Haemodynamic, renal sodium handling, and neurohormonal effects of acute administration of low dose losartan, an angiotensin II receptor antagonist, in preascitic cirrhosis

N Girgrah, P Liu, J Collier, L Blendis, F Wong

Abstract

Background—The renin-angiotensin system may be implicated in the subtle sodium handling abnormality in preascitic cirrhosis.

Aims—To assess the role of angiotensin II in sodium homoeostasis in preascitic cirrhosis, using losartan, its receptor antagonist.

Patients—Nine male, preascitic cirrhotic patients, and six age matched, healthy male controls.

Methods—A dose response study using 2.5, 5, 7.5, and 10 mg of losartan was performed on a daily 200 mmol sodium intake, followed by repeat studies with the optimal dose, 7.5 mg of losartan, to determine its effects on systemic and renal haemodynamics, renal sodium handling, and neurohormonal factors.

Results—Preascitic cirrhotic patients had significantly reduced baseline urinary sodium excretion compared with controls (154 (8) versus 191 (12) mmol/day, p<0.05), associated with significantly reduced systemic angiotensin II levels (6.0 (1.7) versus 39.5 (10.0) pmol/l, p=0.002). Losartan 7.5 mg normalised renal sodium handling in the preascitic cirrhotic patients (202 (12) mmol/day, p=0.05 versus baseline), without any change in systemic or renal haemodynamics, but with significantly increased systemic angiotensin II levels (7.8 (2.3) pmol/l, p=0.05 versus baseline). Losartan had no effect on renal sodium handling in controls.

Conclusions—In preascitic cirrhotic patients, the subtle renal sodium retention, paradoxically associated with low systemic neurohumoral factor levels, is improved with low dose losartan, suggesting the involvement of angiotensin II via its direct action on the renal tubule.

Keywords: sodium retention; preascitic cirrhosis; renin-angiotensin-aldosterone system; angiotensin II receptor antagonist; renal haemodynamics

Abnormal sodium homoeostasis is a common complication of liver cirrhosis. A subtle sodium handling abnormality is found in the preascitic stage of cirrhosis, characterised by sodium balance while on a 100 mmol sodium per day diet, but positive sodium balance while on a 200 mmol sodium per day diet. This sodium handling abnormality becomes more severe as the patient’s liver disease progresses until ascites finally develops. The presence of ascites and its complications, such as spontaneous bacterial peritonitis and hepatorenal syndrome, represent major indications for liver transplantation. Attention has therefore focused on elucidating the pathophysiology of this abnormal sodium handling and ascites formation, in order to attain better prognostic indicators and improved, less expensive therapeutic measures.

The sodium handling abnormality in preascitic cirrhotic patients has been shown to be due to sodium retention in the upright posture associated with increased serum levels of aldosterone. These observations suggest that the renin-angiotensin-aldosterone system (RAAS) may play a crucial pathogenetic role in the abnormal renal sodium handling in preascitic cirrhosis. The fact that abnormal sodium handling in cirrhosis has been localised predominantly to the proximal nephron, a site of angiotensin II action, supports this contention. The recent report, in preascitic cirrhotic patients, of a significant increase in intrarenal angiotensin II production with the application of lower body negative pressure which simulates an upright posture, associated with renal sodium retention, further strengthens the early role of the RAAS in the pathophysiology of abnormal sodium handling in cirrhosis. This sodium retention decreases on resumption of the supine posture, at the expense of the development of a hyperdynamic circulation. The associated suppression of systemic plasma renin activity (PRA), angiotensin II, and aldosterone concentrations to low normal levels indirectly indicates that the volume expansion consequent on sodium retention is still present in the supine posture. That is, the supine posture alone is insufficient to correct the sodium retention and volume expansion in cirrhosis.

