Renal distal tubular handling of sodium in central fluid volume homeostasis in preascitic cirrhosis

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Abstract

Background/Aims—Patients with preascitic liver cirrhosis have an increased central plasma volume, and, for any given plasma aldosterone concentration, they excrete less sodium than healthy controls. A detailed study of the distribution of sodium reabsorption along the segments of the renal tubule, especially the distal one, is still lacking in preascitic cirrhosis. **Methods**—Twelve patients with Child-Pugh class A cirrhosis and nine control subjects (both groups on a normosodic diet) were submitted to the following investigations: (a) plasma levels of active renin and aldosterone; (b) four hour renal clearance of lithium (an index of fluid delivery to the loop of Henle), creatinine, sodium, and potassium; (c) dopaminergic activity, as measured by incremental aldosterone response to intravenous metoclopramide.

Results—Metoclopramide induced higher incremental aldosterone responses, indicating increased dopaminergic activity in patients than controls, which is evidence of an increased central plasma volume (+30 min: 160.2 (68.8) v 83.6 (35.2) pg/ml, $p < 0.01$; +60 min: 140.5 (80.3) v 36.8 (36.1) pg/ml, $p < 0.01$). Patients had increased distal fractional sodium reabsorption compared with controls (26.9 (6.7)% v 12.5 (3.4)% of the filtered sodium load, $p < 0.05$). In the patient group there was an inverse correlation between: (a) absolute distal sodium reabsorption and active renin ($r = -0.59$, $p < 0.05$); (b) fractional distal sodium reabsorption and sodium excretion ($r = -0.66$, $p < 0.03$).

Conclusions—These data suggest that in preascitic cirrhosis the distal fractional tubular reabsorption of sodium is increased and critical in regulating both central fluid volume and sodium excretion.

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Keywords: kidney; sodium handling; lithium clearance; liver cirrhosis; dopamine; central fluid volume

Renal sodium retention occurs universally in patients with liver cirrhosis and ascites. Studies in experimental animals have consistently shown that sodium retention precedes ascites formation, emphasising the role of this renal functional abnormality in the pathogenesis of ascites.¹⁻³

In patients with preascitic cirrhosis, subtle changes in body fluid compartments occur,

namely an increase in circulating and/or central plasma volume. This has been shown by several experimental observations: increased distribution volume of ¹³¹I-labelled albumin and ⁵¹Cr-labelled erythrocytes⁴; increased central blood volume measured by radionuclide angiography⁵; increased end diastolic and end systolic left ventricular diameters⁶; suppression of the renin-angiotensin-aldosterone axis⁷⁻⁹; high plasma atrial natriuretic factor concentrations¹⁰; increased endogenous dopaminergic activity.¹¹

The role of dopaminergic activity as a marker of central volume is supported by the observation that plasma dopamine increases after saline infusion or head-out water immersion in normal men,^{12, 13} both procedures being able to increase central plasma volume acutely.

In cirrhotic patients and experimental animals, the increase in plasma volume is not only a critical event preceding the development of ascites; together with the systemic arterial vasodilatation, it is necessary for the full development of the hyperdynamic circulatory syndrome that maintains the portal venous hypertension in liver cirrhosis.^{14, 15}

Much controversy surrounds renal functional abnormalities in patients with preascitic cirrhosis. Some authors have documented a modest reduction in glomerular filtration rate at the preascitic stage.¹⁶⁻¹⁸ On the other hand, others have suggested that glomerular hyperfiltration occurs in well compensated cirrhotics.¹⁹ However, these patients are unable to handle a sodium load normally and develop ascites or oedema when intravenous saline solutions are given, indicating inappropriately elevated tubular sodium and water retention even in the presence of a preserved glomerular filtration rate.²⁰⁻²² Normally most filtered sodium is reabsorbed in the proximal tubule, with fine adjustments to sodium excretion being carried out in the distal tubule. In preascitic cirrhosis,

Abbreviations used in this paper: P-Na, plasma sodium concentration; P-K, plasma potassium concentration; P-Li, plasma lithium concentration; P-Cr, plasma creatinine concentration; U-Na, urinary sodium concentration; U-K, urinary potassium concentration; U-Li, urinary lithium concentration; U-Cr, urinary creatinine concentration; C-Li, renal lithium clearance; C-Na, renal sodium clearance; C-K, renal potassium clearance; C-Cr, renal creatinine clearance; FE-Na, fractional sodium excretion; FE-K, fractional potassium excretion; FE-Li, fractional lithium excretion; FI-Na, filtered sodium load; DD, absolute distal fluid delivery; DDNa, absolute distal sodium delivery; DRNa, absolute distal sodium reabsorption; DFRNa I, distal fractional sodium reabsorption I; DFRNa II, distal fractional sodium reabsorption II.

