Iso-oncotic volume expansion in the nephrotic syndrome

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1. In previous studies we found that albumin infusions caused only a modest natriuresis in the nephrotic syndrome, suggesting that hypovolaemia played no part in the sodium retention of these patients. However, this finding was inconclusive, since the hyper-oncotic of the infused albumin probably opposed sodium excretion.

2. In the present study, we examined the effect of sustained (68 h) plasma volume expansion (+18%), by means of iso-oncotic albumin infusions, on renal function, blood pressure, humoral factors and sodium balance.

3. Plasma atrial natriuretic peptide levels increased almost threefold and renin-angiotensin system activity was suppressed. Glomerular filtration rate remained unchanged, whereas estimated renal plasma flow increased, resulting in a further decrease in filtration fraction.

4. The increase in plasma volume expansion was accompanied by a modest increase in sodium excretion, which, however, was less than the amount of sodium daily infused with the albumin solutions and consumed with the diet, so that net sodium was retained.

5. This observation supports the concept that an intrinsic renal defect causes the sodium retention in the nephrotic syndrome, and argues against the therapeutic use of albumin infusions.

INTRODUCTION

Sodium retention in patients with the nephrotic syndrome is traditionally explained by a decrease in circulating plasma and blood volume secondary to a lowered plasma colloid oncotic pressure (COP). Recent studies have modified this concept, at least for a subgroup of the patients with a nephrotic syndrome [1-4]. Patients with nephrosis usually have normal or high plasma volumes and normal or even elevated blood pressure [1]. Indeed, blood volume can be preserved over a wide range of hypoproteinaemia, due to redistribution of tissue fluid proteins [2]. In addition, no clear relationship appears to exist between blood volume and activity of the renin-angiotensin system [3], and remission of the nephrotic syndrome is accompanied by natriuresis at a time when the plasma COP is still very low [5]. Finally, most patients with a nephrotic syndrome have a low filtration fraction in the presence of an elevated renal blood flow, as is usually observed in nephritis [4].

Clearly, these data are contradictory to the intravascular hypovolaemia concept. However, it can be argued that the normal blood volume during the steady-state nephrotic syndrome is in fact achieved only as the result of renal sodium retention caused by an initially lowered blood volume. Therefore, dynamic manipulations of the blood volume in patients with a nephrotic syndrome may reveal the stimulus for sodium retention in these patients. If a low plasma COP resulting in a lowered blood volume, rather than an intrinsic renal excretion defect, were the ultimate cause of volume retention, blood volume expansion in the oedematous patient should induce a massive natriuresis.

To test this hypothesis, we previously expanded plasma volume in oedematous patients with a nephrotic syndrome, using hyperoncotic albumin infusions [6]. Blood volume rose by 35% in that study, but at the same time plasma albumin concentration increased from 15 to 27 g/l. These subjects demonstrated only a very modest natriuresis in response to this volume expansion and it was concluded that sodium retention was caused by an intrinsic renal defect. However, interpretation of these data is hampered by the concomitant increase in plasma COP. Peritubular increments in COP stimulate proximal reabsorption and may result in sodium retention, as was observed during hyperoncotic albumin infusion in normal subjects [7]. Another problem is that renal de-adaptation to a low volume state may be too slow to result in immediate natriuresis after circulatory restoration [8]. In the present study we therefore studied the effects of sustained plasma volume expansion with iso-oncotic albumin solutions. For this purpose the solutions were prepared individually to match the oncotic pressure of the participating patients.

Key words: albumin, nephrotic syndrome, volume expansion.

Kurzformel: ANP, atrial natriuretic peptide; COP, colloid oncotic pressure; ERPF, estimated renal plasma flow; GFR, glomerular filtration rate; LBM, lean body mass; MAP, mean arterial blood pressure; PRA, plasma renin activity.

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METHODS

Patients

Eight patients with a nephrotic syndrome (five men, three women) were studied, ranging in age from 19 to 64 (mean 37) years. Histological diagnoses were: membranous glomerulopathy \((n = 2)\), lupus nephritis \((n = 2)\), focal segmental sclerosis \((n = 1)\), minimal lesions \((n = 2)\), membranoproliferative glomerulonephritis \((n = 1)\). They all had oedema, 24 h urinary protein excretion > 3.5 g and a creatinine clearance > 60 ml/min. Excess extracellular fluid was estimated from oedema-free weight after diuretic treatment or remission. None of the patients received diuretics or other medication in the 3 days preceding the study. Some individual data are listed in Table 1. Informed consent was obtained before the study, and the protocol was approved by the University Hospital Committee for Studies in Humans.