Angiotensin II is a key regulator of sodium and fluid homoeostasis. Angiotensin II exerts its effects through binding to angiotensin II receptors. Specific intrarenal receptors of the renin-angiotensin system have been characterised in isolated glomeruli. There is evidence that these receptors are coupled to calcium influx, rather than to other second messenger systems. Losartan, an angiotensin II receptor antagonist, is effective in reducing sodium excretion in patients with congestive heart failure, and is effective in reducing proteinuria both in experimental and human conditions. The recent report, in preascitic cirrhotic patients, of a significant increase in intrarenal angiotensin II production with the application of lower body negative pressure simulating the upright posture, indicates that the renin-angiotensin-aldosterone system may play a crucial pathogenetic role in the abnormal sodium handling in cirrhosis. Losartan, an angiotensin II receptor antagonist, may be a useful therapeutic measure in preascitic cirrhosis.

Abbreviations used in this paper: ACE, angiotensin converting enzyme; GFR, glomerular filtration rate; MAP, mean arterial pressure; PRA, plasma renin activity; RAAS, renin-angiotensin-aldosterone system; RPP, renal plasma flow; RVR, renal vascular resistance; SNS, sympathetic nervous system; SVR, systemic vascular resistance.
angiotensin II have been localised to the glomeruli, renal tubules, and renal vasculature.\textsuperscript{7-10} The development of specific competitive angiotensin II receptor antagonists, unlike angiotensin converting enzyme (ACE) inhibitors, do not affect bradykinin metabolism, and are therefore less vasodepressive;\textsuperscript{11} making them a more attractive probe to assess angiotensin II action.

The aim of this study was to use losartan, an angiotensin II receptor antagonist, as a probe to assess the role of angiotensin II in the regulation of renal sodium handling and the mechanisms involved in preascitic cirrhosis, thus improving our understanding of the pathophysiology of ascites formation.

**Materials and methods**

Ethics approval for the study was granted by the Ethics Committee of The Toronto Hospital. All control subjects and cirrhotic patients gave informed consent for the study.

**Patients**

Nine male, ascites free, biopsy proved cirrhotic patients, aged 57 (4) years (range 36–72), were recruited from the Liver Clinics of The Toronto Hospital. The aetiology of cirrhosis was either alcoholic (n=7), viral hepatitis C (n=1), or poststeatohepatitis (n=1). They were well compensated cirrhotic patients who had no history of ascites or diuretic use. Pugh score was 5.2 (0.2). Serum albumin was 35 (2) g/l, serum bilirubin 15 (2) µmol/l, and prothrombin time 11.4 (1.1) seconds. None of the patients had a history of ascites and absence of ascites was confirmed by ultrasound before enrolment. These patients were therefore termed preascitic cirrhotic patients. All patients were stable and had abstained from alcohol for at least six months prior to entry. Patients with intrinsic renal or cardiovascular disease on history and physical examination or with abnormal urinalysis, chest x-ray, or electrocardiograph were excluded from the study, as were patients who had had an episode of gastrointestinal bleeding within the previous three months. Six age matched healthy male volunteers, aged 49 (4) years (range 36–62) and recruited through advertisement, served as controls. They were normotensive and non-obese, on no medication, and had been abstinent from alcohol for at least one month. None of the control subjects had evidence of liver or renal disease on history, physical examination, and urinalysis.

**Study design**

This strict metabolic study was conducted in the Clinical Investigation Unit of the Toronto Hospital. Both study groups had a run in period of one week during which time they were maintained on a 200 mmol sodium, 1.5 litre fluid per day diet for one week, as preascitic cirrhotic patients have been shown to reach a steady state of subtle sodium retention after being on a 200 mmol per day sodium intake for at least four days.\textsuperscript{7} Twenty four hour urine collections were made for the last three days of this week as an estimate of sodium handling. Daily weights were recorded throughout the study period.