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the site in the nephron at which enhanced sodium reabsorption occurs is not known.²³

Using the fractional lithium clearance technique, a method for determining proximal and distal reabsorption of sodium and water,^{24, 25} Simón *et al*²⁶ observed no difference in proximal tubular handling of sodium between preascitic cirrhotics and controls. On the other hand, Wong *et al*²⁷ described in compensated cirrhosis decreased fractional lithium excretion, a marker of the fraction of filtered sodium load that escapes proximal tubular reabsorption.

The aims of this study were (a) to investigate the distribution of sodium reabsorption in the different renal tubular segments in order to identify the renal tubular site of early sodium retention and (b) to evaluate the interaction between tubular function and central fluid volume, as studied by different markers of effective volemia—that is, plasma active renin and endogenous dopaminergic activity^{11–13}—in a homogeneous group of patients with well compensated preascitic cirrhosis.

Materials and methods

PATIENTS AND CONTROL SUBJECTS

Twelve patients (nine men, three women; age range 39–69 years) with biopsy proven Child-Pugh A liver cirrhosis²⁸ were studied. Patients with previous variceal bleeding, evidence of ascites, use of diuretics, heart failure, intrinsic renal disease, arterial hypertension, diabetes mellitus requiring drug treatment, or endocrine disease were excluded. No steroids, prostaglandin synthesis inhibitors, catecholamines, or antihypertensive drugs were administered for at least one month before the study. Nine healthy subjects (five men, four women; age range 27–65 years) were also studied as the control group. Patients and controls were not matched for weight, age, and size. Alcohol consumption had ceased in all patients at least three months previously and in control subjects was discontinued during the week before the study.

This study, which was performed in compliance with the 1975 Declaration of Helsinki ethical guidelines, was approved by the University of Modena ethics committee. All patients gave informed consent before participation in the study.

PROTOCOL

Before the study, control subjects and patients underwent an equilibration period of five days, during which they received a diet providing 120 mEq sodium and 60 mEq potassium daily.

At 2200 hours on the day before the study, 600 mg lithium carbonate was administered orally. The following morning urine collection was commenced at 0800 hours. Blood samples were taken at the beginning and end of the urine collection period which lasted four hours (until 1200 hours). Urine was collected by spontaneous voiding. Water intake was fixed at 1.5 litres in the course of the four hour period. Patients and controls were maintained supine throughout the four hour clearance period. At midday, after urine collection, they were

allowed to have a light meal. Blood samples at the beginning and at 1200 hours were analysed for plasma concentrations of sodium (P-Na), potassium (P-K), lithium (P-Li), and creatinine (P-Cr). Blood samples at the beginning of the clearance period were also analysed for plasma active renin and aldosterone concentrations. Urine samples were analysed for sodium (U-Na), potassium (U-K), lithium (U-Li), and creatinine (U-Cr) concentrations in the clearance period.

A further two hours of bed rest was commenced at 1400 hours. At the end of this period (time 0: 1600 hours) blood was withdrawn for determination of serum levels of aldosterone. A bolus of metoclopramide (10 mg intravenously; Plasil; Lepetit, Milan, Italy), a dopamine₂-receptor antagonist, was injected, and blood collected at 30 and 60 minutes for measurement of plasma aldosterone. The increase in plasma aldosterone at 30 minutes after dopaminergic blockade is an accepted measure of endogenous dopaminergic activity, because of the tonic inhibitory effect of endogenous dopamine on mineralocorticoid secretion.^{29, 30}

