Sodium homeostasis with chronic sodium loading in preascitic cirrhosis

F Wong, P Liu, L Blendis

Abstract

Background—Preascitic cirrhotic patients receiving 200 mmol of sodium daily for seven days remain in positive sodium balance. Thereafter, sodium handling is unknown.

Aim—To assess renal sodium handling in preascitic cirrhosis on a high sodium diet for five weeks.

Methods—Sixteen biopsy proven preascitic cirrhotics were assessed at weekly intervals for five weeks on a diet of 200 mmol sodium/day using a daily weight diary and weekly 24 hour urinary sodium estimations. Fasting supine neurohormone levels were measured at baseline and weekly for five weeks while haemodynamics were measured at baseline and at five weeks.

Results—The daily diet of 200 mmol of sodium resulted in weight gain and a positive sodium balance for three weeks, associated with significant suppression of plasma renin activity and aldosterone levels, and a significant rise in plasma atrial natriuretic peptide levels (p<0.05). Patients’ weights plateaued during week 4, associated with complete sodium balance and significant suppression of plasma noradrenaline levels (p<0.05). This was followed by a negative sodium balance and weight loss, and finally complete sodium balance, again despite a mean net gain of 2.3 (0.3) kg, associated with a return of plasma renin activity and aldosterone levels to within normal ranges. The lack of increase in central blood volume in addition to the persistent increase in plasma atrial natriuretic peptide levels indicated that residual volume expansion, consequent to persistent weight gain, was distributed on the venous side of the circulation. No free fluid was seen on repeat abdominal ultrasound after five weeks.

Conclusion—Preascitic cirrhotics have a natriuretic “escape” after three weeks on high sodium dietary intake, associated with elevated plasma atrial natriuretic peptide levels and suppression of the renin-angiotensin-aldosterone system. With continued suppressed sympathetic activity, preascitics re-establish complete sodium balance but with a net weight gain and presumed increased intravascular volume, but without ascites. This further elucidates the compensated sodium retaining abnormality that characterises preascitic cirrhosis.

Keywords: preascitic cirrhosis; sodium handling; renin-angiotensin-aldosterone system

A subtle sodium handling abnormality is found at the preascitic stage of cirrhosis, characterised by sodium balance while on a diet of 100 mmol of sodium/day but a positive sodium balance when acutely challenged with either an oral sodium load of 200 mmol/day for seven days or an intravenous sodium load. This sodium retention is associated with an increase in total circulatory volume and an expansion of the central blood volume (CBV). However, sodium handling with an oral sodium load beyond seven days in preascitic cirrhosis is unknown. The concept of chronic sodium retention and blood volume expansion in preascitic cirrhosis has always been challenged as many preascitic cirrhotic patients consume a normal to high sodium intake, and yet they do not show any clinical evidence of fluid retention, such as ascites or ankle oedema. However, the presence of elevated atrial natriuretic peptide (ANP) concentrations, higher central venous pressure, and suppression of the systemic renin-angiotensin-aldosterone (RAAS) and sympathetic activities in the supine position surrogates markers of an expanded blood volume in preascitic cirrhosis, would support the concept of volume expansion, secondary to sodium retention, in these patients. The absence of frank fluid overload in preascitic cirrhosis suggests the presence of a physiological compensatory mechanism that is eventually activated to limit continued sodium retention and further volume expansion.

Therefore, the aims of this study, in preascitic cirrhosis, were: (a) to assess long term renal sodium handling with chronic oral sodium loading of 200 mmol/day by extending our previous one week study for a further period of four weeks; (b) to determine whether this extended increased sodium intake would result in continued sodium and volume retention; and (c) to elucidate the mechanism(s) involved in any escape phenomenon.

Materials and methods

Ethics approval for the study was granted by the ethics committee of Toronto General Hospital, University Health Network. All patients gave informed consent for the study.

Abbreviations used in this paper: Aldo, aldosterone; ANP, atrial natriuretic peptide; CBV, central blood volume; PNA, plasma noradrenaline; PRA, plasma renin activity; UNaV, urinary sodium excretion; RAAS, renin-angiotensin-aldosterone system.
PATIENTS

Sixteen patients (14 males, two females) with biopsy-proven cirrhosis were recruited from the liver clinics of Toronto General Hospital. None had a history of ascites or diuretic use. Absence of ascites was confirmed by ultrasound before enrollment. Oedema was also absent in all patients. These patients were therefore termed preascitic cirrhotic patients. The mean age of the study patients was 49.4 (2.6) years. The demographics of the study patients are shown in Table 1.