Investigational procedure

All patients were admitted to the hospital, placed on a diet containing 60 mmol of sodium/day, and 24 h urine collections were made from 08.00 hours until 08.00 hours the next day. On the third day, at 09.00 hours after an overnight rest and with the patient in the supine position, plasma COP, packed cell volume and plasma volume were measured, and upper-arm cuff blood pressure was monitored for 1 h with an automatic device every 5 min.

The next day (day 4), again after an overnight rest, a clearance study was performed. At 09.00 hours a priming dose of a solution containing inulin (to estimate glomerular filtration rate, GFR) and \(p\)-aminohippurate (to measure estimated renal plasma flow, ERPF) was given, followed by a continuous infusion of this solution throughout the remainder of the study. The subjects drank a water load of 10 ml/kg and additional water equivalent to urine output was supplied for the remainder of the clearance study. After at least 1 h of equilibration, three 20 min urine collections were obtained by spontaneous voiding. Blood specimens were drawn at the midpoint of each collection period. After the third urine collection, an iso-osmotic albumin solution, amounting to 20% of the measured plasma volume, was infused in 60 min. This albumin solution was made iso-osmotic by diluting a 5% albumin solution (sodium content 150 mmol/l) with 0.9% NaCl (saline) until the COP of the solution was identical with that of the patient. After the 60 min expansion period, the patients voided, and three more 20 min urine collections and blood samples were obtained. Immediately before and after this expansion additional blood was collected for the determination of plasma renin activity (PRA), plasma aldosterone concentration, plasma atrial natriuretic peptide (ANP) concentration, packed cell volume and COP.

After the clearance study, the plasma volume elevation was maintained at the same level for a total period of 68 h, that is until 08.00 hours on day 7. This was done by continued infusion of the iso-osmotic albumin by means of an infusion pump, of which the infusion rate was adjusted to keep a constant value of packed cell volume, which was measured every 4 h (patient supine). The daily urine collections were continued, and at 09.00 hours on days 5 and 6, after an overnight rest, blood was drawn for determination of PRA, plasma aldosterone concentration, plasma ANP concentration and COP, after which blood pressure was measured for 1 h.

Laboratory techniques

Plasma volume was measured as supine \(^{131}I\)-albumin distribution volume, with the use of one large (20 ml) blood sample taken at 10 min after the albumin injection, and the Volumetron. This method has been validated by us in the nephrotic syndrome previously [1]. Plasma volume was expressed as ml/kg lean body mass (LBM), the latter being estimated from height and oedema-free weight [1]. Blood and urine samples were analysed for sodium and creatinine (Instrumentation Laboratory Autocal 743 flame photometer). The plasma COP was determined with an oncometer (CCMI, Los Angeles, CA, U.S.A.). PRA, plasma aldosterone concentration and plasma ANP concentration were determined by radioimmunoassay, as described previously [9]. Inulin was hydrolysed to fructose and determined photometrically with indoleacetic acid, and \(p\)-aminohippurate was determined photometrically by a chromogenic aldehyde reaction.

Calculations

Changes in plasma volume were estimated from changes in whole body packed cell volume (whole

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Diagnosis</th>
<th>PRA (nmol·l(^{-1})·h(^{-1}))</th>
<th>COP (mmol·l(^{-1}))</th>
<th>(U_{\text{Na}}) (mmol/24 h)</th>
<th>(C_{\text{Cr}}) (ml/min)</th>
<th>ECFV surplus (litres)</th>
</tr>
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<tr>
<td>1</td>
<td>MBGN</td>
<td>120</td>
<td>12.4</td>
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<td>92</td>
<td>6</td>
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<tr>
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<td>103</td>
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<td>10</td>
<td>88</td>
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<td>85</td>
<td>7</td>
</tr>
<tr>
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<td>27</td>
<td>110</td>
<td>10</td>
</tr>
<tr>
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<td>80</td>
<td>91</td>
<td>10</td>
</tr>
<tr>
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<td>8.0</td>
<td>132</td>
<td>78</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>ML</td>
<td>300</td>
<td>10.5</td>
<td>19</td>
<td>69</td>
<td>12</td>
</tr>
</tbody>
</table>

*Mean of 2 days before expansion.
body PCV = 0.91 × peripheral venous PCV) with the formula derived by van Beaumont [10]:

\[
PV_2 = PV_1 \times \text{PCV}_1(1 - PCV_2)/\text{PCV}_2(1 - PCV_1)
\]

where PV is plasma volume and PCV is packed cell volume.

For this calculation we assumed a constant erythrocyte mass during the study. Mean arterial blood pressure (MAP) was calculated from diastolic blood pressure plus one-third of the pulse pressure.