ANALYTICAL METHODS

P-Na, U-Na, P-Li, U-Li, P-K, and U-K were measured with a flame photometer (Instrumentation Laboratory model 143, Paderno Dugnano, Italy). P-Cr and U-Cr were determined colorimetrically.³¹ Human active renin was determined in EDTA plasma. Active renin was determined by a two site immunoradiometric assay for the measurement of active renin protein (Nichols Institute Diagnostics, San Juan, California, USA). The normal range from our laboratory is 5–47 µU/ml in supine subjects and 7–76 µU/ml when subjects are in the upright posture. Plasma aldosterone concentrations were evaluated by radioimmunoassay, using a kit from Sorin Biomedica (Saluggia, Italy) containing solid phase antibody coated tubes. Intra-assay variability was 7.4%. The normal range from our laboratory is 10–150 pg/ml in the supine position and 35–300 pg/ml in the upright posture.

CALCULATIONS

P-Li was calculated from the formula³²:

$$\frac{\text{P-Li (pre)} - \text{P-Li (post)}}{2.3 \times \log \left(\frac{\text{P-Li (pre)}}{\text{P-Li (post)}} \right)}$$

where P-Li (pre) and P-Li (post) were the plasma lithium concentrations at the beginning and end of the urine collection period respectively. P-Na, P-K, and P-Cr were calculated as the means of the corresponding values at the beginning and end of the urine collection period. Lithium clearance (C-Li), sodium clearance (C-Na), potassium clearance (C-K), and creatinine clearance (C-Cr) were calculated. C-Cr was used as an estimate of glomerular filtration rate. Fractional sodium excretion (FE-Na), fractional potassium excretion (FE-K), and fractional lithium excretion

Table 1 Clinical and biochemical data of the 12 patients with liver cirrhosis

Age (years)	51 (11)
Aetiology	
Alcoholic	2
Hepatitis C virus	8
Hepatitis B virus	1
Autoimmune hepatitis	1
Serum bilirubin (mg/dl)	1.2 (0.5)
Prothrombin time (%)	79 (10)
Serum albumin (g/dl)	3.8 (0.3)
Alkaline phosphatase (IU/l)*	340 (198)
ALT (IU/l)†	208 (119)
Platelet count (cell/mm ³)	89900 (29300)
Oesophageal varices (present/absent)	6/6
Blood urea nitrogen (mg/dl)	35.7 (9.1)
Plasma creatinine (mg/dl)	0.8 (0.1)
Plasma sodium (mEq/l)	140 (2)
Plasma potassium (mEq/l)	3.9 (0.3)

Data are mean (SD). ALT, alanine aminotransferase.

*Normal value <280.

†Normal value <36.

(FE-Li), an index of the fraction of filtered sodium load escaping proximal tubular reabsorption, were calculated from the ratio of C-Na, C-K, and C-Li to C-Cr, respectively.

Assuming that lithium is reabsorbed in the proximal tubule in parallel with sodium and water and that it is neither secreted nor reabsorbed beyond the proximal tubule, from C-Li, U-Na $\times$ V, C-Na, and C-Cr the following parameters were derived as described by Boer *et al*³³:

Filtered sodium load (FI-Na) = P-Na $\times$ C-Cr (mEq/min)
Absolute distal fluid delivery (DD) = C-Li (ml/min)

Absolute distal sodium delivery (DDNa) = C-Li $\times$ P-Na (mEq/min)

Absolute distal sodium reabsorption (DRNa) = DDNa - (U-Na $\times$ V) (mEq/min)

Table 2 Aldosterone and active renin levels in patients and controls

	Patients (n=12)	Controls (n=9)
Morning active renin (μ U/ml)	16.2 (3.9)	20.9 (11.7)
Morning aldosterone (pg/ml)	80.3 (43.2)	112.7 (51.3)
Basal 1600 hour aldosterone (pg/ml)	94.1 (45.4)	111.7 (55.1)
Aldosterone 30 minutes after metoclopramide (pg/ml)	254.4 (109.1)*	195.2 (65.5)*
Aldosterone 60 minutes after metoclopramide (pg/ml)	234.7 (110.6)*	148.4 (61.6)*
Incremental aldosterone response 30 minutes after metoclopramide (pg/ml)	160.2 (68.8)†	83.6 (35.2)
Incremental aldosterone response 60 minutes after metoclopramide (pg/ml)	140.5 (80.3)†	36.8 (39.1)

Data are mean (SD).

