Effects of Eprosartan on Renal Function and Cardiac Hypertrophy in Rats With Experimental Heart Failure

Sergey Brodsky, Konstantin Gurbanov, Zaid Abassi, Aaron Hoffman, Robert R. Ruffolo, Jr, Giora Z. Feuerstein, Joseph Winaver

Abstract—Activation of the renin-angiotensin system may contribute to the derangement in renal and cardiac function in congestive heart failure. The present study evaluated the effects of eprosartan, a selective angiotensin II receptor antagonist, on renal hemodynamic and excretory parameters and on the development of cardiac hypertrophy in rats with aortocaval fistula, an experimental model of congestive heart failure. Infusion of eprosartan (1.0 mg/kg) in rats with aortocaval fistula produced a significant increase (+34%) in total renal blood flow and a sustained decrease (−33%) in the calculated renal vascular resistance. These effects on renal hemodynamics were more pronounced than those observed in sham-operated control rats and occurred despite a significant fall (−12%) in mean arterial blood pressure. Moreover, eprosartan caused a preferential increase in renal cortical blood perfusion and significantly increased glomerular filtration in rats with congestive heart failure. Chronic administration of eprosartan (5.0 mg/kg per day for 7 days through osmotic minipumps inserted intraperitoneally on the day of operation) resulted in a significant enhancement of urinary sodium excretion compared with nontreated rats with heart failure. Moreover, administration of eprosartan to salt-retaining rats with congestive heart failure resulted in a progressive increase and ultimate recovery in urinary sodium excretion. Finally, early treatment with eprosartan blocked the development of cardiac hypertrophy in rats with aortocaval fistula to a larger extent than the angiotensin-converting enzyme inhibitor enalapril. These findings emphasize the importance of angiotensin II in mediating the impairment in renal function and induction of cardiac hypertrophy in heart failure and further suggest that angiotensin II receptor blockade may be a useful treatment of these consequences in severe cardiac failure. (Hypertension. 1998;32:746-752.)

Key Words: angiotensin II ■ angiotensin antagonist ■ fistula, aortocaval ■ hypertrophy ■ renal circulation ■ hemodynamics ■ rats

Activation of the renin-angiotensin-aldosterone system (RAAS) is considered an important reaction and one of the earliest compensatory neurohumoral responses to the decrease in pumping capacity of the failing myocardium in congestive heart failure (CHF).1–3 Although this mechanism may prove to be beneficial in the early stages of CHF, continuous activation of the system may become detrimental to cardiac and renal function.4 Angiotensin II (Ang II) plays a major role in this maladaptive response by promoting systemic vasoconstriction and increasing the abnormal loading conditions in the failing heart. In addition, Ang II, by virtue of its growth-promoting properties, may contribute to the development of cardiac hypertrophy as a result of a direct action on cardiac myocytes.5 Numerous studies have also indicated that activation of the RAAS is involved in mediating the deranged renal function in heart failure.6,7 The kidney appears to be uniquely sensitive to the vasoconstrictor action of Ang II, mainly in the efferent and afferent arterioles as well as on glomerular mesangial cells.8 In addition, Ang II increases tubular reabsorption of sodium, both by direct action on the nephron and by augmenting aldosterone release.9 The resultant renal hypoperfusion and the avid salt and water retention by the kidney may promote circulatory congestion and edema formation, which imposes a further circulatory overload on the failing myocardium. On the basis of these maladaptive responses of Ang II, one can envision that blocking the formation of the peptide may improve myocardial function in CHF. Indeed, angiotensin-converting enzyme (ACE) inhibitors have revolutionized the clinical approach to patients with CHF, and the efficacy of these agents in improving cardiac performance and increasing life expectancy in severe heart failure is well established.10–13 However, it is also known that some of the cardiovascular effects of ACE inhibitors are mediated through their action on the kinin system, since they can be blocked by concomitant administration of bradykinin antagonists.14,15 Thus, other mechanisms not related directly to Ang II blockade may contribute to the beneficial actions of these drugs in heart failure.
The recent advancements in identification and cloning of the Ang II receptor subtypes AT\textsubscript{1} and AT\textsubscript{2} and the understanding that physiological actions of Ang II are mediated largely through activation of the AT\textsubscript{1} receptor subtype have prompted the development of highly selective nonpeptide AT\textsubscript{1} receptor antagonists.\textsuperscript{16,17} These potent agents, of which losartan (DuP 753) was the first to be studied, are of importance as research tools to probe the specific contribution of Ang II to the pathophysiological evolution of CHF, as well as novel therapeutic alternatives to ACE inhibitors. Initial studies with losartan in patients and experimental models of CHF have indicated a beneficial effect of this AT\textsubscript{1} receptor antagonist in augmenting cardiac index and reducing left ventricular preload, systemic vascular resistance, and pulmonary capillary pressure.\textsuperscript{18–21} However, there is a clear paucity of information on the effects of the drug on the kidney, since only limited data are available on the renal actions of this class of drugs in experimental and neurohormonal CHF.\textsuperscript{22–24}