Values are given as means ± SEM. PRA and plasma aldosterone concentration were analysed after logarithmic transformation. Statistical analysis was performed using one-way analysis of variance. If variance ratios obtained by this method reached statistical significance, the differences between the means were analysed at the 1 and 5% significance level by the least significance difference test.

RESULTS

Baseline data

Individual patient data and diagnoses are given in Table 1. PRA was normal in four patients, somewhat low in three patients, and high-normal in one patient (the reference value for PRA on a 60 mmol sodium diet and in the supine position is 200–700 fmol of angiotensin I s⁻¹⁻¹). Plasma COP was variable, but clearly decreased in each subject. Baseline 24 h sodium excretion was also variable. Relative to the intake, three subjects were in negative sodium balance, one in balance, and four in a sodium-retaining state. All patients had oedema and marked fluid excess, and in all patients creatinine clearance was moderately decreased. There was no correlation between baseline sodium excretion and PRA or COP.

Mean plasma volume was 3.54 ± 0.28 litres (Table 2). For comparison with reference values, plasma volume was also expressed per kg LBM: 61.6 ± 3.5 ml/kg LBM in the patients, which is not different from our reference group: 60.0 ± 4.5 ml/kg LBM [1].

GFR (inulin clearance, Table 3) was also moderately decreased, but ERPF (p-aminohippurate clearance) was normal, and thus filtration fraction was decreased.

Effects of acute plasma volume expansion

During the clearance study the plasma volume was expanded by about 18%, reaching supranormal values, whereas plasma COP did not change (Table 2). The amount of iso-oncotic albumin solution infused averaged 821 ± 6 ml/h, containing 27.3 ± 1.2 g of albumin and 123 ± 4 mmol of sodium. The plasma volume expansion was associated with suppression of PRA and plasma aldosterone concentration, and an increase in plasma ANP concentration and blood pressure, all well-known features of volume expansion in healthy subjects.

The plasma volume expansion had no effect on GFR, but increased ERPF and decreased filtration fraction further (Table 3). Sodium excretion increased as well, but the increase was much less than the amount of sodium infused, so that on average the net sodium balance during the clearance study became positive by almost 120 mmol.

Effects of sustained plasma volume expansion

With continued iso-oncotic albumin infusion, plasma volume remained elevated at the same level as obtained immediately after initial expansion, without any change in plasma COP (Table 2). This
correspond with those of the patients in Table 892.

Fig. 1. Individual values of sodium excretion during two control 24 h periods (C1 and C2) and 3 days of plasma volume expansion (E1, E2 and E3). These urine collections were made from 08.00 hours until 08.00 hours the next day. Plasma expansion started at 12.00 hours on E1, and lasted until the end of E3. The numbers correspond with those of the patients in Table 1.

was accompanied by sustained suppression of PRA and plasma aldosterone concentration, and elevation of plasma ANP concentration and blood pressure. Fig. 1 shows that sodium excretion increased in all patients but one, and that wide variation remained. There was no relation between individual natriuretic responses and humoral changes. Mean sodium excretion rose from 61 ± 20 mmol/day (mean of 2 control days) to 99 ± 13, 108 ± 18 and 123 ± 14 mmol/day on, respectively, the first, second and third days of plasma volume expansion (P < 0.05 for each day). This increase in sodium excretion did not compensate for the net amount of sodium infused daily with the albumin solutions (892 ± 7 ml/day, 134 ± 4 mmol of sodium/day) and consumed with the diet (60 mmol/day) (Table 3, Fig. 1). Accordingly, body weight increased. The individual data for sodium excretion, given in Fig. 1, also show that in none of the patients was the increase in sodium excretion sufficient to cause a negative sodium balance.

**DISCUSSION**

In the present study, sustained iso-oncotic expansion of the plasma volume up to 118% of its original value did not induce a major natriuresis in oedematous patients with the nephrotic syndrome. GFR in these subjects was normal or moderately decreased, and the expansion was associated with suppression of PRA, and elevation of plasma ANP concentration, renal plasma flow and blood pressure. Nonetheless, the natriuretic response was modest, and insufficient to produce a negative sodium balance.

We previously reported that oedematous nephrotic patients undergoing volume expansion with hyperoncotic albumin sustained over 20 h showed no more than a modest increase in sodium excretion [6]. Larger increments in sodium excretion were found after acute hyperoncotic albumin expansion in children with minimal lesions [11] and in a less homogeneous group of adults [12]. In general, however, the sodium excretion rate in these studies remained lower than expected during intravascular expansion, a large sodium excess and (sub)normal renal function, which was the state generated in each of these studies. Still, it remains difficult to conclude from these observations that a renal defect contributed to the sodium retention, since increased peritubular oncotic pressure due to the hyperoncotic albumin probably limited the natriuretic response [13, 14]. Indeed, we found a paradoxical decrease in sodium excretion when similar hyperoncotic albumin expansion was applied in sodium-restricted healthy subjects [7]. Therefore, in the present study we carefully maintained plasma oncotic pressure by individual adjustment of the oncotic pressure of the infused albumin solution. In this circumstance the increase in renal plasma flow and decrease in filtration fraction, such as occurred upon plasma expansion, would in fact not only increase peritubular hydrostatic pressure and but also decrease peritubular oncotic pressure, and thus suppress tubular sodium reabsorption. Nonetheless, the data show that even then the natriuresis remains modest.

