The Effect of Single Oral Low-Dose Losartan on Posture-Related Sodium Handling in Post-TIPS Ascites-Free Cirrhosis

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Post-TIPS ascites-free patients with cirrhosis and previous refractory ascites demonstrate subtle sodium retention when challenged with a high sodium load. This is also observed in pre-ascitic patients with cirrhosis. This phenomenon is dependent on an intrarenal angiotensin II (ANG II) mechanism related to the assumption of erect posture. We investigated whether similar mechanisms were involved in post-TIPS ascites-free patients, by studying 10 patients with functioning TIPS and no ascites. We measured the effect of changing from supine to erect posture on sodium excretion at baseline and after single oral low dose losartan (7.5 mg) which has been shown to blunt proximal and distal tubular sodium reabsorption in pre-ascites. At baseline, the assumption of erect posture produced a reduction in sodium excretion (from 0.30 ± 0.06 to 0.13 ± 0.02 mmol/min, $P = .05$), which was mainly due to an increase in proximal tubular reabsorption of sodium (PTRNa) (69.7 ± 3.1% to 81.1 ± 1.8%, $P = .003$). The administration of losartan resulted in a blunting of PTRNa (supine 69.7 ± 3.1% to 63.9 ± 3.9%, $P = .01$ and erect 81.1 ± 1.8% to 73.8 ± 2.4%, $P = .01$), accompanied by an increased distal tubular reabsorption of sodium in both postures, with no overall improvement in sodium excretion on standing. In conclusion, post-TIPS ascites-free patients with cirrhosis exhibit erect posture-induced sodium retention. We speculate that (1) this effect is partly mediated by the effect of ANG II on PTRNa and (2) that the inability of low dose losartan to block the erect posture-induced sodium retention may be related to the erect posture-induced rise in aldosterone which is unmodified by losartan. (HEPATOLOGY **2006;44:640-649.**)

The pathogenesis of sodium retention and ascites formation in patients with cirrhosis is not fully understood. However, it is clear that sinusoidal portal hypertension plays a pathogenetic role,[1-3] as reduction in sinusoidal portal pressure using a transjugular intrahepatic portosystemic stent shunt (TIPS) in patients with cirrhosis and refractory ascites resulted in either resolution or reduction of ascites.[4-8] However, other mechanisms are also likely to be involved, because post-TIPS ascites-free patients with cirrhosis continue to demonstrate a degree of sodium retention when challenged with a sodium load despite a normal portal-systemic gradient.[9] This occurs despite an adequately filled effective arterial blood volume (EABV) as shown by normal plasma renin activity, plasma aldosterone, and norepinephrine (PNE) levels,[9] suggesting that it is not underfilling of the EABV as described by the Peripheral Arterial Vasodilatation Hypothesis[10] that is responsible for the sodium retention on sodium challenge in these patients.

Post-TIPS ascites-free patients with cirrhosis appear to be in sodium balance when they are not challenged by high sodium load.[9] Therefore, in many ways, their sodium handling appears to be similar to that of pre-ascitic patients who are also ascites-free. In pre-ascitic patients with cirrhosis, sodium balance is achieved when they are either on a low-sodium diet of 22 mmol/day or 100 mmol/day,[11] but subtle sodium retention occurs when

Abbreviations: ANG II, angiotensin II; ANF, atrial natriuretic factor; BUN, blood urea nitrogen; CBV, central blood volume; CCVV, central cardiac and vascular volume; CO, cardiac output; DDNa, distal sodium delivery; DTRNa, distal tubular sodium reabsorption; EABV, effective arterial blood volume; EDV, end diastolic volume; ESV, end systolic volume; FENa, fractional sodium excretion; GFR, glomerular filtration rate; FF, filtration fraction; Hgb, hemoglobin; INR, international normalized ratio. LLV, left lung volume; MAP, mean arterial pressure; PAH, para-amino-hippurate; PNE, plasma norepinephrine; PTRNa, proximal tubular sodium reabsorption; RLF, right lung volume; RPF, renal plasma flow; RVR, renal vascular resistance; RAAS; renin-angiotensin-aldosterone system; SVR, systemic vascular resistance; TIPS, transjugular intrahepatic portosystemic shunt; UNaV, urinary sodium excretion.

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challenged with a high sodium diet of 200 mmol/day.[12] Similar to the post-TIPS ascites-free patients, pre-ascitic patients also have a low to normal neurohormonal profile, especially in the supine posture,[13], confirming the presence of an adequately filled EABV in the supine posture. The subtle sodium retention of pre-ascitic patients with cirrhosis has been shown to be related to the assumption of the erect posture[14,15] associated with activation of the renin-angiotensin-aldosterone system (RAAS) in that posture.[16] There is intrarenal activation of angiotensin,[17] and increased plasma aldosterone levels[16] on standing in pre-ascitic patients. In contrast, we have previously demonstrated that normal subjects do not retain sodium on standing.[17] We therefore postulated that the same posture-related pathogenetic mechanisms in pre-ascitic patients with cirrhosis are also responsible for the subtle sodium retention in post-TIPS ascitic-free cirrhotic patients who have previously had refractory ascites.

Because elimination of ascites is neither immediate nor effective in 100% of post-TIPS patients, the investigation of the tubular handling of sodium in post-TIPS ascites free patients with angiotensin II (ANG II) or aldosterone antagonists may help to understand sodium excretion in the post-TIPS period. Therefore, the aims of this study were (1) to investigate the role of posture in the subtle sodium retention in post-TIPS ascites-free patients who have previously had refractory ascites, and (2) whether any subtle sodium retention is related to the erect posture-induced activation of the renin-angiotensin-aldosterone system. We chose a single, oral, low dose of an ANG II receptor antagonist, 7.5 mg losartan, as a probe to indirectly investigate the role of intrarenal activation of ANG II on tubular sodium handling. A low dose (7.5 mg) of losartan has been shown in pre-ascitic patients to induce a natriuresis without any systemic hemodynamic effects, suggesting an intra-renal action,[18] and this was sufficient to blunt the sodium retention induced by the erect posture.[17] Therefore, the same low-dose losartan should be the ideal tool in post-TIPS ascites-free patients who have a similar hemodynamic profile.