In the present study we evaluated the effects of eprosartan, a nonbiphenyl tetrazole Ang II antagonist with potent renal vasodilatory activity,\textsuperscript{25,26} in rats with aortocaval (A-V) fistula, an experimental model of CHF. Previously, we demonstrated that this model is characterized by renal manifestations and neurohumoral changes that closely mimic those observed in patients with severe CHF.\textsuperscript{6,27,28} Moreover, we have shown that renal retention of salt and water in this experimental model is largely dependent on the degree of activation of the RAAS.\textsuperscript{6} In addition, rats with A-V fistula develop severe eccentric cardiac hypertrophy as a result of volume overload.\textsuperscript{27,29,30} In view of these characteristics, it was of interest to study the effects of eprosartan on renal function and cardiac hypertrophy in this experimental model of heart failure.

**Methods**

Experiments were conducted on a local strain of male Wistar rats weighing 280 to 380 g that were maintained on a standard rat diet (containing 0.5% to 0.6% NaCl) and water ad libitum. CHF was induced by creating an arteriovenous fistula between the abdominal aorta and inferior vena cava according to the method of Stumpe et al.,\textsuperscript{21} as adapted in our laboratory.\textsuperscript{6,27,28} In short, the abdominal aorta and inferior vena cava were exposed through a midabdominal incision under halothane anesthesia, and an anastomosis was surgically created in the common wall of the 2 vessels (1.0 to 1.2 mm OD, side to side). After surgery, the animals were allowed to recover and were then transferred into individual metabolic cages for daily measurements of urinary sodium and water excretion. Sham-operated rats served as controls.

**Acute Studies**

Six to 7 days after the operation, rats were anesthetized by intraperitoneal injection of thiothribut arterial (Inactin) (100 mg/kg, RBI), placed on a thermoregulated table (37°C), and prepared for hemodynamic and renal clearance measurements.\textsuperscript{6,28} After tracheotomy, polyethylene tubes (PE-50) were inserted into the left carotid artery and right jugular vein for blood pressure monitoring, blood sampling, and infusion of the various solutions. The urinary bladder was then catheterized by PE-50 through a suprapubic incision for timed urine collections. A solution of 0.9% saline was infused intravenously by a syringe pump, at a rate equal to 1.0% to 1.5% of body weight per hour, throughout the experiment. After a 60-minute equilibration period, the following experimental protocols were performed.

**Effects of Eprosartan on Renal Hemodynamics and Mean Arterial Pressure**

Measurements of total renal blood flow (RBF) were performed by an ultrasonic flowmeter (model T026, Transonic Corp) with the use of an ultrasonic flow probe (type 1R8) placed around the midpoint of the left renal artery, as previously described.\textsuperscript{39} Arterial blood pressure was continuously monitored with a pressure transducer (model 156PC05GWL, Microswitch) connected to the arterial line. Data of RBF and mean arterial pressure (MAP) were continuously recorded by a computerized data acquisition system with the use of Labtech Notebook software. Renal vascular resistance (RVR) was calculated by the standard formula (RVR=MAP/RBF). In preliminary experiments we evaluated the effects of incremental doses of the drug (0.3, 1.0, and 3.0 mg/kg) on MAP and RBF in rats with CHF. On the basis of these experiments, the dose of 1.0 mg/kg was chosen for assessment in the present study. After surgery and equilibration, baseline measurements were obtained for 30 minutes. Eprosartan, dissolved in 20%/80% ethanol/saline mixture, was then injected intravenously at a dose of 1.0 mg/kg over a 5-minute period to control (n=6) and CHF (n=6) rats. Hemodynamic recordings were obtained for an additional 60 minutes after administration of the drug.

