>p value (higher vs lower renin group)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>83 ± 13</td>
<td>82 ± 14</td>
<td>84 ± 12</td>
<td>NS</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>89 ± 9</td>
<td>86 ± 8</td>
<td>92 ± 10</td>
<td>p &lt; .1</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>27 ± 7</td>
<td>29 ± 7</td>
<td>25 ± 8</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>12 ± 5</td>
<td>12 ± 5</td>
<td>11 ± 5</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac index (/min/m²)</td>
<td>2.1 ± 0.4</td>
<td>1.9 ± 0.4</td>
<td>2.2 ± 0.5</td>
<td>p &lt; .1</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g-m/m²)</td>
<td>8 ± 9</td>
<td>19 ± 9</td>
<td>25 ± 10</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne·sec·cm⁻²)</td>
<td>1858 ± 468</td>
<td>1853 ± 429</td>
<td>1863 ± 591</td>
<td>NS</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>4 ± 3</td>
<td>6 ± 3</td>
<td>2 ± 1</td>
<td>^A</td>
</tr>
<tr>
<td>PA (ng/dl)</td>
<td>55 ± 64</td>
<td>73 ± 56</td>
<td>35 ± 35</td>
<td>^</td>
</tr>
<tr>
<td>Arginine vasopressin (pg/ml)</td>
<td>1.6 ± 1.4</td>
<td>1.8 ± 1.5</td>
<td>1.3 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Norepinephrine (pg/ml)</td>
<td>561 ± 260</td>
<td>597 ± 263</td>
<td>523 ± 258</td>
<td>NS</td>
</tr>
<tr>
<td>Epinephrine (pg/ml)</td>
<td>89 ± 66</td>
<td>94 ± 53</td>
<td>84 ± 85</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min/1.73 m²)</td>
<td>66 ± 31</td>
<td>66 ± 25</td>
<td>67 ± 36</td>
<td>NS</td>
</tr>
<tr>
<td>% H₂O excreted (%)</td>
<td>51 ± 28</td>
<td>45 ± 27</td>
<td>57 ± 30</td>
<td>NS</td>
</tr>
<tr>
<td>Urinary sodium excreted (meq/5 hr)</td>
<td>9 ± 9</td>
<td>7 ± 9</td>
<td>11 ± 10</td>
<td>NS</td>
</tr>
<tr>
<td>Basal plasma sodium (meq/l)</td>
<td>135.9 ± 4.0</td>
<td>134.8 ± 5.0</td>
<td>137.2 ± 2.8</td>
<td>p &lt; .05</td>
</tr>
<tr>
<td>Basal effective plasma osmolality (mOsm/kg H₂O)</td>
<td>267.5 ± 6.2</td>
<td>264.8 ± 7.8</td>
<td>270.3 ± 4.4</td>
<td>p &lt; .01</td>
</tr>
<tr>
<td>Minimal urinary osmolality (mOsm/kg H₂O)</td>
<td>276 ± 154</td>
<td>295 ± 161</td>
<td>255 ± 145</td>
<td>NS</td>
</tr>
<tr>
<td>Osmol clearance (ml/min)</td>
<td>1.8 ± 0.7</td>
<td>1.7 ± 0.8</td>
<td>1.8 ± 0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

^ABy definition plasma renin and aldosterone values were lower in the low renin group (lower renin ≤ 2.5 ng/ml/hr, higher renin > 2.5 ng/ml/hr).

creased while pulmonary capillary wedge pressure and systemic vascular resistance decreased. An increase in water excretion was prazosin’s only other long-term effect.

The effects of captopril and prazosin on plasma sodium, arginine-vasopressin, and water excretion during the day 2 study are difficult to interpret because plasma sodium and plasma osmolality had decreased in the patients receiving captopril and tended to decrease in the patients receiving prazosin (table 2). A decrease in these variables may have contributed to the decrease in plasma arginine-vasopressin and to the de-

TABLE 2
Changes in hemodynamics and determinants of water excretion with prazosin and captopril

<table>
<thead>
<tr>
<th></th>
<th>Prazosin</th>
<th>Captopril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Day 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>85 ± 12</td>
<td>86 ± 11</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>88 ± 9</td>
<td>82 ± 11B</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>28 ± 7</td>
<td>25 ± 7A</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>11 ± 5</td>
<td>11 ± 4</td>
</tr>
<tr>
<td>Cardiac index (/min/m²)</td>
<td>2.0 ± 0.5</td>
<td>2.3 ± 0.5B</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g·m/m²)</td>
<td>22 ± 9</td>
<td>22 ± 8</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne·sec·cm⁻²)</td>
<td>1965 ± 609</td>
<td>1544 ± 385B</td>
</tr>
<tr>
<td>Plasma sodium (meq/l)</td>
<td>135.5 ± 4.1</td>
<td>134.9 ± 3.5</td>
</tr>
<tr>
<td>Basal effective plasma osmolality (mOsm/kg H₂O)</td>
<td>266 ± 6</td>
<td>266 ± 7</td>
</tr>
</tbody>
</table>

Values are mean ± SD.