Patients and Methods

Ethical approval for the study was granted by the Research Ethics Board of University Health Network, University of Toronto, Toronto, Canada, and all patients gave informed consent for the study.

Patients. Ten post-TIPS, ascites-free patients with cirrhosis who previously had refractory ascites were recruited from the Liver Clinic at the Toronto General Hospital, University Health Network over a period of 9 months. There were 9 males and 1 female. The mean age of the patients was 52.2 ± 3.2 years (mean ± SEM). The cause of cirrhosis was alcohol (6 patients), alcohol and chronic hepatitis C virus infection (2 patients), and chronic hepatitis B virus infection (2 patients). All were stable ambulatory patients. The diagnosis of cirrhosis was made by liver biopsy in all patients prior to TIPS insertion. TIPS insertion for refractory ascites (according to the revised diagnostic criteria of the International Ascites Club[1]) had been undertaken 17.4 ± 4.2 months prior to study enrollment. All patients with alcohol-related cirrhosis had abstained from alcohol for at least 6 months prior to their TIPS insertion and had remained abstinent prior to study enrollment and during the period of the study. Patients with intrinsic renal or cardiovascular disease on history or examination or as demonstrated by abnormalities in urinalysis, renal ultrasound, chest radiograph or electrocardiograph were excluded from TIPS insertion, as were patients with a Child-Pugh score of >12, preexisting hepatic encephalopathy, hepatocellular carcinoma, or portal vein thrombosis. The TIPS procedure was performed as described in detail by Wong et al.[19] All patients were ascites-free within 6 months after TIPS without diuretic therapy. Seven of the 10 patients had one or more TIPS revisions during the period between TIPS insertion and enrollment (mean number of revisions 2.6 ± 0.6).

One month before enrollment into the study, all patients underwent an abdominal doppler ultrasound to confirm TIPS patency (shunt flow velocities > 100 cm/sec at portal venous, mid-TIPS, and hepatic venous ends) as well as absence of ascites. The mean Child-Pugh score at enrollment was 5.7 ± 0.4. None of the patients were on any vasoactive medications (diuretics or beta-blockers). Six patients were on a stable dose of lactulose, 1 patient was on lamuvidine, and 1 patient was on omeprazole during the study period. Patient demographics and laboratory parameters at enrollment are shown in Table 1.

Study Design (Fig. 1). This study was conducted in the Physiology Laboratory at Toronto General Hospital, University Health Network.

Before the start of the study, all patients underwent a physical examination to ensure that there was no clinical evidence of cardiovascular, pulmonary or renal diseases, and that the patients had no peripheral edema. All patients were then counseled by the dietitian about their low (22 mmol) and high (200 mmol) sodium diets, as well as caffeine-containing food items which they had to avoid during the study.

The study began (day 1) with all study patients starting a run-in period of 1 week during which they were maintained on a low-sodium diet (22 mmol/day, 1 L fluid intake/day). This sodium wash-out period was to ensure that all patients began the study at the same baseline sodium status. At the end of this one-week run-in period

Table 1. Patient Demographics and Laboratory Parameters at Enrollment

Parameter	Value
N	10
Age (years)	52.2 ± 3.2
Male:female ratio	9:1
Hgb (male 140-180 g/L, female 120-160g/L)	131 ± 4
Platelets (150-400 billion/L)	134 ± 14
INR (0.9-1.1 sec)	1.35 ± 0.05
AST (<35 U/L)	49 ± 10
ALT (<40 U/L)	29 ± 9
ALP (<110 U/L)	127 ± 19
Albumin (38-50 g/L)	35 ± 2
Bilirubin (<22 μmol/L)	19 ± 4
Serum Na^+ (135-140 mol/L)	140 ± 1
Serum K^+ (3.5-5.0 mmol/L)	4.0 ± 0.2
BUN (3.0-8.9 mmol/L)	4.4 ± 0.5
Serum creatinine (57-110 μmol/L)	61 ± 6
Child-Pugh score	5.7 ± 0.4
Etiology	
Alcohol alone	6
Alcohol + hepatitis C	2
Hepatitis B	2
Time period since TIPS (days)	523 ± 126
Number of TIPS revisions (per patient)	2.6 ± 0.6

Abbreviations: Hgb, hemoglobin; INR, international normalized ratio; BUN, blood urea nitrogen.

(days 6 and 7), two 24-hour urine collections were performed to measure urinary sodium excretion (UNaV) and to ensure compliance with sodium washout.