**Effects of Eprosartan on Renal Regional Blood Flow**

For measurements of renal regional blood flow, the left kidney was exposed in control (n=6) and CHF rats (n=6) and placed in a Plexiglas holder with warm mineral oil (37°C) poured on the surface of the kidney at frequent intervals. Cortical and medullary blood flow (CBF and MBF, respectively) were measured simultaneously by laser-Doppler flowmetry with a dual-channel flowmeter (model 4001, Master Perimed AB) with 2 needle probes (Periflux 411), as previously described.\textsuperscript{39} Calibrated probes were placed perpendicular to the surface of the cortex and inserted into the outer medulla at a depth of 4 to 5 mm. Recordings of 30 seconds were obtained at 5-minute intervals during the baseline period. Eprosartan was then administered as described in the previous protocol, followed by 2 minutes of continuous recordings and then at 5-minute intervals for an additional 60 minutes. Regional blood flow was calculated in perfusion units (PU) by multiplying the velocity by the concentration of the moving blood cells and expressed as percent change from baseline value.

**Effects of Eprosartan on Renal Clearance Parameters**

To evaluate the acute effects of the drug on glomerular filtration rate (GFR) and urinary sodium excretion, additional groups of control (n=7) and CHF (n=7) rats were prepared as described in previous protocols, with the exception that the abdominal cavity was not opened. A solution of 2% inulin in 0.9% saline was continuously infused throughout the experiment. After surgery and equilibration, 2 baseline periods of 30 minutes each were obtained. Eprosartan was then administered intravenously, followed by 3 additional clearance collections. Urine was collected into preweighed tubes, and urine volume was determined gravimetrically. Blood samples (0.3 mL) were obtained between each 2 clearance periods and at the end of the experiment. Plasma was separated by centrifugation and kept at 4°C until assayed for inulin and electrolytes.

**Chronic Studies**

These studies were designed to evaluate the effects of long-term administration (7 days) of eprosartan through osmotic minipumps (model 2001, Alzet Pharmaceutical) on urinary sodium excretion and on the development of cardiac hypertrophy in rats with experimental heart failure. Eprosartan was dissolved in a solution of 5% sodium bicarbonate (80 mg/mL) and adjusted to a final concentration sufficient to deliver 5 mg/kg per day for 7 days, according to the specifications of the manufacturer.

**Effects of Eprosartan on Daily Sodium Excretion**

Two experimental approaches were used. In the first approach (early treatment protocol), osmotic minipumps containing either eprosartan (n=8 experiments) or vehicle (n=6 experiments) were implanted...
into the peritoneal cavity during the creation of the A-V fistula. Rats with sham operation treated with eprosartan served as a control (n=5). After the operation the animals were transferred into metabolic cages, and daily measurements of urinary sodium excretion were performed for 7 days.

In the second approach (late treatment protocol), a preselected group of rats with decompensated heart failure and avid sodium retention was subjected to eprosartan treatment. In these rats (n=8), daily sodium excretion in the first 6 postoperative days was <100 μmol/24 hours. Previously, we reported that this subgroup develops symptoms of severe congestion and usually succumbs to eprosartan treatment. In these rats (n=8), daily sodium excretion in the first 6 postoperative days was <100 μmol/24 hours. Previously, we reported that this subgroup develops symptoms of severe congestion and usually succumbs to eprosartan treatment.