STUDY DESIGN

This strict metabolic study was conducted in the Physiology Laboratory at Toronto General Hospital under the supervision of a dietician. It was essential that all patients started the study at the same baseline sodium status. However, dietary sodium intake of preascitic cirrhotic patients at home varies over a wide range. Therefore, all study patients had a stabilisation period of one week from day −7 to day 0 during which time they were maintained on a diet of 44 mmol sodium, 1 litre fluid restriction per day. On day −1, a 24 hour urine collection to measure urinary sodium excretion (UNaV) was obtained to ensure compliance with sodium washout.

Baseline measurements were performed on day 0. Patients were admitted at 8 am fasting. An intravenous catheter was inserted shortly after admission and patients were allowed to rest in a quiet room for two hours before blood was collected without a tourniquet for plasma ANP, noradrenaline (PNA), plasma renin activity (PRA), and aldosterone (Aldo) levels. All study subjects then underwent measurement of CBV and cardiac ventricular volumes using radionuclide angiography in the Nuclear Cardiology Department. The technique of CBV measurement has been previously described.3 Quality assurance studies in our Nuclear Cardiology Laboratory have established the standard error of the estimate of left ventricular ejection fraction calculation to be less than 2% using a semiautomated technique. The standard error of the estimate of ventricular volume calculation is less than 5 ml.1

The study began with the preascitic cirrhotic patient being placed on a diet of 200 mmol sodium, 1.5 litre fluid restriction per day, which was maintained throughout the remainder of the study. To ensure dietary compliance, patients were instructed to consume only food items permitted on their dietary instruction sheets and were reviewed by a dietician on a weekly basis. Caffeine-containing beverages and food items were withheld during the study period and all study subjects were asked to refrain from smoking. All patients were required to maintain a daily weight chart, and performed 24 hour urine collections for the last two days of each week for measurements of UNaV throughout the study period. The average of the 24 hour UNaV of the two days represented UNaV for that particular week. Patients were monitored on a weekly basis, together with repeated fasting supine hormone estimations. At the end of week 5 of the study, hormonal measurements, CBV, and cardiac ventricular measurements were repeated in exactly the same manner as the baseline measurements. An abdominal ultrasound was also performed at the end of week 5 to determine whether ascites had collected during the study period.

ANALYTICAL TECHNIQUES AND ASSAYS

Serum and urinary electrolytes, complete blood count, prothrombin time, and liver function tests were performed using standard laboratory automated techniques. Blood samples for ANP, PNA, PRA, and Aldo determinations were collected on ice with the tubes for ANP containing ethylene diamine tetraacetic acid and aprotinin. Plasma was separated by refrigerated centrifugation and stored at −70°C until assay. Plasma ANP was measured using radioimmunoassay (Peninsular Laboratories, Belmont, California, USA).24 PRA was estimated by immunoassay of angiotensin I generated from plasma within 45 min of incubation at 37°C and at 5.5 and at 37°C under conditions inhibiting further conversion of angiotensin I (Rianen Assay System Angiotensin I[125] kit; Dupont

Table 1  Demographics of the study patients

<table>
<thead>
<tr>
<th>n</th>
<th>16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>49.4 (2.6)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>14/2</td>
</tr>
<tr>
<td>Hb (g/l) (normal 120–140)</td>
<td>141 (4)</td>
</tr>
<tr>
<td>Platelets (&lt;10^11) (normal 150–400)</td>
<td>99 (10)</td>
</tr>
<tr>
<td>INR (normal 0.8–1.2)</td>
<td>1.21 (0.04)</td>
</tr>
<tr>
<td>Albumin (g/l) (normal 38–50)</td>
<td>40 (2)</td>
</tr>
<tr>
<td>Bilirubin (µmol/l) (normal &lt;16)</td>
<td>21 (4)</td>
</tr>
<tr>
<td>Pugh score</td>
<td>5.9 (0.4)</td>
</tr>
<tr>
<td>AST (U/l) (normal &lt;35)</td>
<td>76 (16)</td>
</tr>
<tr>
<td>ALT (U/l) (normal &lt;39)</td>
<td>82 (19)</td>
</tr>
<tr>
<td>ALP (U/l) (normal &lt;109)</td>
<td>74 (9)</td>
</tr>
<tr>
<td>Na (mmol/l) (normal 135–145)</td>
<td>139 (1)</td>
</tr>
<tr>
<td>K (mmol/l) (normal 3.2–5.0)</td>
<td>4.0 (0.1)</td>
</tr>
<tr>
<td>Creatinine (µmol/l) (normal &lt;109)</td>
<td>78 (4)</td>
</tr>
<tr>
<td>BUN (mmol/l) (normal 3.0–7.0)</td>
<td>4.5 (0.4)</td>
</tr>
<tr>
<td>Aetiology</td>
<td>HCV 5; alcohol 6; HBV 2; Wilson’s disease 1; haemochromatosis 1</td>
</tr>
</tbody>
</table>