In week 2, on day 8, subjects were placed on a high sodium diet (200 mmol/day, 1.5 L fluid intake/day) that was maintained throughout the remainder of the study. To ensure dietary compliance, patients were given meal plans and instructed to consume only food items permitted on their dietary instruction sheets. Caffeine-containing beverages and food items were withheld during the study period and all patients were asked to refrain from smoking. Two 24-hour urine collections were made on days 13 and 14 to ensure dietary compliance. At 10 pm on day 14, all study subjects received lithium carbonate (300 mg) orally. Lithium clearance was used as a measure of the delivery of fluid and solutes to the distal nephron, and therefore can indirectly reflect the tubular reabsorption of sodium proximal to the distal nephron (PTRNa).[20]

Baseline measurements were taken on days 15 and 16. On day 15, patients were admitted at 8 am after an overnight fast. An intravenous catheter was inserted shortly after admission, and patients were allowed to rest in a supine position in a quiet room for 2 hours before blood

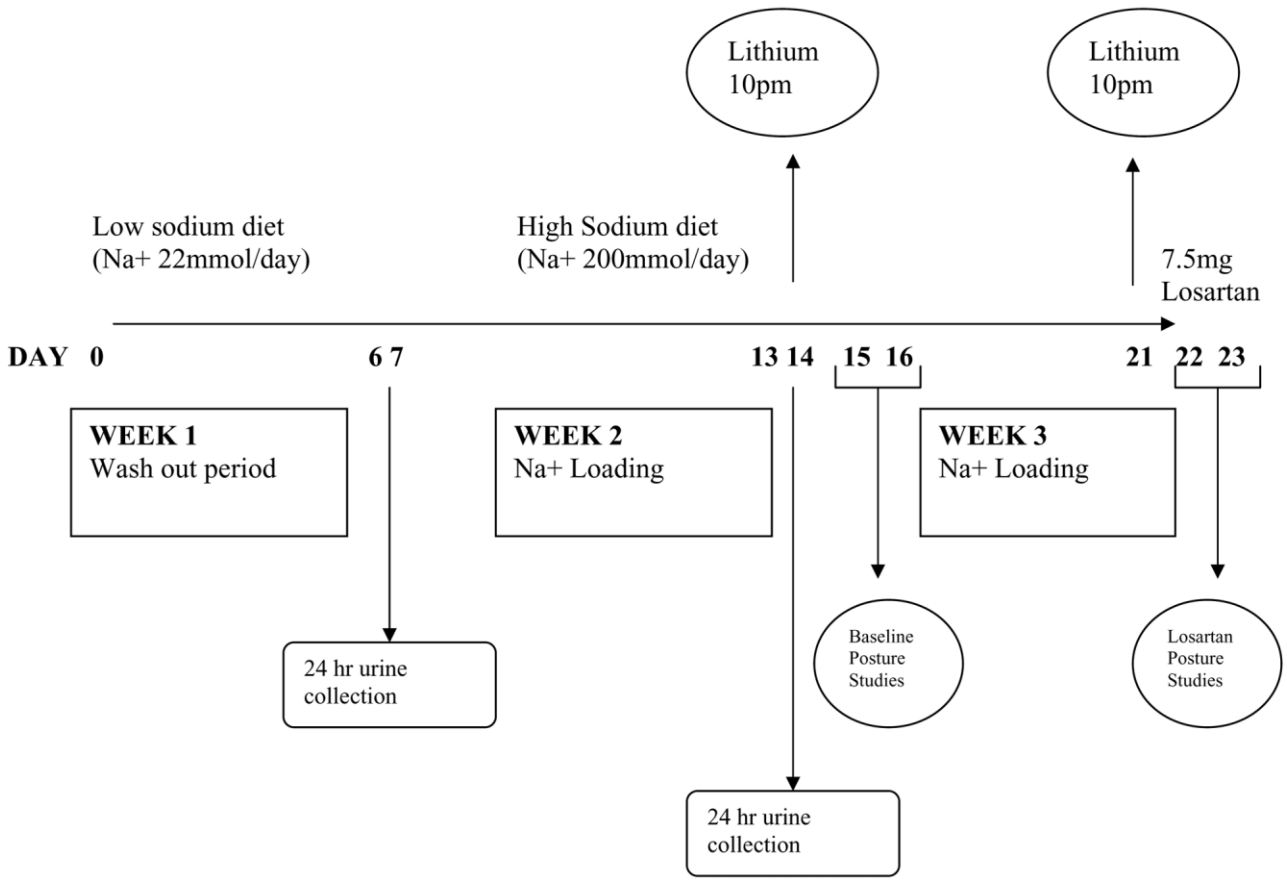

Fig. 1. Study design and timeline.

was collected, via the indwelling catheter without a tourniquet, for determination of plasma renin, ANG II, aldosterone, PNE, and atrial natriuretic factor (ANF) levels. The glomerular filtration rate (GFR), renal plasma flow (RPF), lithium clearance, and UNaV were measured for 2 periods of 1 hour each, with patients in the supine posture and voiding while supine. The filtration fraction (FF) was also calculated. On completion of the renal study in the supine posture, all study subjects assumed the erect posture. After 2 hours in this position, the same protocol was repeated. Inulin clearance was used as a measure of GFR, and para-amino-hippurate (PAH) clearance was used as an index of RPF. On day 16, after fasting for 6 hours and maintaining the supine posture, radionuclide angiography was carried out to measure cardiac chamber and central blood volumes (CBV), which also indirectly reflect the fullness of the EABV. Parameters of systemic hemodynamics—cardiac output and systemic vascular resistance in particular—were calculated from the cardiac measurements. All measurements were repeated in the erect posture after 2 hours of standing.

On day 21 at 10 pm, lithium carbonate (300 mg) was again administered. On days 22 and 23, with the patients continuing on their 200 mmol sodium/day diet, and after receiving a single oral dose of 7.5 mg of losartan at 6 am each day, the aforementioned renal and cardiac studies were repeated in the same sequence. The renal study began at 10 am and the radionuclide angiography study was performed at 12 noon the following day after a 6-hour fast. Losartan was given at 6 am, because its peak effect occurs 4 to 6 hours after the dose, but persistent changes are still evident 24 hours after the dose.[18]

Procedures. *Lithium, Para-amino-hippurate, and Inulin Clearances.* The techniques of lithium, PAH and inulin clearances have been previously described.[20-22] Because urine catheters had not been used to collect urine during the study, a regular oral intake of 100 mL of water/hour was given to maintain urine volume and minimize the risk of incomplete collections affecting the calculations of clearances. The average of the 2 collections for each of the baseline and post-losartan periods represented the renal sodium handling, RPF, and GFR for that particular period.