^p < .05; ^p < .005 vs control; ^p < .05 1 month vs day 2.
with lower renin had a decrease in pulmonary capillary wedge pressure and only patients with higher renin had increased right atrial pressure. Patients with lower renin had decreased plasma epinephrine while those with higher renin had increased plasma norepinephrine. Only patients with lower renin levels had increased water excretion and decreased daily furosemide requirements.

The decrease in plasma arginine-vasopressin and in minimal urine osmolality that was observed in patients with lower renin (figure 4) was independent of the type of vasodilator used, occurring with both captopril and prazosin.

**Figure 1.** Captopril decreased most aspects of neurohumoral overstimulation while prazosin did not. These differences were even more marked after 1 month of therapy. * p < .05; ** p < .005 vs control; † p < .05; †† p < .005 for 1 month vs day 2. Values are mean ± SE.

**Figure 2.** Captopril improved renal function, increasing creatinine clearance, osmolal clearance, and water and sodium excretion. Prazosin had no effect. * p < .05; ** p < .005 vs control; † p < .05; †† p < .005 1 month vs day 2. Values are mean ± SE. High renin group had renin values greater than 2.5 ng/ml/hr.
prazosin. Patients with higher renins had no long-term change in plasma arginine-vasopressin or in minimal urine osmolality with either vasodilator.

Discussion

This study demonstrates (1) that captopril produces long-term beneficial renal and neurohumoral effects that prazosin does not despite the fact that they cause similar hemodynamic improvement, (2) that these changes are at least partially dependent on the initial neurohumoral and hemodynamic status of the patients, (3) that these renal and neurohumoral changes are even greater after 1 month of continuous therapy, (4) that through hemodynamic improvement vasodilators may chronically interrupt vasopressin overstimulation, and (5) that the initial state of stimulation of the renin-angiotensin system could be used to individualize therapy in patients with severe congestive heart failure.

The long-term efficacy of vasodilators has been assessed in a number of ways, including clinical status,1,2 hemodynamic effects1,2 neurohumoral effects,2 and changes in exercise tolerance,15 but not all of these parameters change in a similar way in a given patient. For example, Massie et al.16 found a poor correlation between hemodynamic changes with captopril and changes in exercise tolerance, and in our study we found that patients with higher renin levels had a loss of some of the initial beneficial effects of prazosin, and in some cases even a worsening with respect to some of the parameters measured, despite persistent improvement in some hemodynamic parameters. For this reason, for the purpose of this discussion, we will not use an arbitrary hemodynamic definition of tachyphylaxis but will consider tachyphylaxis as having occurred when some of the initial beneficial effects of a drug has been lost.

Higher renin levels, lower renin levels, and long-term effects of vasodilators. In this study, the differential response of patients with higher and lower renin levels to the addition of prazosin illustrates the importance of
TABLE 3
Changes in hemodynamics and determinants of water excretion in patients with higher and lower renin levels

<table>
<thead>
<tr>
<th></th>
<th>Lower renin</th>
<th>Higher renin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>Day 2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>84 ± 12</td>
<td>88 ± 11</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>89 ± 11</td>
<td>82 ± 12⁺</td>
</tr>
<tr>
<td>Pulmonary capillary wedge pressure (mm Hg)</td>
<td>25 ± 8</td>
<td>23 ± 8</td>
</tr>
<tr>
<td>Right atrial pressure (mm Hg)</td>
<td>10 ± 5</td>
<td>10 ± 5</td>
</tr>
<tr>
<td>Cardiac index (l/min/m²)</td>
<td>2.1 ± 0.6</td>
<td>2.4 ± 0.5⁺</td>
</tr>
<tr>
<td>Left ventricular stroke work index (g-m/m²)</td>
<td>23 ± 12</td>
<td>23 ± 12</td>
</tr>
<tr>
<td>Systemic vascular resistance (dyne-sec-cm⁻¹)</td>
<td>1966 ± 742</td>
<td>1487 ± 394b</td>
</tr>
<tr>
<td>Plasma sodium (meq/l)</td>
<td>137.0 ± 2.4</td>
<td>136.9 ± 2.2</td>
</tr>
<tr>
<td>Basal effective plasma osmolality (mOsm/kg H₂O)</td>
<td>269 ± 5</td>
<td>269 ± 6</td>
</tr>
</tbody>
</table>

Values are mean ± SD.
⁺p < .05; ⁸p < .005 vs control; ｃp < .05; ｂp < .005 1 month vs day 2.