Hb, haemoglobin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; BUN, blood urea nitrogen; HCV, hepatitis C virus; HBV, hepatitis B virus.
Sodium loading in preascitic cirrhosis

Weeks 1–5

Table 2  Central blood volume, pulmonary vascular volumes, central cardiac vascular volumes, and systemic haemodynamics in preascitic cirrhotic patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Lost salt</th>
<th>High salt ×5 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP (mm Hg) (normal 100–140)</td>
<td>119 (4)</td>
<td>122 (5)</td>
</tr>
<tr>
<td>DBP (mm Hg) (normal 60–90)</td>
<td>65 (3)</td>
<td>67 (3)</td>
</tr>
<tr>
<td>MAP (mm Hg) (normal 70–105)</td>
<td>84 (3)</td>
<td>85 (3)</td>
</tr>
<tr>
<td>HR (beats/min) (normal 60–100)</td>
<td>62 (3)</td>
<td>64 (2)</td>
</tr>
<tr>
<td>EDV (ml) (normal 112 (9))</td>
<td>117 (8)</td>
<td>128 (9)</td>
</tr>
<tr>
<td>ESV (ml) (normal 52 (6))</td>
<td>42 (4)</td>
<td>52 (5)</td>
</tr>
<tr>
<td>EF (%) (normal &gt;50)</td>
<td>65 (2)</td>
<td>60 (2)</td>
</tr>
<tr>
<td>Stroke volume (ml) (normal 71 (5))</td>
<td>76 (5)</td>
<td>76 (5)</td>
</tr>
<tr>
<td>SVR (dyn s/cm²) (normal 4150–6675)</td>
<td>4762 (228)</td>
<td>4910 (421)</td>
</tr>
<tr>
<td>CBV (ml) (normal 2214 (173))</td>
<td>2357 (143)</td>
<td>2675 (171)</td>
</tr>
<tr>
<td>COsV (ml) (normal 1522 (106))</td>
<td>2031 (112)</td>
<td>2172 (136)</td>
</tr>
<tr>
<td>R Lung vol (ml) (normal 220 (20))</td>
<td>288 (21)</td>
<td>256 (21)</td>
</tr>
<tr>
<td>L Lung vol (ml) (normal 185 (18))</td>
<td>218 (18)</td>
<td>217 (24)</td>
</tr>
</tbody>
</table>

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HR, heart rate; EDV, end diastolic volume; ESV, end systolic volume; EF, ejection fraction; CO, cardiac output; SVR, systemic vascular resistance; CBV, central blood volume; COsV, central cardiac and vascular volume; R Lung vol, right lung vascular volume; L Lung vol, left lung vascular volume.

Company, Wilmington, Delaware, USA). Samples that yielded values <0.1 ng/l/s were then reassayed and incubated for three hours. Plasma Aldo was assayed using a radioimmunoassay technique with a commercial kit (Coat-A-Count Aldosterone kit; Diagnostic Products Corporation, Los Angeles, California, USA). PNA concentrations were determined using high performance liquid chromatography, as described by Eriksson and Persson17 and by Weicker and colleagues18 with modifications.

Calculation

End diastolic, end systolic, and CBVs were measured directly during radionuclide angiography. Stroke volume, cardiac output, and systemic vascular resistance 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, cardiac output was corrected for body surface area to yield the cardiac index.

Statistical analysis

All results are expressed as mean (SEM). Differences between means of baseline and subsequent weekly measurements for each variable in each group were determined by one way analysis of variance. 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 was rejected at the 0.05 probability level.