**Effects of Eprosartan on Cardiac Hypertrophy: Comparison With ACE Inhibition**

After the completion of the 7 days of eprosartan treatment, animals from the early and late treatment protocols were killed by decapitation. Their chest was opened and the heart was removed instantaneously, placed on absorbent paper to remove excess of blood, and then weighed to calculate the heart/body weight ratio. Sham-operated control animals (n=6) served as control. To compare the effect of eprosartan to that of ACE inhibition, an additional group of rats with A-V fistula (n=7) was studied. In these rats, the ACE inhibitor enalapril (Merck & Co) was added to the drinking water on the day of operation, at a dose of 100 mg/L, and continued for 7 additional days. In preliminary experiments, we found that treatment with this dose for 3 days was sufficient to block the hypertensive and renal vasoconstrictor effects of bolus injections of angiotensin I, in a dose range of 100 to 300 ng/kg (data not shown).

**Chemical Analysis**

Concentrations of inulin in plasma and in the urine were measured by the anthrone method. Sodium concentration in plasma and urine was determined by flame photometry (model IL 943, Instrumentation Laboratories).

**Statistical Analysis**

One-way ANOVA was used for group comparisons and repeated-measures ANOVA for comparison of treatment values with baseline values in each group. The Tukey or Dunnett test was used for post-ANOVA evaluation, as appropriate. For comparison of the graphs representing control and experimental groups, 2-way ANOVA was used. A value of P<0.05 was considered statistically significant. Data are expressed as mean±SEM.

**Results**

**Acute Studies**

**Dose-Response Relationships of Eprosartan on MAP and RBF**

Table 1 summarizes the data on the effects of incremental doses of eprosartan on MAP and RBF in rats with A-V fistula. As shown, eprosartan produced a dose-related decrease in MAP and an increase in RBF when administered at doses of 0.3 and 1.0 mg/kg. In the higher dose of 3.0 mg/kg, the drug induced a marked hypotensive response and no increase in RBF. On the basis of these observations, the dose of 1.0 mg/kg was chosen in the protocols of the acute studies.

**Effects of Eprosartan on Renal and Intrarenal Hemodynamics**

Figures 1 and 2 summarize the data on the acute effects of eprosartan on renal hemodynamics and intrarenal distribution of blood flow in rats with CHF and control animals. Rats with CHF had a significantly lower MAP than control animals (CHF: 111±7 mm Hg; control: 128±3 mm Hg; P<0.05), and infusion of eprosartan resulted in a further reduction in MAP in both groups. Baseline RBF was lower in CHF rats (1.4±0.1 mL/min per 100 g body wt) than in controls (2.8±0.2 mL/min per 100 g body wt; P<0.001). Likewise, RVR was higher in rats with CHF than in controls (CHF: 26.5±5.21 resistance units; control: 15.8±0.7 resistance units; P<0.001). Administration of the drug resulted in a significant increase in RBF in both control rats (from 2.8 to 3.6 mL/min per 100 g body wt; P<0.05) and rats with CHF (from 1.4 to 1.9 mL/min per 100 g body wt; P<0.01). Moreover, when calculated as percent change from baseline value, the increase in RBF in rats with CHF was of a significantly higher magnitude and of longer duration than that observed in control animals (Figure 1). Likewise, eprosartan caused a
more prominent and sustained reduction in RVR in rats with CHF than in control animals (Figure 1, bottom panel). Thus, the effects of the Ang II receptor antagonist on renal hemodynamics were more pronounced and more sustained in rats with CHF and occurred despite a further decrease in MAP (\(\sim -12\%\)) after administration of the drug.

The beneficial effects of eprosartan on RBF and RVR are also reflected in Figure 2, which depicts the alterations in the intrarenal distribution of blood flow as evaluated by laser-Doppler flowmetry. As shown, eprosartan caused a marked and sustained increase in cortical perfusion (\(\sim +28\%\), peak response) in rats with CHF compared with a significantly lower (\(\sim +17\%\)) and more transient response observed in sham-operated controls (Figure 2, top panel). In contrast, in the medulla the drug produced similar changes in blood perfusion in both groups, which were not statistically different from baseline values (Figure 2, bottom panel). These findings suggest that Ang II blockade caused a preferential increase in CBF and improved cortical perfusion in rats with heart failure.