Radionuclide Angiography Scan. This technique of CBV measurements is previously described.[13] The ejection fraction and the cardiac volumes were analyzed with semi-automated software described previously[13], and quality assurance studies in our Nuclear Cardiology Laboratory established the standard error of the estimate of left ventricular ejection fraction calculation to be less than 2% with the semi-automated technique. The standard error of the estimate of ventricular volume calculation is less than 5 mL.[23]

Analytical Techniques and Assays. Serum and urinary electrolytes, complete blood count, prothrombin time and liver function tests were performed with standard laboratory automated techniques. Blood samples for ANG II, ANF, PNE, plasma renin levels, and aldosterone determinations were collected on ice with the tubes for ANG II and ANF containing ethylene diamine-tetraacetic acid and aprotinin respectively. Plasma was separated by refrigerated centrifugation and stored at –70 °C until assay.

Plasma ANG II was measured by radioimmunoassay (Peninsula Laboratories, Belmont, CA). Plasma renin levels were measured by using the Active Renin Immunoradiometric Kit (Nichols Institute Diagnostics, San Clemente, CA). Plasma aldosterone was assayed with a radioimmunoassay technique using a commercial kit (Coat-A-Count Aldosterone Kit, Diagnostic Products Corp., Los Angeles, CA). Plasma norepinephrine concentrations were determined with high-performance liquid chromatography, as described[24] with modifications.[25] ANF was measured by radioimmunoassay (Peninsular Laboratories, Belmont, CA). Inulin concentrations in plasma and urine were measured with a modified technique of Walser et al.,[22] and those of PAH by the spectrophotometric method of Brun.[21]

Calculations. Inulin and PAH clearances were calculated as (urine concentration ÷ plasma concentration) × urinary flow rate, and are expressed as milliliters per minute. Renal vascular resistance [RVR ($dyn \cdot sec \cdot cm^{-5}$)] was calculated as (mean arterial pressure ÷ renal blood flow) × 80, where renal blood flow is equal to RPF ÷ (1 – hematocrit).

FF was calculated as the ratio of GFR/RPF.

Lithium clearance was calculated as [urinary Li] ÷ [serum Li] × urinary flow rate

Proximal tubular reabsorption of sodium (PTRNa) (in %) was calculated as [(GFR – lithium clearance) ÷ GFR] × 100.

Distal delivery of sodium (DDNa) (in mmol/min) was calculated as (GFR × serum [Na]) × (1 – PTRNa)

Distal tubular reabsorption of sodium (DTRNa) (in %) was calculated from [(DDNa – UNaV) ÷ DDNa] × 100%.

Fractional sodium excretion (FENa) (in %) was estimated as (UNa ÷ (GFR × serum [Na])) × 100%

The mean arterial pressure (MAP), the systemic vascular resistance (SVR), and the central cardiac and vascular blood volume (CCVV) were calculated as follows: MAP (mmHg) = [(systolic blood pressure – diastolic blood pressure) ÷ 3] + diastolic blood pressure.