Normal healthy individuals have been shown to block the vasoconstrictive response of angiotensin II with 10 mg of losartan\textsuperscript{14} and a natriuretic response was shown after 100 mg of losartan.\textsuperscript{15} However, an optimal dose of losartan for both vasodilatory and natriuretic effects in cirrhotic patients is not known. Therefore, a dose response study was first conducted with control subjects and cirrhotic patients receiving single sequential doses of 2.5, 5, 7.5, and 10 mg losartan at 8 00 am on different days, two days apart. The day the patient received 2.5 mg losartan was taken as day 1 of the study. On the day of medication, the patient was monitored with hourly blood pressure measurements for 12 hours, together with a 24 hour urine collection to determine urinary sodium excretion. The maximal hypotensive effect of losartan was expected to be approximately four to six hours after drug administration, although the pharmacological effect could last up to 24 hours.\textsuperscript{14} Any patient who experienced a fall in mean arterial blood pressure of more than 10 mm Hg with a particular dose of losartan did not receive further doses of losartan and was observed for a further 24 hours from the time of maximal fall in mean blood pressure. The optimal dose of losartan was defined as the dose that produced improved sodium excretion (>20%) with minimal reduction in mean arterial pressure (<10 mm Hg).

After completion of the dose response study and with a rest period of two days, with control subjects and preascitic cirrhotic patients continuing with their sodium intake of 200 mmol and 1.5 litre fluid per day, in order to maintain the sodium retaining state, baseline haemodynamic and renal studies were performed. In the evening at 10 00 pm prior to the baseline studies, or day 9 of the study, all study subjects received lithium carbonate 300 mg orally for measurement of lithium clearance, used as a measure of proximal tubular reabsorption of sodium.\textsuperscript{16} Assessments of baseline renal function, systemic haemodynamics, and neurohumoral factors were performed on day 10. Shortly after 8 00 am, an intravenous catheter was inserted. After two hours of bedrest in the supine position, blood was collected from all study subjects via an indwelling catheter without a tourniquet for measurement of serum electrolytes, plasma renin activity (PRA), plasma angiotensin II, and aldosterone levels. Measurements of inulin clearance, an index of glomerular filtration rate (GFR), p-aminohippurate clearance, an index of renal plasma flow (RPF), lithium clearance, and urinary sodium excretion were made for two periods of
one hour each, with patients voiding while supine. Mean arterial pressure (MAP) and heart rates were assessed hourly during the renal study. In the afternoon at 2:00 pm, after fasting for at least six hours, all study subjects were transferred to the Nuclear Cardiology Department for measurements of central blood volume and systemic haemodynamics using radionuclide angiography. An additional 24 hour urine collection was made for estimation of urinary sodium excretion on the same day.

After a further period of seven days, while maintained on the 200 mmol sodium, 1.5 litre fluid per day diet, the haemodynamic and renal studies were repeated using the optimal dose of losartan. Study subjects received 300 mg lithium at 10:00 pm on the evening prior to the repeat studies. On the following morning at 6:00 am, all subjects received the optimal dose of losartan as assessed in the dose response study. Subsequently, measurements of renal and systemic haemodynamics, sodium excretion (both during the two hour renal study period and over 24 hours), central blood volume, and neurohumoral factors were repeated in exactly the same manner as the baseline measurements.

PROCEDURES

**Inulin, p-aminohippurate, and lithium clearances**

The techniques of inulin, p-aminohippurate, and lithium clearances have been reported previously. The average of the two collections for both the baseline and losartan studies represented the parameters measured during that particular study period.

**Central blood volume measurements**

Detailed description of the technique of central blood volume measurements using radionuclide angiography has been described previously. Briefly, red blood cells were labelled using technetium-99m pertechnetate. The cardiac volumes were measured based on regional activity corrected for attenuation and analysed using a semiautomated software. Quality assurance studies in our Nuclear Cardiology Laboratory have established the standard error of the estimate of ventricular volume calculation to be less than 5 ml.