*p<0.001 compared with corresponding 1600 hour basal values (Student's *t* test for paired data).

†p<0.01 compared with values in control subjects (Student's *t* test for unpaired data).

Table 3 Renal sodium handling parameters in cirrhotic patients and in control subjects

	Patients (n=12)	Controls (n=9)
Creatinine clearance (ml/min/1.73 m ² BSA)	143.6 (38.6)*	181.5 (37.2)
FI-Na (mEq/min)	19.05 (7.03)*	30.4 (6.4)
U-Na $\times$ V (μ Eq/min)	140 (80)	168 (30)
C-Li (ml/min)	30.7 (9.3)	27.5 (6.7)
FE-Na (%)	0.76 (0.39)	0.7 (0.11)
FE-K (%)	9.4 (9.2)	7.5 (1.60)
FE-Li (%)	27.5 (21.2)	18.2 (6.4)
DDNa (mEq/min)	4.25 (1.30)	3.9 (1.0)
DRNa (mEq/min)	4.14 (1.23)	3.7 (1.06)
DFRNa I (%)	26.9 (6.7)**	12.5 (3.4)
DFRNa II (%)	97.5 (1.9)	93.7 (2.5)

Data are mean (SD).

BSA, body surface area; U-Na, urinary sodium concentration; C-Li, renal lithium clearance; FE-Na, fractional sodium excretion; FE-K, fractional potassium excretion; FE-Li, fractional lithium excretion; FI-Na, filtered sodium load; DDNa, absolute distal sodium delivery; DRNa, absolute distal sodium reabsorption; DFRNa I, distal fractional sodium reabsorption I; DFRNa II, distal fractional sodium reabsorption II.

*p<0.01, **p<0.05 compared with controls (Student's *t* test for unpaired data).

Distal fractional sodium reabsorption I (DFRNa I) = DRNa/FI-Na (%)

Moreover, distal fractional sodium reabsorption was also evaluated, in an alternative manner, as a percentage of absolute distal sodium delivery from the formula:

Distal fractional sodium reabsorption II (DFRNa II) = DRNa/DDNa (%)

Finally it should be noted that, throughout the study, the expression "distal tubule" indicates all the segments of renal tubule beyond the proximal one.

STATISTICAL ANALYSIS

Results are expressed as mean (SD). Statistical analysis was performed using Student's *t* test for paired or unpaired data³⁴, as shown in tables 2 and 3 and fig 1. Correlation coefficients were derived using Spearman's rank correlation.³⁵ Results were considered significant at p<0.05. The incremental aldosterone response at 30 and 60 minutes after metoclopramide is expressed as the mean (SD) of the individual incremental aldosterone responses.

Results

Table 1 gives the main baseline clinical and laboratory findings of the cirrhotic patients. Age was not different from controls (49 (13) years).

Mean values of plasma active renin and aldosterone measured at 0800 hours in subjects in a reclining position did not differ significantly between patients and controls, both being lower in the group of cirrhotic patients (table 2). Incremental plasma aldosterone responses were significantly greater in patients than in control subjects both 30 and 60 minutes after intravenous metoclopramide administration (table 2), indicating increased endogenous dopaminergic activity in the cirrhotic group.

Table 3 shows mean data for renal sodium handling in cirrhotics and controls. Cirrhotic patients had significantly lower values for glomerular filtration rate and filtered sodium load than controls. DFRNa I was significantly higher in the preascitic cirrhotics (table 3).

There was a positive correlation between glomerular filtration rate and C-Li in the control group (*r* = 0.64, p<0.05) but not in patients. In the patient group inverse correlations were observed between active renin plasma levels and the following parameters: dopaminergic activity (expressed as incremental aldosterone plasma

Figure 1 Inverse correlation between morning plasma levels of active renin and dopaminergic activity, evaluated from the incremental aldosterone plasma values 30 minutes after intravenous metoclopramide (IAPV), in Child-Pugh A cirrhotic patients.

Figure 2 Inverse correlation between morning plasma levels of active renin and renal lithium clearance (C-Li), an index of fluid delivery to the loop of Henle, in Child-Pugh A cirrhotic patients.