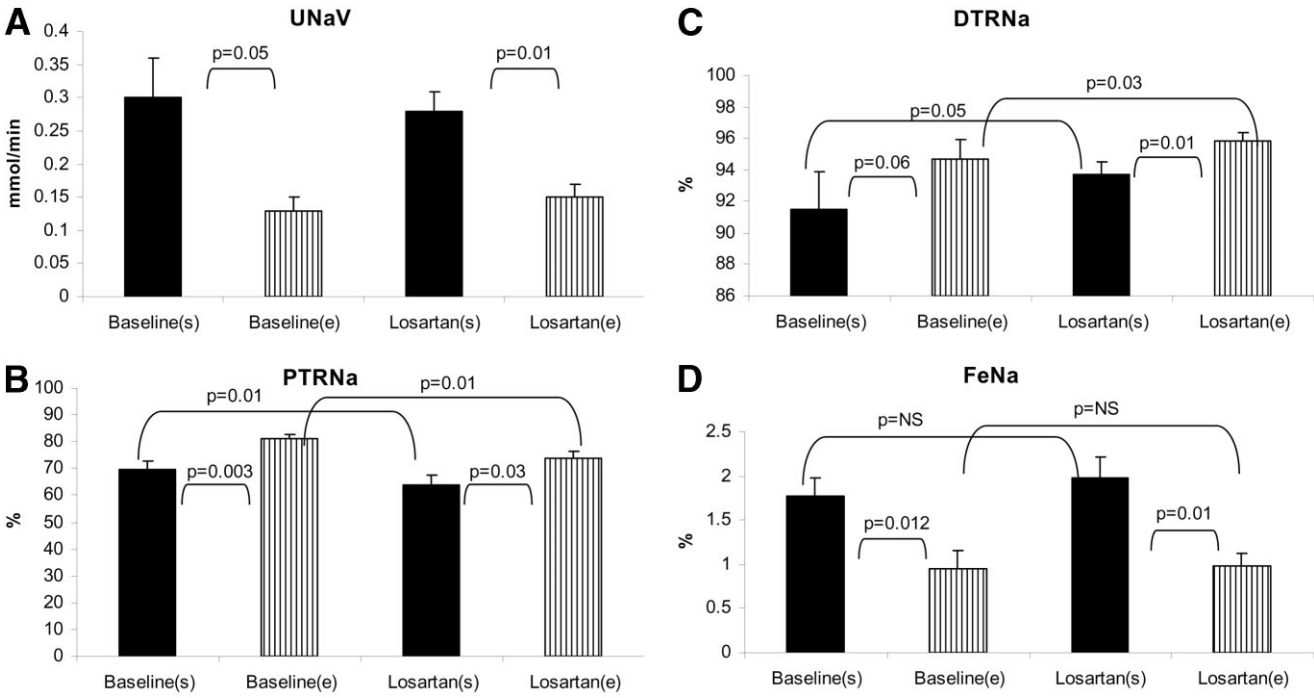

Fig. 2. Detailed analysis of renal sodium handling after posture changes and after oral low dose losartan. (s) = supine, (e) = erect. (A) UNaV decreases on the assumption of the erect posture both at baseline and after losartan administration. (B) PTRNa increases on standing both at baseline and after losartan. Losartan blunts the increased PTRNa both in the supine and erect postures. (C) DTRNa rises on the assumption of the standing posture both before and after oral single-low-dose losartan. DTRNa is higher after losartan when compared with baseline in both the supine and standing postures. (D) FeNa decreases on standing. Losartan administration has no effect in FeNa.

SVR (dyn · sec · cm^{-5}) = [MAP ÷ cardiac output] × 80

CCVV (central cardiac and vascular volume) (mL) = CBV – right and left pulmonary vascular volumes where CCVV represents the blood volume in cardiac chambers and great vessels and CBV represents the total amount of blood volume from the thoracic inlet to the diaphragm.

Statistical Analysis. All results are expressed as mean ± SEM. The general linear model for repeated measures was used with significance taken at the .05 probability level. The SPSS 9.0 statistical package (SPSS Inc., Chicago, IL) was used to analyze the results.

Results

Weight. Weight at the beginning of the whole study (day 0) was 77.4 ± 5.3 kg and remained unchanged for the first week while patients were on a low sodium diet (77.6 ± 5.3 kg on day 7). After introduction of a high sodium diet, patients gained weight (day 14, 79.4 ± 5.4 kg and day 21, 79.2 ± 5.3 kg). This weight gain was statistically significant ($P = .02$ comparing day 0 with day 14 and day 21).

Twenty-Four-Hour Urine Collections. The urinary volume increased from 1.40 ± 0.24 L/day on day 7 to 1.88 ± 0.26 L/day at the end of week 2 (days 13+14) ($P = .02$). UNaV on a low sodium diet was 66 ± 14 mmol/day (day 7) and increased significantly ($P < .001$) to 145 ± 14 mmol/day (days 13+14), confirming compliance with the prescribed sodium diets for the respective weeks.

(1) Baseline Studies. *Sodium Metabolism (Fig. 2).* Post-TIPS ascites-free patients with cirrhosis demonstrated sodium retention when changing from the supine to the erect posture, with a significant reduction in UNaV (from 0.30 ± 0.06 mmol/min in the supine posture to 0.13 ± 0.02 mmol/min in the erect posture, $P = .05$) and urinary volume (from 4.5 ± 1 mL/min in the supine posture to 2.5 ± 0.8 mL/min in the erect posture, $P = .02$). This was mainly due to a significant increase in PTRNa (69.7 ± 3.1% in the supine posture to 81.1 ± 1.8% in the erect posture, $P = .003$). As a result, the DDNa was significantly reduced on the assumption of the erect posture (3.97 ± 0.5 mmol/min in the supine posture to 2.7 ± 0.4 mmol/min in the erect posture, $P = .03$). Despite this, a further smaller increase was observed in the DTRNa (91.5 ± 2.4% in the supine posture to 94.7 ± 1.2% in the erect posture, $P = .06$), leading to an overall reduction in the FENa (1.8 ± 0.2% in the supine posture to 0.95 ± 0.2% in the erect posture, $P = .012$).

Systemic and Renal Hemodynamics and Vascular Volumes (Table 2). The reduction in renal sodium excretion

Table 2. Systemic and Renal Hemodynamics and Vascular Volumes

Parameter	Baseline			Post-losartan		
	Supine	Erect	*P*	Supine	Erect	*P*
HR (n = 60-100 bpm)	67 ± 3.4	66 ± 3.9	NS	72 ± 4.4	71 ± 3.8	NS
MAP (n = 70-105 mm Hg)	89.8 ± 2.9	88.9 ± 3.1	NS	92.7 ± 4.3	92.7 ± 5	NS
CO (n = 4.2-6.6 L/min)	7.9 ± 1.6	7.5 ± 0.9	NS	6.9 ± 1.2	7.6 ± 0.9	NS
SVR (n = 700-1600 dyn·sec·cm^5)	1394 ± 307	1074 ± 127	NS	1367 ± 216	1245 ± 261	NS
EDV (n = 106 ± 20 mL)	177 ± 17	160 ± 31	NS	173 ± 18	155 ± 25	NS
ESV (n =39 ± 12 mL)	61 ± 8	52 ± 9	NS	61 ± 10	58 ± 13	NS
RLV (n = 107 ± 10 mL/m^2)	80 ± 11	90 ± 19	NS	82 ± 10	74 ± 8	NS
LLV (n = 127 ± 12 mL/m^2)	77 ± 9	90 ± 18	NS	85 ± 8	81 ± 10	NS
CBV (n = 1280 ± 100 mL/m^2)	703 ± 82	818 ± 179	NS	708 ± 58	651 ± 73	NS
CCVV (n = 880 ± 61 mL/m^2)	546 ± 69	636 ± 143	NS	622 ± 100	564 ± 58	NS
GFR (n = 90-120 mL/min/m^2)	95 ± 8	88 ± 9	NS	92 ± 11	86 ± 13	NS
RPF (n = 460-550 mL/min/m^2)	604 ± 130	674 ± 130	NS	692 ± 109	591 ± 94	NS
RVR (n = 10-16 × 10^{3}dyn·sec·cm^{-5})	7166 ± 873	9283 ± 1410	NS	8182 ± 1208	7525 ± 966	NS
FF (%) (n = 16-22)	17.8	16.1	NS	15.3	16.3	NS