Results

Sodium handling and weight change

On consuming a daily diet of 44 mmol sodium, preascitic cirrhocritics promptly lost weight (80.27 (3.70) to 79.16 (3.71) kg (p<0.001) or −1.17 (0.20) kg (fig 1). UNaV at the end of the one week washout period was 52 (6) mmol/l (fig 2). On changing to a diet of 200 mmol sodium/day, there was an immediate and significant weight gain, with most of the gain occurring in week 1 (79.16 (3.71) to 81.63 (3.74) kg; p<0.01). This continued until the end of week 3 when the weight gain began to plateau (fig 1). The initial weekly weight gain with sodium loading was associated with a mean positive sodium balance until the end of week 3. Sodium balance was finally achieved between week 3 and week 4 (fig 2). Thereafter, patients developed a negative sodium balance with UNaV exceeding sodium intake by the end of week 4 (fig 2). This negative sodium balance was associated with loss of weight (figs 1, 2). Thereafter, renal sodium excretion began to decrease until all patients finally reached sodium balance again at the end of week 5 (fig 2). The overall mean weight change throughout the five week study period was +3.11 (0.26) kg (from 79.16 (3.71) to 82.13 (3.74) kg) from the end of the washout period (p<0.05) or 2.32 (0.34) kg from their usual weight (from 80.27 (3.70) to 82.13 (3.74) kg) (p<0.05). None of the patients developed leg oedema or ascites either clinically or on repeat ultrasound examination at the end of the study.

Systemic haemodynamic and blood volumes

Sodium loading with 200 mmol/day for five weeks did not significantly alter cardiac ventricular volumes in preascitic cirrhotic patients. Therefore, ejection fraction also did not change. As there were no alterations in heart rate or mean arterial pressure with sodium loading, no significant changes in cardiac output or systemic vascular resistance were observed (table 2). Similarly, CBV, pulmonary vascular volumes, and central cardiac vascular volume did not show any significant change when preascitic cirrhotic patients consumed a high sodium diet for five weeks (table 2).

Plasma hormone levels

Preascitic cirrhotic patients showed significant suppression of PRA (p<0.05) and Aldo levels (p<0.05), and an increase in plasma ANP levels (p<0.05) when they consumed a high
**Table 3** Hormonal profile with low and high sodium intake in preascitic cirrhotic patients

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANP (pg/ml) (normal 24 (2))</td>
<td>45.5 (5.29)</td>
<td>68.3 (8.2)*</td>
<td>84.1 (12.2)*</td>
<td>110.2 (18.5)*</td>
<td>72.1 (14.4)*</td>
<td>66.5 (8.3)*</td>
</tr>
<tr>
<td>PRA (ng/l/s) (normal 0–0.58)</td>
<td>0.25 (0.10)</td>
<td>0.15 (0.06)</td>
<td>0.11 (0.03)*</td>
<td>0.10 (0.02)*</td>
<td>0.12 (0.05)</td>
<td>0.24 (0.09)</td>
</tr>
<tr>
<td>Aldosterone (pmol/l) (normal 27–444)</td>
<td>156 (58)</td>
<td>102 (25)</td>
<td>110 (34)</td>
<td>88 (12)*</td>
<td>104 (26)</td>
<td>146 (60)</td>
</tr>
<tr>
<td>PNA (nmol/l) (normal 0.8–3.4)</td>
<td>1.6 (0.6)</td>
<td>1.5 (0.7)</td>
<td>1.6 (0.6)</td>
<td>1.3 (0.4)</td>
<td>0.9 (0.2)*</td>
<td>0.8 (0.4)*</td>
</tr>
</tbody>
</table>

ANP, atrial natriuretic peptide; PRA, plasma renin activity; PNA, plasma noradrenaline.

*p<0.05 versus baseline.

sodium diet for three weeks (table 3). By the end of week 4, there was suppression of sympathetic nervous activity, as indicated by a significant decrease in PNA levels (1.62 (0.62) \( \div 0.82 (0.45) \) nmol/l; \( p<0.05 \) (table 3). By the end of week 5, PRA and Aldo levels had risen, and did not differ significantly from baseline, whereas PNA levels remained significantly depressed and plasma ANP levels significantly elevated (table 3).

**Discussion**

We have previously demonstrated that preascitic cirrhotic patients rapidly reached sodium balance on a low sodium diet and that subtle sodium retention occurred when these patients were challenged with a daily sodium intake of 200 mmol/day for one week. The findings of the current study confirm these observations and indicate that sodium retention continues for a further two weeks before patients reach a state of sodium balance, albeit at the expense of an increase in weight, suggesting an increase in total body fluid volume, which is localised in compartments other than the central chest cavity.