**Effects of Eprosartan on Renal Clearance Parameters**

The acute effects of eprosartan on GFR and sodium excretion are summarized in Table 2. As reported previously,\(^2,7\) baseline GFR was significantly lower in rats with CHF than in control animals (CHF: 0.88±0.13 mL/min; control: 1.79±0.17 mL/min; \(P<0.05\)). After eprosartan, GFR increased significantly in CHF rats (from 0.88±0.13 to 1.62±0.27 mL/min; \(P<0.05\)) but not in control rats (Table 2). Likewise, baseline value of fractional sodium excretion was significantly reduced in rats with CHF (control: 0.63±0.21%; CHF: 0.16±0.06%; \(P<0.05\)). Administration of eprosartan resulted in a significant increase in sodium excretion in control animals but not in rats with CHF (Table 2).

**Chronic Studies**

**Effects of Eprosartan on Daily Sodium Excretion**

Figure 3A summarizes the data on the effects of chronic administration of eprosartan on urinary sodium excretion in control and CHF rats in which an osmotic minipump, containing either the drug or vehicle, was inserted intraperitoneally.

**Figure 2.** Effects of eprosartan on renal CBF (top) and MBF (bottom) in control group (■) and in CHF rats (●). Data are expressed as percent change from baseline value. *Statistically significant compared with baseline value in the same group.

**Figure 3.** A, Effects of chronic eprosartan (Epro) administration on daily urinary sodium excretion in rats with experimental heart failure. Hatched area represents the averaged daily sodium excretion in the last 3 days before operation (baseline period). Lines representing the eprosartan-treated and vehicle-treated groups of rats with A-V fistula are significantly different (by 2-way ANOVA). B, Effect of chronic administration of eprosartan on urinary sodium excretion in rats with decompensated heart failure. Data are based on 7 experiments. Eprosartan-loaded minipumps were inserted intraperitoneally on day 6 after creation of the A-V fistula. *Statistically different compared with pretreatment value.

**TABLE 2. Effects of Eprosartan on Renal Clearance Parameters in Control and CHF Rats**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Control</th>
<th>CHF</th>
<th>Control</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1.79±0.17</td>
<td>0.88±0.13†</td>
<td>0.63±0.21</td>
<td>0.16±0.06†</td>
</tr>
<tr>
<td>30</td>
<td>2.14±0.27†</td>
<td>1.28±0.28†</td>
<td>1.13±0.20</td>
<td>0.28±0.13†</td>
</tr>
<tr>
<td>60</td>
<td>2.08±0.20</td>
<td>1.60±0.32‡</td>
<td>1.73±0.35</td>
<td>0.20±0.07‡</td>
</tr>
<tr>
<td>90</td>
<td>1.61±0.13</td>
<td>1.62±0.27*</td>
<td>1.94±0.47*</td>
<td>0.23±0.05†</td>
</tr>
</tbody>
</table>

\(\%E_{\text{Na}}\) indicates percentage of filtered sodium excreted.

*\(P<0.05\) compared with baseline value in the corresponding group.

†\(P<0.05\) compared with the same clearance period in the control group.
Figure 4. Changes in the heart/body weight ratio (expressed as percentage), an index of cardiac hypertrophy, in the various experimental groups. The mean (horizontal line) and individual values are shown in each experimental group. See text for further details. Epro indicates eprosartan.

Effects of Eprosartan on Cardiac Hypertrophy: Comparison With ACE Inhibition

Figure 4 shows the effects of treatment with eprosartan (early and late treatment protocols) and with the ACE inhibitor enalapril on the heart/body weight ratio in rats with experimental CHF. The heart/body weight ratio, an index of cardiac hypertrophy, increased from 0.36 ± 0.01% in control rats to 0.49 ± 0.03% in rats with CHF (P < 0.001). Interestingly, early treatment with eprosartan was highly beneficial in preventing the increase in heart/body weight ratio in rats with CHF (0.36 ± 0.01%; P = NS compared with control animals). In contrast, early treatment with enalapril did not prevent the increase in heart/body weight ratio (0.47 ± 0.03%; P = NS compared with CHF rats without any treatment). Similarly, in rats with CHF in which eprosartan was started 1 week after the A-V fistula operation (late treatment group in Figure 4), the drug did not decrease heart/body weight ratio (0.55 ± 0.01%). Thus, early but not late administration of eprosartan was more effective than ACE inhibition in attenuating the volume overload induced cardiac hypertrophy in rats with A-V fistula.