Abbreviations: NS, not significant; HR, heart rate; MAP, mean arterial pressure; SVR, systemic vascular resistance; EDV, end diastolic volume; ESV, end systolic volume; RLV, right lung volume; LLV, left lung volume; CBV, central blood volume; CCVV, central cardiac and vascular volume; GFR, glomerular filtration rate; RPF, renal plasma flow; RVR, renal vascular resistance; FF, filtration fraction; CO, cardiac output.

on assuming the erect posture in the post-TIPS ascites-free patients was not due to any change in renal hemodynamics. Glomerular filtration rate, RPF, RVR, and filtration fraction were unaltered when these patients changed from supine to erect posture. Likewise, there was no change in systemic hemodynamics. Mean arterial pressure, heart rate, cardiac output, and SVR were unaltered on assuming the erect position. Similarly, CBV, CCVV, right and lung vascular volumes were also unchanged. End-systolic volume and end-diastolic volume were also similar in supine and erect positions.

Hormonal Profile (Fig. 3). On assuming the erect po

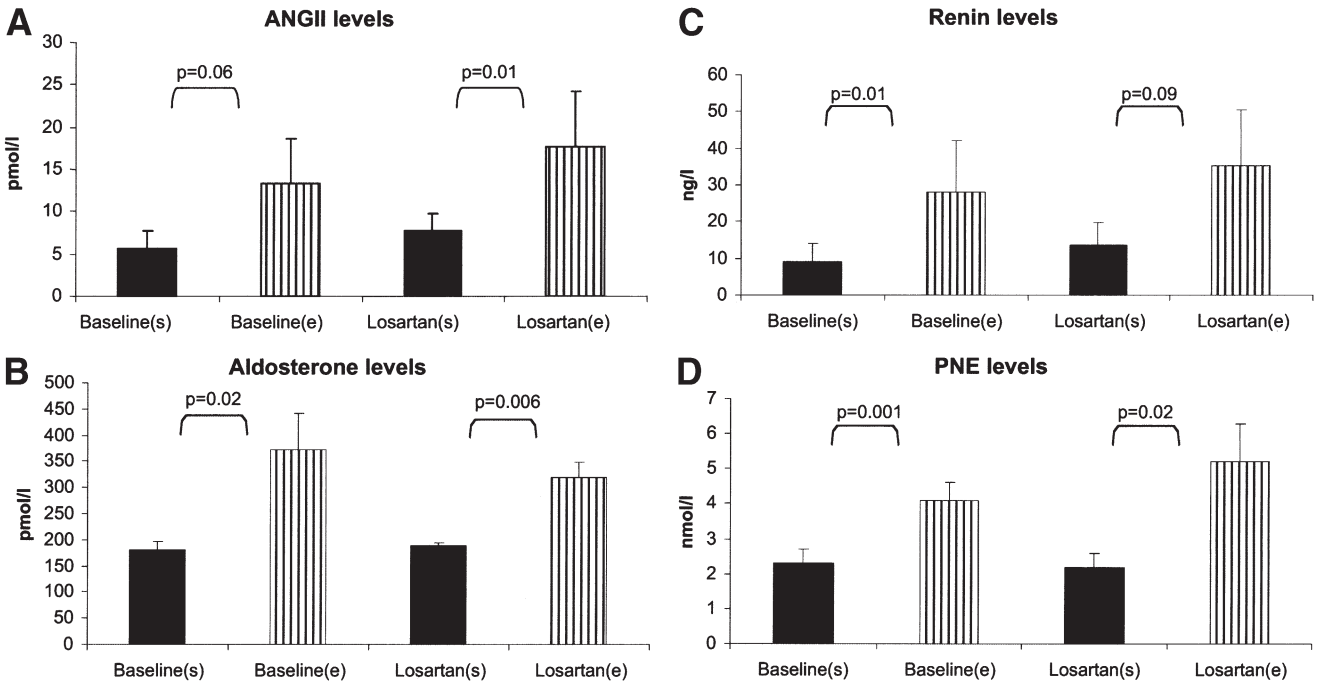

Fig. 3. Systemic hormonal levels seen with change in posture and after losartan. (s) = supine, (e) = erect. ANG II (normal levels): 0.8-15.9 pmol/L; Aldosterone (normal levels): 27-860 pmol/L; Renin (normal levels): 0-20.2ng/L; PNE (normal levels): 0.8-3.4 nmol/L. (A) ANGII levels rise on standing but are not significantly different after losartan administration. (B) Aldosterone levels also rise on standing but are not different after losartan. (C) Renin levels rise on standing but are not affected by losartan. (D) PNE levels are higher after standing but are unaffected by losartan.

sition, there was a rise in the plasma renin levels (9.1 ± 5.0 ng/L in the supine posture to 28.2 ± 14.0 ng/L in the erect posture, $P = .01$), the plasma ANG II (5.6 ± 2.2 pmol/L in the supine posture to 13.3 ± 5.4 pmol/L in the erect posture, $P = .06$), plasma aldosterone (181 ± 17 pmol/L in the supine posture to 373 ± 69 pmol/L in the erect posture, $P = .02$), and PNE (2.3 ± 0.4 nmol/L in the supine posture to 4.1 ± 0.5 nmol/L in the erect posture, $P = .001$). The ANF levels, however, remained normal and unchanged when changing from the supine (9.9 ± 1.7 ng/L) to the erect posture (10.3 ± 3.1 ng/L, P = NS. Normal < 15 ng/L).