the initial neurohumoral and hemodynamic status of patients with congestive heart failure on the choice of a specific vasodilator. In the patients with lower renin, the hemodynamic effects of prazosin were maintained over the long term and were sufficient to lead to a long-term decrease in some aspects of neurohumoral overstimulation and were sufficient to improve water excretion. However, in the sicker patients with higher

PRAZOSIN

CAPTOPRIL

FIGURE 4. Captopril increased sodium and water excretion in patients with higher and lower renin. However, this occurred with a decrease in minimal urinary osmolality in patients with higher renin. Prazosin increased water excretion and decreased minimal urinary osmolality in the lower renin group, but had no effect in the higher renin group. * p < .05; ** p < .005 vs control; † p < .05; ‡ p < .005 for 1 month vs day 2. Values are mean ± SE.
TABLE 3 (Continued)

<table>
<thead>
<tr>
<th></th>
<th>Captopril</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower renin</td>
<td>Higher renin</td>
</tr>
<tr>
<td>Control</td>
<td>Day 2</td>
<td>1 month</td>
</tr>
<tr>
<td>84 ± 13</td>
<td>84 ± 12</td>
<td>79 ± 8*</td>
</tr>
<tr>
<td>93 ± 8</td>
<td>84 ± 12*</td>
<td>87 ± 10*</td>
</tr>
<tr>
<td>26 ± 7</td>
<td>23 ± 8*</td>
<td>22 ± 5*</td>
</tr>
<tr>
<td>12 ± 5</td>
<td>12 ± 5</td>
<td>9 ± 3*</td>
</tr>
<tr>
<td>2.2 ± 0.7</td>
<td>2.3 ± 0.5</td>
<td>2.4 ± 0.5</td>
</tr>
<tr>
<td>25 ± 10</td>
<td>24 ± 8</td>
<td>28 ± 9*</td>
</tr>
<tr>
<td>1761 ± 368</td>
<td>1582 ± 341*</td>
<td>1595 ± 339*</td>
</tr>
<tr>
<td>137.4 ± 3.3</td>
<td>135.7 ± 4.1</td>
<td>137.4 ± 3.7</td>
</tr>
<tr>
<td>272 ± 6</td>
<td>266 ± 10*</td>
<td>270 ± 7C</td>
</tr>
</tbody>
</table>

Because of a decrease in arterial pressure. The controversy as to whether prazosin causes long-term beneficial hemodynamic changes in patients with congestive heart failure has not been settled by this study. However, because patients with higher and lower renin had such different long-term responses to vasodilators, it may be that differences in patient populations and the concomitant use of spironolactone in some studies may at least partially explain why some investigators have

FIGURE 5. Both vasodilators decreased the furosemide requirements of patients with lower renin but only captopril decreased the furosemide requirements of patients with higher levels. Only captopril decreased plasma creatinine. *p < .05; **p < .005 for 1 month vs control. Values are mean ± SE.
demonstrated long-term beneficial effects while others have not. 17-23 Because cross-tolerance from one vasodilator to another does not always occur, mechanisms other than neurohormonal overstimulation must also be involved in the production of tachyphylaxis to vasodilators.

The superior effects of captopril as compared with prazosin on renal function are consistent with previous studies and are probably mostly the result of the important adverse intrarenal effects of angiotensin II recently described by Ichikawa et al. 24 Our results are compatible with their findings, but because in our study these changes occurred while both vasodilators were causing similar hemodynamic changes, our results further underline the importance of the intrarenal effects of angiotensin II blockade on renal function. Another factor that may have contributed to the differences that we found between the two drugs is changes in renal blood flow. Captopril has been shown to improve renal blood flow in patients with congestive heart failure, 25, 26 while prazosin has been shown to have little effect on renal blood flow in these patients. 27

Captopril increased sodium excretion while prazosin did not. Our results suggest that although the decrease in aldosterone caused by captopril certainly contributed to improved sodium excretion, this was not the major mechanism, since sodium excretion only increased between the day 2 and 1 month studies, a period during which the aldosterone level did not change. The major reason for increased sodium excretion with captopril was probably intrarenal and the result of (1) decreased effect of angiotensin II on the kidney, 24 (2) decreased proximal tubular reabsorption of sodium because of decreased sympathetic outflow, 28 and (3) unmeasured factors such as local changes in levels of kinins or prostaglandins. 29 Increased sodium excretion and increased osmolar clearance may have led to passive water excretion in patients receiving captopril and may help explain why the patients with higher renin receiving captopril had increased water excretion without a change in plasma vasopressin or minimal urine osmolalities.