Discussion

The present study demonstrated that eprosartan, a highly specific, nonpeptide AT\(_1\) receptor antagonist, caused a remarkable improvement in renal function and attenuated the development of cardiac hypertrophy in rats with experimental heart failure. Thus, acute administration of the antagonist resulted in a sustained reduction in RVR associated with a marked increase in total RBF and in renal cortical perfusion. These beneficial actions of eprosartan on renal hemodynamics in rats with CHF were associated with a significant increase in GFR. Moreover, when administered on a chronic basis, eprosartan induced an impressive natriuretic response in rats with decompensated CHF and avid sodium retention. Finally, early treatment with eprosartan was highly effective in preventing the development of cardiac hypertrophy, exceeding that produced by ACE inhibition, in this experimental model of cardiac failure.

The findings of the present study are therefore important in 2 main aspects. First, they lend further support to the concept that Ang II, acting through its AT\(_1\) receptor subtype, plays a major role in the pathogenesis of renal dysfunction and cardiac hypertrophy in heart failure. Second, they provide evidence that direct blockade of the AT\(_1\) receptor may be used as an effective approach to counteract the detrimental actions of Ang II on the kidney and cardiac muscle in heart failure. Thus, this newly developed group of pharmacological blockers may find increasing use in the future as an additional or alternative therapy to the well-characterized ACE inhibitors.

The experimental model used in the present study, rats with A-V fistula, is characterized by several features that closely mimic the pathophysiological consequences of CHF in patients. In particular, this model displays the characteristic neurohumoral activation of heart failure, with increased sympathetic activity, activation of the RAAS, high circulating levels of the atrial natriuretic peptide, and rapid development of severe eccentric cardiac hypertrophy due to volume overload.6,27,30,32 The renal manifestations in this model include marked decrease in RBF with a selective decline in cortical perfusion, decreased GFR, and a tendency to avid retention of salt and water by the kidney that may lead to extracellular volume expansion and edema formation.6,28 Previous studies in these rats, as well as in dogs with A-V fistula, have suggested that the alterations in renal handling of sodium in this model are highly dependent on the increased activity of the RAAS.6,32,35 Indeed, activation of the RAAS is considered to play a major role in the pathogenesis of the deranged renal hemodynamics and augmented tubular sodium reabsorption in CHF.1,8,35 Ang II contributes significantly to the decrease in renal perfusion and the diminished GFR through its vasoconstrictor effect on the efferent and afferent arterioles as well as by promoting mesangial contraction.8 Although Ang II may
be important in maintaining GFR in the initial stages of heart failure; in more advanced states GFR tends to decrease as a result of the Ang II–mediated intense afferent arteriolar vasoconstriction and diminished ultrafiltration coefficient. The findings of the present study demonstrate that removal of the influence of Ang II by eprosartan resulted in a marked improvement in renal hemodynamics and GFR in rats with CHF. Furthermore, as shown by the measurements of renal regional blood flow, eprosartan preferentially increased renal cortical perfusion. This restoration of blood flow to the renal cortex, an area mostly involved in filtration, could be an additional mechanism by which eprosartan caused the elevation in GFR. However, despite this impressive increase in RBF and GFR, acute administration of eprosartan was not associated with a comparable increase in sodium excretion. This could be related to the concomitant decrease in MAP caused by the drug, which apparently counteracted its potential natriuretic action. Indeed, when eprosartan was administered for 7 days through osmotic minipumps, the natriuretic properties of the drug became manifest. The ability of eprosartan to increase sodium excretion in rats with CHF when administered on a chronic basis is apparently due to a combination of several potential mechanisms. These include the favorable action of the drug on renal hemodynamics and GFR, its ability to antagonize the direct action of Ang II on tubular sodium reabsorption, and lastly, the potential effect of the drug on aldosterone secretion. Of interest was the observation that the natriuresis evoked by eprosartan in rats with decompensated CHF became significantly elevated over pretreatment value only on day 4 of treatment and later. Taken together with the lack of natriuretic action in the acute studies, despite the prominent hemodynamic effect of the drug, these findings might suggest that the natriuretic effect of the drug is not related to its action on renal hemodynamics. Rather, the chronic effects of eprosartan could be mediated mainly by antagonizing the action of Ang II on tubular sodium reabsorption or its effect on aldosterone release. However, since plasma levels of the drug were not measured in the present study, we cannot rule out the possibility that this delayed natriuretic response may be related to other factors, eg, delivery of the drug by osmotic minipumps.