(2) Following a Single Low Dose (7.5 mg) of Losartan. *Sodium Metabolism (Fig. 2).* Following a single low dose (7.5 mg) of losartan, the UNaV changed from 0.28 ± 0.03 mmol/min in the supine posture to 0.15 ± 0.02 mmol/min in the erect posture ($P = .01$). Urinary volume also decreased from 4.1 ± 0.7 to 2.5 ± 0.5 mL/min ($P = .02$) when changed from the supine to the erect posture. These changes were accompanied by significant increases in both PTRNa (from 63.9 ± 3.9% to 73.8 ± 2.4%, $P = .03$) and DTRNa (from 93.7 ± 0.8% to 95.8 ± 0.6% $P = .01$) with assumption of the erect posture, resulting in a significant reduction in FENa (2.3 ± 0.4% in the supine posture to 1.1 ± 0.2% in the erect posture, $P = .01$).

Systemic and Renal Hemodynamics and Vascular Volumes (Table 2). A single oral low dose of 7.5 mg of losartan had no effect on either the renal or the systemic hemodynamics, or cardiac parameters, or cardiac volume measured with the change in posture.

Hormonal Profile (Fig. 3). After the administration of a single low dose of 7.5 mg of losartan, the assumption of the erect posture in post-TIPS ascites-free patients with cirrhosis was associated with a rise in the plasma renin (13.6 ± 6.0 ng/L in the supine posture to 35.4 ± 15.2 ng/L in the erect posture, $P = .09$), plasma ANG II (7.8 ± 2.0 pmol/L in the supine posture to 17.6 ± 4.7 pmol/L in the erect posture, $P = .01$), plasma aldosterone (189 ± 20 to 318 ± 30 pmol/L, $P = .006$), and PNE levels (2.2 ± 0.4 nmol/L in the supine posture to 5.2 ± 1.1 nmol/L in the erect posture, $P = .02$). Plasma ANF remained unchanged on assuming the erect posture (10.2 ± 1.9 ng/L in the supine posture versus 12.5 ± 2.9 ng/L in the erect posture, P = NS).

(3) Comparison Between Baseline Posture Changes and Post-Losartan Posture Changes. *Sodium Metabolism (Fig. 2).* PTRNa was blunted by losartan in both supine (baseline 69.7 ± 3.1% to post-losartan 63.9 ± 3.9%, $P = .01$) and erect positions (baseline 81.1 ± 1.8% to 73.8 ± 2.4% post-losartan, $P = .01$). DDNa was higher after losartan administration in both supine (baseline 3.97 ± 0.5 mmol/min to post-losartan 4.7 ± 0.7 mmol/min, $P = .03$) and erect postures (baseline 2.7 ± 0.4 mmol/min to post-losartan 3.9 ± 0.24 mmol/min ($P = .06$). The DTRNa was higher post-losartan in both the supine (baseline 3.7 ± 0.5 to post-losartan 4.4 ± 0.6 mmol/L, $P = .05$) and in the erect postures (baseline 2.5 ± 0.4 to post-losartan 3.8 ± 0.6 mmol/L, $P = .03$). Therefore losartan did not affect FeNa in either the supine (baseline 1.8 ± 0.2% to post-losartan 2.3 ± 0.4%, P = NS) and erect positions (baseline 0.95 ± 0.2% to post-losartan 1.1 ± 0.2%, P = NS). Urinary sodium excretion was therefore unaffected by low dose losartan in the supine (0.30 ± 0.05 mmol/min at baseline versus 0.28 ± 0.03mmol/min with losartan, P = NS) and erect positions (0.13 ± 0.02 mmol/min versus 0.15 ± 0.03 mmol/min with losartan, P = NS). Likewise, urinary volume was similar in both the supine (4.5 ± 3.2 mL/min at baseline versus 4.1 ± 2.2 mL/min with losartan, P = NS) and erect positions (2.5 ± 2.5 mL/min at baseline versus 2.5 ± 1.6 mL/min with losartan, P = NS) when baseline values were compared with post-losartan values.

Vascular Volumes, Systemic and Renal Hemodynamics. The administration of a single low dose losartan did not affect any of these measurements.

Hormonal Profile (Fig. 3). The administration of a single low dose of losartan did not change the systemic hormonal levels when compared with the baseline values for each of the postures.

Discussion

TIPS is a unique model of cirrhosis without sinusoidal portal hypertension. We have previously demonstrated that patients with a functioning TIPS and therefore no sinusoidal portal hypertension, exhibit subtle renal sodium retention when they are challenged with high sodium load (200 mmol/day).[9] Sinusoidal portal hypertension is clearly important in the pathogenesis of cirrhotic ascites,[1-3] as demonstrated by the resolution or improvement of ascites after TIPS insertion.[4-8] However, we believe this subtle sodium retention in these patients is not solely related to the presence of portal hypertension because the functioning TIPS normalizessinusoidal portal pressure.

Other factors that have been shown to be involved in the pathogenesis of sodium retention in cirrhosis include liver dysfunction[26,27] and a reduction in EABV secondary to systemic arterial vasodilatation. For example, Wensing et al. have shown in both a carbon tetrachloride rat model of cirrhosis[26] and in human cirrhosis[27] that the onset of sodium retention is related to a certain threshold of liver dysfunction. Although we did not quantify liver function

formally, we believe that the liver dysfunction in these post-TIPS ascites patients was not severe as their mean Child Pugh score was 5.7 ± 0.4. In addition, liver function was unaltered during the study and therefore the differences in renal sodium handling we observed in the current study on assuming the erect posture cannot be attributed to changes in liver function itself. We also believe that a reduction in EABV was not responsible for the subtle sodium retention in these patients since they demonstrated low-normal hormonal levels (renin, ANG II, aldosterone, PNE) which suggest an adequately filled circulation.