Figure 3 Inverse correlation between absolute distal tubular reabsorption of sodium (DRNa) and morning plasma levels of active renin in Child-Pugh A cirrhotic patients.

values 30 minutes after metoclopramide administration) ($r = -0.64$, $p < 0.05$) (fig 1), C-Li ($r = -0.60$, $p < 0.05$) (fig 2), and DRNa ($r = -0.59$, $p < 0.05$) (fig 3). In the cirrhotic group we found a positive correlation between C-Li and sodium excretion ($r = 0.68$, $p < 0.02$) and an inverse one between DFRNa II and sodium excretion ($r = -0.66$, $p < 0.03$).

In the patient group, there was no significant correlation between morning plasma aldosterone levels and any of the following parameters of renal sodium handling: sodium excretion ($r = -0.15$, $p > 0.05$), DFRNa I ($r = 0.09$, $p > 0.05$) and DFRNa II ($r = 0.04$, $p > 0.05$). However, in the control group, there was a significant correlation between morning aldosterone levels and both of these parameters: DFRNa I ($r = 0.71$, $p < 0.05$) and sodium excretion ($r = -0.68$, $p < 0.05$).

Discussion

Cirrhotic patients with ascites have an arterial vascular compartment that is underfilled, as arterial pressure is low despite the increased plasma volume and cardiac index. This is due to the peripheral arterial vasodilatation that occurs despite overactivity of endogenous vasoconstrictor systems—that is, secondary hyperaldosteronism, increased activity of the sympathetic nervous system, and non-osmotic hypersecretion of vasopressin.^{36–39}

However, in preascitic cirrhosis there is good evidence that the arterial vascular bed is overfilled: three groups of investigators have reported that plasma renin activity and aldosterone are suppressed in preascitic cirrhosis.^{40–42} This supports the idea that there is a period of vascular overfilling before the appearance of ascites.^{1, 2, 43} This notion is also supported by the observation that cirrhotics without ascites or with early ascites formation display increased end diastolic diameters of the left ven-

tricle, indicative of expanded intravascular volume.^{6, 44}

The total amount of sodium retained by cirrhotic patients before ascites development is dependent on the balance between sodium intake, relatively small and fixed non-renal sodium losses, and the sodium excreted in the urine.

Despite controversial findings of increased¹⁹ or decreased^{16–18} glomerular filtration rate in preascitic cirrhosis, these patients are unable to handle an oral or intravenous sodium load, indicating increased tubular (proximal or distal) sodium retention even in the presence of preserved glomerular filtration rate.^{20–22}

On average, our patients displayed clearly, although not significantly, reduced concentrations of plasma aldosterone and active renin compared with controls (table 2). Unlike previous studies, which identified suppressed plasma renin activity at this disease stage,^{40–42} we measured the circulating concentration of active renin protein by an immunoradiometric assay. In effect, patients with liver cirrhosis may have decreased plasma levels of renin substrate—that is, angiotensinogen—which leads to an underestimation of renin concentration when measured as plasma renin activity.^{45, 46}

Compared with controls, our patients showed evidence of increased endogenous dopaminergic activity, expressed as higher incremental plasma aldosterone response after intravenous injection of the antidopaminergic drug metoclopramide (table 2). This well recognised test takes advantage of the inhibitory effect of endogenous dopamine on adrenal mineralocorticoid secretion.^{47–49} In other words, the higher the incremental aldosterone response after metoclopramide, the higher the baseline endogenous dopaminergic activity counteracting aldosterone secretion.

Based on the data presented, the increased dopaminergic activity seems to be a reliable marker of an expanded central fluid volume, as we found an inverse correlation between active renin and the incremental aldosterone response after metoclopramide administration (fig 1). This is supported by the previous observation that plasma dopamine increases after saline infusion or head-out water immersion in normal men,^{12, 13} both procedures being able to increase central plasma volume acutely.

The increased dopaminergic function and the decreased circulating immunoreactive renin and aldosterone suggest that there was overfilling of the vascular bed in our group of preascitic cirrhotics while on a normal sodium diet.