Previous reports have shown that sodium challenge in preascitic cirrhotic patients with 200 mmol/day for one week was associated with reductions in PRA and plasma Aldo, but not PNA levels, in the supine position which together with increased ANP levels suggested intravascular volume expansion. That is, sodium retention and volume expansion occurred in preascitic cirrhosis despite suppression of the antinatriuretic effects of the RAAS and enhanced ANP activity. We have now shown in this study that sodium retention and volume expansion continued beyond one week. There are many explanations for sodium retention in preascitic cirrhosis. We have previously demonstrated that application of negative lower body pressure, simulating an upright posture, resulted in intrarenal activation of the RAAS, associated with renal sodium retention. This was despite many reports of reduced systemic PRA and Aldo levels in preascitic cirrhosis, all of which measured PRA and Aldo with patients in the supine posture. Bernardi et al confirmed that upright posture in preascitic cirrhosis was associated with increased plasma Aldo levels. That is, the upright posture in preascitic cirrhosis is at least partly responsible for the sodium retention in these patients. Subtle activation of the sympathetic nervous system in preascitic cirrhosis may also be responsible for their sodium retention as persistently elevated PNA levels have been observed despite one week of sodium loading in these patients. Finally, reduced effectiveness of ANP in preascitic cirrhosis may also contribute to their sodium retention and volume expansion, as elevated ANP levels frequently coexist with avid sodium retention, and physiological stimulation of ANP secretion is often accompanied by subnormal increases in natriuresis.

However, many investigators object to the concept of sodium retention in preascitic cirrhosis as these patients clinically do not have any evidence of fluid retention such as ascites or ankle oedema. Our serial assessments of sodium handling in preascitic cirrhosis have demonstrated that these patients eventually reached a state of sodium balance despite continued high sodium intake, thereby preventing the development of ascites or fluid retention. This was achieved by a further increase in ANP secretion, coupled with suppression of the RAAS, and eventual suppression of sympathetic nervous activity, as evidenced by decreased PNA levels by four weeks of sodium loading. Therefore, a reduction in antinatriuretic forces, coupled with increased natriuretic effects of higher plasma ANP levels, was sufficient to induce natriuresis. The fact that ANP decreases sympathetic activity centrally might also have contributed to suppression of sympathetic nervous activity with prolonged sodium loading, further promoting the onset of natriuresis. Once natriuresis began, it exceeded sodium intake, possibly reflecting an attempt of the body's homeostatic mechanisms to return the volume status to "normal". Another possible explanation for natriuresis was that preascitic cirrhotic patients had "escaped" from the sodium retaining effects of aldosterone, thereby permitting increased sodium excretion despite prolonged sodium loading. However, the achievement of a new steady state of sodium balance in preascitic cirrhosis occurred at the expense of an expanded total body fluid volume, as these patients experienced significant weight gain at the end of their sodium loading period, and plasma ANP levels remained elevated, indicating persistent atrial distension. That is, despite a significant increase in natriuretic forces and reduction in antinatriuretic forces, sodium excretion could not return the body to normal volume status. In other words, the body's homeostatic mechanisms are maladapted in preascitic cirrhosis.

Several investigators, including ourselves, have demonstrated low PRA and Aldo levels in preascitic cirrhosis after sodium loading for one week. However, none of the previous studies had followed patients chronologically for five weeks. After continued suppression of RAAS activity with sodium loading for at least three weeks, reactivation of the RAAS
Sodium loading in preascitic cirrhosis

day was associated with a 6% reduction in
explanation, as a low sodium diet of 50 mmol/
splanchnic circulation. Although we did not
would tend to localise the excess volume to the
sure. An increase in portal pressure in cirrhosis
reflected by an increase in central venous pres-
levels with sodium loading representing an
more, the finding of increased plasma ANP
volumes, or systemic haemodynamics. Further-

increase in atrial stretch indicates that the
mechanisms, including increased ANP levels
hypodynamic stability.29

counteract the vasodilating e
of the body’s inbuilt defence mechanism to
occurred following sodium escape by the end

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et al.


8 Moller S, Sondergaard L, Mogelvang J, et al. Decreased right heart blood volume determined by magnetic reso-


11 Iwao T, Oho K, Nakano R, et al. High plasma cardiac natriuretic peptides associated with enhanced atrial guanosine monophosphate production in preascitic cirrho-


15 Goodman JM, McLaughlin PR, Pilyer MJ, et al. Impaired cardiopulmonary responses to exercise in moderate hyper-


17 Eriksson BM, Persson BA. Determination of catecho-


In summary, preascitic cirrhotic patients retain sodium when challenged with a high sodium intake. These patients do not continue to retain sodium indefinitely, as homeostatic mechanisms, including increased ANP levels and suppressed RAAS and sympathetic activity, eventually re-establish a new steady state of sodium balance, but at the expense of an increased intravascular volume. However, pa-

The authors wish to thank Dr Gordon Moe of St Michael’s Hospital, Toronto, for performing the ANP assays, Dr Jeff Tong and Dr PY Wong of the Toronto General Hospital for perform-
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