**Analytical techniques and assays**

Standard analytical methods were used to measure serum and urinary electrolytes and lithium. Blood samples for PRA, plasma angiotensin II, and aldosterone determinations were collected on ice with tubes for angiotensin II containing EDTA and aprotonin. Plasma was separated by refrigerated centrifugation and stored at −70°C until assay. Plasma renin activity was estimated by the radioimmunoassay of angiotensin I generated from plasma after one hour incubation at pH 5.5 and at 37°C in conditions inhibiting the further conversion of angiotensin I (Rianen assay system Angiotensin I [125I] kit, Dupont Company, Wilmington, Delaware, USA). Samples that yielded values of less than 0.1 ng/l/s were then reassayed and incubated for three hours. Plasma angiotensin II was measured by radioimmunoassay (Radioimmunoassay for Angiotensin II kit (human), Peninsula Laboratories, Belmont, California, USA). Plasma aldosterone was assayed using a radioimmunoassay technique with a commercial kit (Coat-A-Count Aldosterone kit, Diagnostic Products Corporation, Los Angeles, California, USA). Inulin concentrations in plasma and urine were measured by a modified technique of Walser et al. and p-aminohippurate, by a spectrophotometric method of Brun.

**Calculations**

Inulin and p-aminohippurate clearances were corrected for body surface area and expressed per 1.73 m². Renal vascular resistance (RVR) for each clearance period = MAP + renal blood flow; renal blood flow = RPF/(1 − packed cell volume). Proximal tubular reabsorption of sodium was calculated using lithium clearance and GFR, whereas the distal tubular reabsorption of sodium was calculated from inulin clearance, serum sodium concentrations, urinary sodium concentrations, and urinary volume.

The end diastolic, end systolic, and central blood volumes were directly measured during radionuclide angiography. Stroke volume, cardiac output, and systemic vascular resistance (SVR) were then calculated from standard formulae. All volume measurements can be affected by body size and were therefore corrected for body surface area using the subject’s height and weight. Likewise, the cardiac output was corrected for body surface area to yield the cardiac index.

**Statistical analysis**

All results were expressed as mean (SEM). Differences between the means of the baseline and postdose observations during the dose response study for each variable in each group were determined by one way analysis of variance (ANOVA). For independent variables, paired and unpaired Student’s t tests were used to analyse two means of each variable. Differences were considered significant if the null hypothesis could be rejected at the 0.05 probability level.

**Results**

**Dose response study**

The mean 24 hour urinary sodium excretion in the preascitic cirrhotic patients for the three days prior to the dose response study was 147 (7) mmol/day, confirming that they were in a state of sodium retention. With the initial dose of 2.5 mg of losartan, there was an immediate natriuresis in the preascitic cirrhotic patients. However, this did not achieve statistical significance (table 1). With increasing doses of losartan, the natriuresis observed in the cirrhotic patients was maintained. The 7.5 mg dose, in contrast to 10 mg, did not result in a significant fall in the MAP (table 1) during the 12 hour observation period; it was therefore chosen as the optimal dose of losartan in this study. The fall in MAP with 10 mg of losartan was transient, observed three hours after losartan administration in the cirrhotic patients only;
MAP gradually returned to baseline during the next 24 hours. The control subjects did not show any significant change in either urinary sodium excretion, MAP, or heart rate during the dose response study (table 1).

**RESPONSE TO 7.5 mg LOSARTAN**

**Sodium homoeostasis**

Baseline studies were conducted on day 10, when all parameters had returned to levels similar to those prior to the dose response study. Urinary sodium excretion, both measured over a 24 hour period and during the two hour renal study period, was significantly lower in the preascitic cirrhotic patients compared with controls (154 (8) mmol/day versus 191 (12) mmol/day over the 24 hour collection period, \( p<0.05 \), table 2; and 0.16 (0.03) mmol/min versus 0.36 (0.05) mmol/min during the two hour renal study period, \( p<0.01 \), fig 1). The significantly reduced renal sodium excretion in the cirrhotic patients was due to an increase in the tubular reabsorption of sodium proximal to the distal tubule (73.64 (1.80)% versus 60.30 (4.95)% in controls, \( p=0.02 \), fig 1). This resulted in a significant decrease in the fractional excretion of sodium in the cirrhotic patients (1.26 (0.23)% versus 1.91 (0.15)% in the controls, \( p=0.05 \)).