A second pitfall in the interpretation of the effects of volume expansion in the nephrotic syndrome may be a too short observation period. It is conceivable that the renal de-adaptation from any chronic hypovolaemic state is too slow to turn into major volume excretion immediately after volume expansion. For instance, it takes a few days for sodium excretion to increase adequately after the switch from a low to a high sodium diet [8]. Recently, it was demonstrated that the natriuretic response to iso-oncotic plasma volume expansion was delayed for ~2 h in normal subjects [15]. Therefore, expansion sustained over days may be preferable to assess the volume dependency of fluid retention in the nephrotic syndrome. The few data available again concern short-lasting infusions with hyperoncotic albumin, repeated each day. Using such a regimen over several weeks. Eder et al. [16] were able to remove all the oedema in a child, but did not manage to produce any diuresis in one adolescent patient. Later, Brown et al. [17] were unable to induce a negative sodium balance in three adult nephrotic patients with such albumin infusions repeated for 3 days. In the present study we continued the iso-oncotic expansion for 68 h. Although blood pressure and plasma ANP concentration remained elevated, and PRA and plasma aldosterone concentration remained low, the increase in sodium excretion was too modest to create a negative sodium balance.

Our data lend further support to the idea that an intrinsic renal defect is relevant for the sodium retention of nephrotic subjects. The relevance of this factor may, however, vary individually, and one
should be careful to extrapolate these data to all patients with the nephrotic syndrome. A hypovolaemic factor contributing to sodium retention may, in particular, be present in patients with severely decreased plasma oncotic pressure, stimulated PRA and severe sodium retention [3]. This especially occurs in a subgroup of patients with minimal lesions, which may explain why a beneficial effect of albumin infusion is more often met in children [1]. Such patients were not among those of our study. Nonetheless, there were clear differences in basal as well as expansion-induced sodium excretion rates among our patients (Fig. 1), although a relation with PRA or severity of the decrease in plasma COP was not apparent. In fact, at least three of our patients were able to maintain a negative sodium balance on the 60 mmol sodium diet before the expansion phase. Apparently, the kidneys of nephrotic patients can respond, to varying extents, to volume stimuli, as is also manifest from the consistent increase in sodium excretion observed upon plasma volume expansion. Clearly, the failure of nephrotic kidneys to excrete sodium is not absolute, but variable in severity. This defect is apparent from the fact that sodium excretion cannot be raised to the level that would be appropriate for the increase extracellular fluid volume, neither in basal conditions nor after elevation of intravascular volume. This holds for all the patients presently studied, since none of them responded with an adequate natriuresis, irrespective of whether the baseline sodium excretion rate was very low or ‘normal’, and irrespective of their plasma oncotic pressure.

It is interesting to compare our data with those obtained during head-out water immersion, which is another model for iso-oncotic volume expansion. Compared with the present data, similar [18] or somewhat greater [19–21] natriuresis has been obtained with this model when applied in nephrotic patients. The decrease in PRA and plasma aldosterone level [19–21] and stimulation of plasma ANP level [18, 20] obtained with this manoeuvre were roughly comparable with that seen after acute albumin infusion in the present study. Changes in renal haemodynamics were also similar [18]. These data indicate convincingly that patients with the nephrotic syndrome can respond to volume expansion, but can hardly be used as proof for hypovolaemia as the factor underlying the sodium retention. For example, a prompt natriuretic response to water immersion has also been found in patients with marked loss of renal function [22]. Also, it was found recently that the immersion-induced increase in sodium excretion in nephrotic subjects was clearly less than in normal subjects, although the increase in plasma ANP concentration in the former was greater [18]. A drawback of the water immersion model is that it can only be applied in short-term studies, and it is not a feasible method with which to study the effect of iso-oncotic volume expansion sustained for days. For that purpose, studies such as the present are the only means available.

In summary, our findings show that sustained iso-oncotic volume expansion in adult patients with the nephrotic syndrome does not adequately increase sodium excretion; this indicates the importance of an intrarenal defect underlying the sodium retention, and argues against the therapeutic use of such infusions.

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REFERENCES