As a whole, the effects of captopril were even more beneficial after 1 month of therapy than after 2 days of therapy. Most of these beneficial effects were due to delayed improvement in the patients with lower renin, but certain variables, such as stroke work index and sodium excretion, increased only after 1 month of therapy in both higher and lower renin groups. These results suggest that captopril not only blocks reflex increases in the renin-angiotensin system, but may also have important actions on other systems, the full effects of which can only be appreciated over the long term. One possible mechanism may be the result of the prolonged decrease in sympathetic tone caused by captopril. If, as proposed by Cohn et al. 30 continuous sympathetic overstimulation is harmful to already energy-depleted failing myocardium, 31 then the decrease in circulating catecholamines caused by captopril may lead to long-term improvements in myocardial function. Certainly, the long-term beneficial hemodynamic effects of β-blockers in patients with congestive cardiomyopathy supports this concept. 32 Changes in levels of kinins, prostaglandins, or other substances with important local and systemic effects that are known to be directly or indirectly affected by angiotensin II could be other mechanisms by which a delayed beneficial effect of captopril may be explained. 29, 33

**Vasopressin and the long-term effects of vasodilators.** Our study confirms that vasopressin is elevated in patients with congestive heart failure 6, 34 and is an important determinant of water excretion, but it also indicates that intrarenal factors are important.

In patients with lower renin activity receiving either prazosin or captopril, improvements in cardiac hemodynamics were accompanied by a significant decrease in arginine-vasopressin, by a decrease in minimal urine osmolality, and by an increase in water excretion. These changes occurred despite the lack of change in plasma sodium, in plasma osmolality, or in osmolar clearance, and despite a decrease in arterial pressure, right atrial pressure, and in pulmonary capillary wedge pressure. These changes suggest that resetting of the osmostat may have occurred due to the unloading of specific ventricular receptors important in the nonosmotic stimulation of vasopressin. 35-37

In patients with higher renin, levels of arginine-vasopressin did not decrease after 1 month of therapy. However, water excretion increased in patients receiving captopril, suggesting that intrarenal factors also play an important role in controlling water balance in these patients. Why arginine-vasopressin was suppressed over the long term only in the lower renin group remains speculative, but because patients with higher renin tend to have more severe heart failure it could be that the long-term hemodynamic improvement caused by vasodilators in these patients was insufficient to adequately correct the factors leading to increased arginine-vasopressin release. However, the hemodynamic improvement may have been sufficient to chronically reset the osmostat, with plasma arginine-vasopressin remaining constant in these patients despite a decrease in arterial pressure and no change in plasma sodiums or in plasma osmolalities. 35
Recent studies suggest that in hyponatremic patients with congestive heart failure receiving furosemide and captopril, plasma sodium tends to normalize while in those receiving other vasodilators it does not.26, 38 Dzau and Hollenberg found that these differences were only apparent when furosemide was given with a vasodilator, suggesting that a synergistic effect occurred between furosemide and captopril.26 Our results are consistent with these findings because when diuretics were withheld, both drugs led to improved water excretion, and minimal urine osmolality was less dependent on the choice of vasodilator than on the initial hemodynamic and neurohumoral profile of the patient. Considering the marked beneficial renal effects of angiotensin II blockade on renal function, improved renal homeostasis with captopril is the most likely cause of the advantage of the administration of captopril instead of another vasodilator along with furosemide to patients with congestive heart failure and hyponatremia. Our long-term study suggests that in therapeutic doses, captopril has little or no direct effect on plasma arginine-vasopressin levels of patients with congestive heart failure. In summary, the results of this study indicate that despite causing similar hemodynamic changes, the vasodilators captopril and prazosin cause significantly different renal and neurohumoral changes; captopril normalizes overstimulated compensatory mechanisms to a greater extent than prazosin. These differences were particularly evident in patients with severe heart failure and markedly stimulated renin-angiotensin systems. The direct and indirect neurohumoral effects of captopril may be one of the reasons less tachyphylaxis occurs with captopril as compared with other vasodilators.

We thank Drs. Jacques Durr and Marshall Lindeimer for their generous gift of antiserum 2849. We are grateful to Dr Julien Marc-Aurèlle for his support during the completion of this study and we thank Nicole Ruel for expert technical assistance, Diane Abastado for secretarial expertise, and the Coronary Care Unit staff and Ginette Gaudette, R.N., for their assistance in the care of our patients.

References

30. Cohn JN, Levine B, Oliviari MT, Garberg V, Lura D, Francis GS,
Differential long-term intrarenal and neurohormonal effects of captopril and prazosin in patients with chronic congestive heart failure: importance of initial plasma renin activity.

B Mettauer, J L Rouleau, D Bichet, C Kortas, C Manzini, G Tremblay and K Chatterjee

_Circulation_. 1986;73:492-502
doi: 10.1161/01.CIR.73.3.492

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 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/73/3/492

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/