Initial reports alluding to the therapeutic benefits of Ang II antagonists in heart failure have dealt primarily with their cardiovascular effects rather than the kidney. Only a few studies have provided data on the renal effects of this class of drugs in this cardiovascular disorder. In a model of ovine heart failure, acute administration of losartan was able to maintain GFR and urinary sodium excretion despite a fall in renal perfusion pressure. Likewise, in dogs with CHF due to rapid atrial pacing, chronic administration of TVC-116, a biphenyl tetrazole Ang II antagonist, prevented the decrease in GFR, renal plasma flow, and sodium excretion. Also, acute administration of losartan was found to improve the natriuretic response to atrial natriuretic peptide in rats with A-V fistula. The present study indicates that eprosartan is another Ang II antagonist that is highly effective in preserving renal function in heart failure. Taken together with the previous data, our findings suggest that the favorable effects of these agents on the cardiovascular system in CHF may be mediated, in part, by improving renal function and promoting salt and water excretion, thus unloading the failing myocardium.

Finally, of interest and of no less importance was the observation on the effects of eprosartan on cardiac hypertrophy in experimental heart failure. Our data demonstrate that early treatment with the drug significantly attenuated and actually prevented the increase in cardiac muscle mass in this experimental model of CHF. Previous studies have suggested that in addition to the mechanical stress exerted on the myocardium as a result of Ang II–mediated increased afterload, activation of the local (intracardiac) RAAS may play a crucial role in inducing cardiac hypertrophy and remodeling in CHF. This growth activity is thought to involve upregulation of cardiac ACE and is the result of Ang II–induced expression of growth factors in myocytes as well as increased formation of connective tissue by fibroblasts and mesenchymal cells. Indeed, rats with A-V fistula are characterized by increased myocardial expression of renin mRNA and ACE mRNA in proportion to the severity of cardiac dysfunction. Moreover, ACE inhibitors have been found to be effective in retarding left ventricular hypertrophy in rats with CHF induced by coronary ligation and in preventing ventricular enlargement in patients with left ventricular dysfunction after myocardial infarction.

Initial studies with the Ang II antagonist losartan indicated that early treatment with the drug reduced cardiac hypertrophy and inhibited myocardial collagen deposition after myocardial infarction in rats. Interestingly, Ruzicka et al reported that only the Ang II antagonist losartan, but not the ACE inhibitor enalapril, was able to effectively reduce the development of overload-induced cardiac hypertrophy in a model similar to that used in the present study. This discrepancy occurred despite a comparable systemic hemodynamic effect of both drugs and was attributed to increased cardiac Ang II generation by pathways resistant to ACE inhibition. The findings of the present study lend further support to the latter report by demonstrating the higher efficacy of eprosartan, compared with ACE inhibition, in limiting the progress of cardiac hypertrophy in response to volume overload. Our findings also indicate that delayed administration of eprosartan, ie, after cardiac enlargement became established, did not result in regression of the hypertrophic response to volume overload. However, this interpretation should be taken with caution since drug administration in the chronic protocols lasted for no more than a week, a period that might have been too short to note regression of preformed remodeling of the cardiac muscle. Certainly, a more prolonged treatment is necessary before the potential clinical implications of this finding can be assessed.

In summary, the present study demonstrates that the nonpeptide AT1 receptor antagonist eprosartan is highly effective in improving renal hemodynamics, promoting sodium excretion, and attenuating cardiac hypertrophy in rats with experimental heart failure induced by A-V fistula. Selective blockade of the AT1 receptor may therefore be viewed as an additional important and efficient therapy in CHF.
Eprosartan in Experimental CHF

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