With 7.5 mg of losartan, renal sodium handling was normalised in the cirrhotic patients. Both the 24 hour urinary sodium excretion (202 (12) mmol/day, \( p=0.05 \) versus baseline) and the two hour urinary sodium excretion during the renal study period (0.27 (0.04) mmol/min, \( p=0.01 \) versus baseline) increased significantly (fig 1). This was associated with a weight loss of 0.32 (0.06) kg over the 24 hour period. The improved renal sodium handling in the cirrhotic patients was due to a significant decrease in the tubular handling of sodium.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Haemodynamic and sodium excretion response following increasing single oral doses of losartan during the dose response study</th>
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<tbody>
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<td>Baseline</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<td>Controls</td>
<td>96 (3)</td>
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<td>Cirrhotic patients</td>
<td>89 (3)</td>
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<td>Heart rate (beats/min)</td>
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<td>Controls</td>
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<td>Cirrhotic patients</td>
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<td>24 hour urinary sodium excretion (mmol/day)</td>
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<td>Controls</td>
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<td>Cirrhotic patients</td>
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\* \( p<0.05 \) versus controls, † \( p<0.05 \) versus baseline.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Renal sodium handling, systemic and renal haemodynamics, and central blood volume before and after 7.5 mg losartan</th>
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<tr>
<td></td>
<td>Baseline</td>
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<tr>
<td>Urinary sodium excretion (mmol/day)</td>
<td></td>
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<tr>
<td>Controls</td>
<td>191 (12)</td>
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<tr>
<td>Cirrhotic patients</td>
<td>154 (8)*</td>
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<tr>
<td>Mean arterial pressure (mm Hg)</td>
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<tr>
<td>Cirrhotic patients</td>
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<td>Heart rate (beats/min)</td>
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<td>Controls</td>
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<td>Cirrhotic patients</td>
<td>69 (2)</td>
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<td>Renal plasma flow (ml/min/1.73 m²)</td>
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<td>Controls</td>
<td>484 (52)</td>
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<td>Cirrhotic patients</td>
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<td>Glomerular filtration rate (ml/min/1.73 m²)</td>
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<td>Controls</td>
<td>119 (13)</td>
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<td>Cirrhotic patients</td>
<td>90 (9)</td>
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<tr>
<td>Renal vascular resistance (dyne/s/cm⁵)</td>
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<td>Controls</td>
<td>8574 (746)</td>
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<tr>
<td>Cirrhotic patients</td>
<td>11843 (1038)</td>
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<tr>
<td>Central blood volume (ml/m²)</td>
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<td>3146 (359)</td>
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<td>Cirrhotic patients</td>
<td>3331 (415)</td>
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<td>Cardiac index (l/min/m²)</td>
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<td>Controls</td>
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<td>Cirrhotic patients</td>
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<td>Systemic vascular resistance (dyne/s/cm⁵)</td>
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<tr>
<td>Controls</td>
<td>1264 (133)</td>
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<tr>
<td>Cirrhotic patients</td>
<td>1408 (40)</td>
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</table>

\* \( p<0.05 \) versus controls, † \( p<0.05 \) versus baseline.

Figure 1 (A) Urinary sodium excretion, (B) proximal tubular reabsorption of sodium, and (C) fractional excretion of sodium before and after 7.5 mg losartan in the cirrhotic patients and controls.
compared with controls (6 (2) pmol/l versus 40
significantly lower in the preascitic cirrhotic patients
measured in the supine posture, were signifi-
cantly different between the two groups (table 2).