In order to identify the site of increased sodium reabsorption in the nephron, we studied our patients using the lithium clearance and fractional excretion technique.^{24, 25} The following conclusions are based on the assumption that C-Li is an index of proximal sodium reabsorption. It should be noted that the mean FE-Na in our cirrhotic patients exceeded the threshold below which the reliability of C-Li as an index of salt and fluid delivery from the proximal tubule is questionable. In fact, studies

in humans showed that a decrease in C-Li due to lithium reabsorption beyond the proximal tubule occurs only at values of FE-Na close to 0.02%.^{32 50-52}

According to previous literature,¹⁶⁻¹⁸ our preascitic cirrhotics had a lower glomerular filtration rate and filtered sodium load than controls, although they did not exhibit hyponatraemia or hyperreninaemia. They also displayed a higher distal fractional reabsorption of sodium (expressed as a percentage of FI-Na) (table 3). These data suggest that the proximal tubule is unlikely to be the segment of the nephron responsible for the enhanced sodium retention in the preascitic patient.

The inverse correlation of active renin with C-Li (fig 2) actually underlines a compensatory role for the proximal renal tubule. In other words, it is able to deliver more fluid and sodium to the loop of Henle during a progressive increase in circulating fluid volume. Indeed, this compensatory role could be due to the increased dopaminergic activity we identified in patients, as dopamine exerts strong diuretic and natriuretic effects acting on renal cortical dopamine receptors, and inhibits the Na⁺-K⁺-ATPase activity in proximal tubule segments.^{53 54} At this disease stage, this mechanism of compensation is efficient, as C-Li also correlated directly with net sodium excretion.

In contrast, the avidity of the sodium retention displayed by the distal nephron, which is increased in patients with respect to healthy controls, is critical in regulating the increased central fluid volume and the net sodium excretion, because absolute distal reabsorption of sodium correlates inversely with the active renin plasma levels (fig 3), and DFRNa II correlates inversely with sodium excretion.

Our data indicate that there is enhanced sodium retention in the distal tubule, but this is not related to plasma aldosterone. In effect the net sodium excretion and the fractional distal sodium reabsorption were clearly independent of basal aldosterone plasma concentrations, as already shown in recumbent preascitic cirrhotics.^{9 16 55} In contrast, in the control group, we found the predicted correlations between morning aldosterone levels and both of these parameters: DFRNa I and sodium excretion.

In other studies dealing with preascitic cirrhosis, Simón *et al*⁶ observed that C-Li and fractional proximal sodium reabsorption were not different from control subjects, and Wong *et al*²⁷ identified reduced values of FE-Li in patients with compensated alcoholic cirrhosis. However, Wong *et al*²⁷ observed an increased glomerular filtration rate in those compensated cirrhotics, an observation at variance with others.¹⁶⁻¹⁸ In agreement with our results, the same investigators also noted that the values of distal tubular reabsorption of sodium (expressed as the reabsorbed percentage of distal delivery of sodium) were increased in patients compared with controls.²⁷

Recently, in rats with experimental liver cirrhosis Jonassen *et al*⁶ observed a consistent increase in the volume of the thick ascending limb of the loop of Henle epithelium and

increased NaCl reabsorption at this nephron site, an aldosterone independent tubule segment. Our results and those of Jonassen *et al* are clearly at variance with the previous observation by Wood *et al*,²² who deduced avid proximal tubular reabsorption of sodium in compensated cirrhosis by using the free water clearance technique in the presence of hypotonic diuresis.²² This technique, now obsolete because of the introduction of the lithium clearance and fractional excretion measurement, is based on the assumption that water loading abolishes antidiuretic hormone secretion and that the distal nephron is impermeable to water in the absence of this hormone. It is generally accepted, however, that this technique underestimates tubular fluid delivery to the loop of Henle because of antidiuretic hormone independent distal water reabsorption in the thin descending limbs of the loop of Henle and the collecting ducts.^{57 58}

In conclusion, in our group of non-azotemic preascitic cirrhotics, we have confirmed enhanced responses of plasma aldosterone to intravenous metoclopramide (an expression of increased activity of the dopaminergic system) and the depression of the renin-aldosterone axis, all suggesting an increased central fluid volume. This phenomenon could be related, at least in our patients, to a decreased glomerular filtration rate and filtered sodium load and the enhanced fractional distal tubular reabsorption of sodium.

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