Therefore, could another factor such as erect posture be responsible for the subtle sodium retention in these post-TIPS ascites-free patients? The phenomenon of posture-related abnormal sodium handling has previously been described in pre-ascitic patients with cirrhosis and portal hypertension.[14] In that group of patients, the mechanism by which sodium retention was achieved was thought to be related to RAAS activation in the erect posture,[15,17] specifically intrarenal ANG II[17] and aldosterone.[15] Although these post-TIPS ascites-free patients in the current study differ from the pre-ascitic patients in that they no longer have sinusoidal portal hypertension, they are similar in the degree of liver dysfunction and hormonal profile.[17,18] It is therefore possible that the same erect posture-induced activation of RAAS is responsible for the subtle renal sodium retention in post-TIPS ascites-free patients. If that was true, then the posture-related sodium retention in cirrhosis would be independent of portal hypertension.

Our study demonstrates that the subtle renal sodium retention seen in post-TIPS ascites-free patients with cirrhosis and previous refractory ascites is indeed related to the assumption of erect posture. Patients showed a reduction in sodium excretion and urinary volume on assuming the erect position. This was mediated by tubular factors rather than by changes in systemic or renal hemodynamics. There was an increase in PTRNa on assuming the erect posture, and hence a reduced DDNa, accompanied by an increased DTRNa. This suggests that sodium handling in these post-TIPS ascites-free patients was abnormal at both the proximal and distal tubules. This is because the glomerulotubular balance, a physiological process, demands that the sodium reabsorbed at a particular nephron site to be proportional to the amount of sodium being delivered to it.[28] Therefore, an unchanged filtered sodium load from an unchanged GFR on standing found in these post-TIPS ascites-free patients should lead to an unchanged PTRNa. What we observed was an increased PTRNa in the erect posture. Likewise, a reduced DDNa on standing as was found in these patients should result in a reduced DTRNa.[28] But for these post-TIPS ascites-free patients, there was an excess amount of sodium being reabsorbed despite a reduced DDNa, above what was expected from the glomerulotubular balance. It is interesting to note that the same abnormalities in proximal and distal tubular handling have been reported in pre-ascitic patients with cirrhosis,[17] suggesting that these abnormalities are related to the presence of cirrhosis rather than portal hypertension *per se*.

To test the hypothesis that the same sodium retaining mechanism that is operational in pre-ascitic cirrhosis also applies to post-TIPS ascites-free patients, we used oral, low-dose losartan as a probe to investigate the role of ANG II in mediating this posture-induced increase in sodium retention. We specifically chose 7.5 mg of losartan because this has been shown in pre-ascitic patients with similar hemodynamics and hormonal profile to not influence systemic hemodynamics, and therefore removes any confounding effects of systemic hemodynamic changes. The same dose of losartan has been shown to blunt erect posture-induced sodium retention in pre-ascitic cirrhosis with an increase in the overall sodium excretion on standing.[17] A similar blunting of overall sodium retention was not observed in this group of post-TIPS ascites-free patients with cirrhosis. A detailed analysis of tubular sodium metabolism at different nephron sites has provided the explanation. Using lithium clearance technique, we have shown that oral low-dose losartan can *blunt* the increase in PTRNa in both the supine and erect postures in these post-TIPS ascites-free patients, suggesting that ANG II is involved in mediating excess sodium reabsorption in the proximal nephron. However, we were unable to show the expected compensatory rise in serum ANG II levels. The concentration of ANG II in the proximal tubular fluid is 1000-fold that of plasma[29] and directly increases PTRNa.[30,31] We speculate that the lack of rise in systemic ANG II levels, may be partly related to the fact that the intrarenal ANG II released is metabolized within the kidney, leaving the systemic baseline and post-losartan renin levels unchanged. The effects of low-dose losartan in post-TIPS ascites-free patients differs from that observed in pre-ascitic patients, in whom low-dose losartan could only blunt the increase in PTRNa in the erect posture. This would suggest that ANG II in these post-TIPS ascites-free patients is involved in sodium retention in the proximal tubule in both the erect and supine postures.

With respect to sodium reabsorption in the distal nephron (loop of Henle and distal tubule/collecting duct), apart from what is being governed by glomerulotubular balance, many hormones including aldosterone and ANG II are also involved.[32-36] Because the pre- and postlosartan aldosterone levels were unchanged, we would not have expected a change in DTRNa. The observed increase in DTRNa, especially in the erect posture may be explained by an increased sensitivity to aldosterone (leading to loss of glomerulotubular balance). This contrasts with the pre-ascitic patients, who have lower aldosterone levels with the same dose of losartan,[17] and no increase in DTRNa is observed, even in the erect posture. It is possible that a higher dose of losartan may be able to reduce the aldosterone levels sufficiently to effect no net change in the DTRNa, in order to allow an overall increase in renal sodium excretion.

In summary, post-TIPS ascites-free patients with cirrhosis have an abnormality in both their proximal and distal tubular handling of sodium, which is exaggerated in the erect posture. These sodium handling abnormalities are independent of sinusoidal portal hypertension. We speculate that the sodium retention in the proximal tubule is mediated at least partially, by intrarenal activation of ANG II, while the increased distal tubular reabsorption of sodium may be related to heightened aldosterone sensitivity. Further studies with a combination of losartan and an aldosterone antagonist may be able to unmask the natriuretic effects of low-dose losartan in this population of post-TIPS ascites-free patients with cirrhosis.

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