Neurohumoral factors
Baseline systemic angiotensin II levels, measured in the supine posture, were signifi-
cantly lower in the preascitic cirrhotic patients
compared with controls (6 (2) pmol/l versus 40
(10) pmol/l in controls, p<0.01). With 7.5 mg
losartan, supine systemic levels of angiotensin
II increased significantly in cirrhotic patients (8
(2) pmol/l, p<0.05 versus baseline) but not in
controls (fig 2). Systemic angiotensin II levels
in cirrhotic patients, however, remained con-
sistently lower than those in controls (fig 2).
The baseline supine PRA was also significantly
lower in cirrhotic patients (0.13 (0.02) ng/l/s)
compared with controls (0.32 (0.08) ng/l/s,
p<0.05, fig 2). With 7.5 mg losartan, there was
a significant increase in PRA in preascitic
cirrhotic patients (0.45 (0.06) ng/l/s versus
0.13 (0.0) 2 ng/l/s at baseline, p=0.05, fig 2).
The change in PRA in control subjects (0.47
(0.07) ng/l/s), however, was minimal (fig 2).
Likewise, supine baseline plasma aldosterone
levels were lower in preascitic cirrhotic patients
compared with controls (95 (15) pmol/l versus
136 (30) pmol/l in controls, p>0.05) and did
not change with losartan (100 (11) pmol/l in
cirrhotic patients and 112 (17) pmol/l in
controls) in both groups.

Discussion
The results of this preliminary study confirm
previous findings that preascitic cirrhotic pa-
tients have subtle sodium retention when
placed on a 200 mmol sodium as opposed to a
100 mmol sodium per day intake,4 5 21 manifested as a reduced urinary sodium excretion,
associated with suppression of systemic RAAS
in the supine posture. The acute use of a low
dose angiotensin II receptor antagonist re-
sulted in normalisation of this subtle sodium
handling abnormality in preascitic cirrhotic
patients, despite unchanged renal and systemic
haemodynamics.

A 200 mmol sodium per day diet was chosen
for this study for several reasons. Preascitic cir-
rhotic patients have previously been shown to
come into a steady state of subtle sodium
retention after four days of this sodium intake,5 6
and therefore the study would not require a
long run in period. Secondly, this level of
sodium intake, although higher than that
contained in the usual “no added salt diet of
100–130 mmol sodium per day” that the
patients were accustomed to, was similar to
their usual diet with a few additional high salt
items and therefore easily manageable. Thirdly,
this level of sodium retention was sufficient to
assess the natriuretic effect of losartan.

This subtle sodium handling abnormality in
preascitic cirrhosis has been shown to result in
intravascular volume expansion,28 29 The su-
pine posture is the means whereby some of this
excess volume can be eliminated,28 as may have
occurred in the present study, since the central
blood volume in the cirrhotic patients was not
significantly increased. Therefore, this study
was performed in the supine posture to exa-
mine what additional mechanisms are involved in
the pathophysiology of sodium retention in
preascitic cirrhosis.

The proximal renal tubule has previously been
identified as an important site of renal
sodium retention in cirrhosis.4 21 The two most
likely candidates for increased proximal
tubular reabsorption of sodium in preascitic

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Figure 2. (A) Plasma renin activity, (B) plasma
angiotensin II levels, before and after 7.5 mg losartan in
cirrhotic patients and controls.

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Losartan in cirrhosis

cirrhotic patients are: (1) an increase in renal sympathetic nervous system (SNS) activity, since a subtle increase in systemic SNS activity, unmasked by a high sodium diet, has been observed in preascitic cirrhosis; (2) alternatively, an increase in intrarenal production of angiotensin II, possibly mediated by portal hypertension.

Recent work from our laboratory showed that, in preascitic cirrhosis, the application of lower body negative pressure at −20 mm Hg for 30 minutes, which simulates an upright posture, led to a significant increase in renal angiotensin II production, together with unchanged renal SNS activity, as measured by renal noradrenaline spillover technique. This indicates that activation of the intrarenal RAAS may be the first of a series of events involved in the abnormality in sodium homoeostasis in preascitic cirrhosis. All components of the RAAS are present within the kidney, thereby allowing significant amounts of angiotensin II to be formed intrarenally. The logical extension of this observation is to manipulate the RAAS to assess the resultant changes in renal sodium excretion. Recent characterisation of angiotensin II receptors in various tissues with the subsequent development of angiotensin II receptor antagonists, has provided an exciting investigative tool to assess angiotensin II function. The prototype, losartan, being less vasodepressive than ACE inhibitors, has consistently been shown to be well tolerated with minimal side effects, thus making it a very attractive probe for the study of angiotensin II effects on sodium handling in cirrhosis.

The effects of losartan on systemic and renal haemodynamics, and neurohumoral factors has been extensively evaluated in healthy normal volunteers and in patients with systemic hypertension or congestive cardiac failure. While the effects of losartan last for up to 24 hours, a clear dose dependent relation exists between losartan and the observed effects. Therefore, in order to produce as pure an angiotensin II action as possible without the confounding effect of systemic hypotension, a low dose of losartan was required. Our dose response study indicated that a dose of 7.5 mg of losartan was the optimal dose that produced a natriuresis without any deleterious systemic effects. Therefore, in order to produce as pure an angiotensin II action as possible without the confounding effect of systemic hypotension, a low dose of losartan was required. Our dose response study indicated that a dose of 7.5 mg of losartan was the optimal dose that produced a natriuresis without any deleterious systemic effects. However, this remains speculative, as portal pressure was not measured in this study, and the dose we used was substantially smaller than the portal pressure lowering dose reported.

The increase in urinary sodium excretion following the acute administration of a low dose of losartan was not accompanied by any change in the central blood volume or cardiac volumes. This may at first seem surprising since the negative sodium balance would be expected to be accompanied by a negative volume balance. This may be due to the fact that the volume change after a single low dose of losartan was insufficient to alter the central blood volume. Alternatively, the change in volume may not have been measured in the central compartment, but rather in another circulatory bed such as the splanchnic circulation.

The fact that the sodium retaining effects of angiotensin II can be dissociated from its haemodynamic effects has provided important insights into the pathogenesis of sodium retention in cirrhosis. An increased tubular reabsorption of sodium may represent the first abnormality in the sodium homoeostasis in these patients. As the cirrhotic disease progresses, abnormalities in the circulation may then contribute to further sodium retention in these patients.

The neurohormones at baseline were lower in the preascitic cirrhotic patients, significantly so with systemic angiotensin II levels. This is consistent with the finding of subtle renal sodium retention, suggesting intravascular volume expansion. Following the acute administration of 7.5 mg losartan, angiotensin II receptor blockade leading to activation of the RAAS through removal of the negative feedback mechanism, should have caused an increase in PRA in both groups. However, PRA only increased significantly in the cirrhotic patients but not in the controls. The most likely explanation is that in the cirrhotic patients, additional mechanisms such as an increased sensitivity of the renal baroreceptor mechanism stimulate renal renin release. The angiotensin II thus formed must have been produced intrarenally, possibly at a tissue level, and then metabolised intrarenally, as the systemic levels of angiotensin II remained low following losartan compared with the controls and consequently, the plasma aldosterone levels remained unchanged.

The ability of a single low dose of losartan to effect a natriuresis without any deleterious systemic hypotensive effects certainly establishes its clinical advantage over ACE inhibitors.
Further studies still need to be performed to determine whether the long term administration of low dose losartan can maintain the natriuretic response in preasitic cirrhotic patients. If positive, this may normalise their volume status and prevent or delay the development of the hyperdynamic circulation. Similar studies also need to be performed to assess the effects of losartan in ascitic patients.

In summary, the use of a single low dose of the angiotensin II receptor antagonist, losartan, in preasitic cirrhotic patients improved renal sodium handling and normalised the subtle sodium handling abnormality in these patients unmasked by a 200 mmol sodium diet. This occurred without any significant change in systemic or renal haemodynamics, suggesting a direct renal tubular effect of losartan in inducing a natriuresis. This study therefore supports the pivotal role of the RAAS in the control of sodium homeoeostasis in preasitic cirrhosis.

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