Renal salt and water handling in water immersion in the nephrotic syndrome

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Summary

1. Eleven nephrotic patients were immersed up to the neck in 1·3 m of water at 34°C for 4 h.
2. A diuresis began, within the first hour of, and continued throughout, immersion. The urine osmolality fell significantly and decreased to hypotonic levels in the first hour of immersion and increased gradually during the remainder of immersion and postimmersion.
3. Throughout immersion there was a steady increase in urinary sodium and chloride excretion and a sharp fall in the postimmersion hour.
4. Overall fractional excretion of sodium and of chloride increased steadily throughout immersion and fell during the post-immersion hour.
5. There was an increase in urinary potassium excretion on immersion but no change in fractional excretion of potassium. There was an initial increase in distally reabsorbed sodium/chloride on immersion, as expressed by positive values of \( C_{\text{HCO}_3} \) in the first hour of immersion.
6. Plasma aldosterone levels were initially elevated in only two out of nine patients. There was a significant fall in plasma aldosterone levels on immersion, but there was no correlation between sodium/chloride handling and aldosterone levels on immersion.

Key words: nephrotic syndrome, tubular function, urinary chloride, urinary sodium, water, water immersion.

Introduction

In normal man, and in the patient suffering from cirrhosis of the liver, immersion in 1·3 m of water up to the neck in a seated position at 34°C is associated with a brisk hypotonic diuresis and natriuresis, associated with a decrease in plasma aldosterone and antidiuretic hormone (ADH) levels [1-9]. In the nephrotic subject there is a similar diuresis associated with excretion of about 35 mmol of sodium in the urine in 4 h, and a mean loss of 2-2 kg of weight, only 1-2 litres of urine being passed. About 1 kg of weight is lost as sweat [10]. The present results of water immersion in a series of 11 non-selected nephrotic patients are presented with special reference to the handling of sodium and water on immersion.

Materials and methods

Subjects

The patients were 11 nephrotic patients (eight males, three females) aged 17-64 years suffering from membranous glomerulopathy (4), lipid nephrosis (2), interstitial nephritis (1), focal glomerulosclerosis (3) and diabetic glomerulosclerosis (1). Frusemide therapy was stopped 3-7 days before immersion. Prednisone therapy was stopped in all nine patients who were given it 1 week or more before the test. All the patients took 50 mmol of sodium daily.

The patients had control diurnal rhythm urine collections while seated outside the bath from 09.00 to 16.00 hours. On the day of the immersion experiment they were given a loading dose of inulin at 09.00 hours and 1 h was allowed
for equilibration. At 10.00 hours urine and plasma collections were commenced at hourly intervals. The patient was immersed in the bath at 11.00 hours where he remained for 4 h, apart from being helped out for spontaneous micturition and blood sampling at hourly intervals. Pulse and blood pressure were recorded every 15 min and temperature every hour. They were seated outside the bath for 1 h after immersion, after which time the experiment was terminated.

A constant-rate infusion of inulin was continued during the experiment. The patients were allowed to drink electrolyte-free fluids, according to their thirst requirements, during the immersion study and on control days. A period of 7 days elapsed between the immersion therapy and subsequent control studies. Inulin, creatinine, proteins and urea nitrogen were measured by automated techniques as reported elsewhere [11], and sodium and potassium by flame photometry on IL model 343 with an internal lithium standard. Urine and plasma osmolalities were measured cryoscopically on an Advanced Instruments Automated Osmometer model no. 3DII. Wilcoxon’s test was used to analyse the data. Because of their non-parametric distribution the data are given as median and quartiles (see the Appendix).

**Results** (see Tables 1 and 2)

### Urine volume

The urine flow rate increased rapidly from a pre-immersion control median of 0.75 ml/min to a peak value of 2.45 ml/min in the third hour of immersion ($P < 0.005$). In the postimmersion hour urine volume decreased to a median value of 1.17 ml/min.

### Urine osmolality ($U_{osm}$)

This was initially hypertonic (475 mmol/kg) in the pre-immersion control hour, but decreased to a median value of 220 mmol/kg in the first hour

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**Table 1. Renal water, sodium and chloride handling in immersion experiments**

Results are median and quartile values. Immersion mean is of the values during 4 h immersion. $V$ = urine flow rate; GFR = glomerular filtration rate; $U_{osm}$ = urine osmolality; $U_{osm}V$ = osmolar excretion rate; $C_{osm}$ = osmolar clearance; $C_{F2O}$ = free water clearance; $U_{Na},V$ = sodium excretion rate; $FE_{Na}$ = fractional excretion of sodium; $U_{Cl}/V$ = chloride excretion rate; $FE_{Cl}$ = fractional excretion of potassium.

<table>
<thead>
<tr>
<th></th>
<th>Pre-immersion hour</th>
<th>Immersion period (h)</th>
<th>Postimmersion hour</th>
<th>Immersion mean</th>
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<tr>
<td></td>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>$U_{osm}$ (mmol/kg)</td>
<td>Median</td>
<td>0.356</td>
<td>0.559</td>
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<td>Quartiles</td>
<td>0.547, 0.247</td>
<td>0.672, 0.440</td>
<td>0.703, 0.350</td>
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<td>1.93</td>
<td>1.92</td>
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<td>1.89, 0.846</td>
<td>2.31, 1.54</td>
<td>2.39, 1.41</td>
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<tr>
<td>$C_{F2O}$ (ml/min)</td>
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<td>Quartiles</td>
<td>0.37, 0.73</td>
<td>2.04, 0.58</td>
<td>1.59, 0.38</td>
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<tr>
<td>$U_{Na}/V$ (mmol/min)</td>
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<td>2.63</td>
<td>86.2</td>
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<td>Quartiles</td>
<td>66.0, 7.2</td>
<td>97.7, 28.2</td>
<td>144.0, 58.3</td>
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<td>$FE_{Na}$ (%)</td>
<td>Median</td>
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<td>0.67</td>
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<td>Quartiles</td>
<td>0.95, 0.14</td>
<td>1.16, 0.4</td>
<td>1.57, 1.02</td>
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<tr>
<td>$U_{Cl}/V$ (μmol/min)</td>
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<td>65.6</td>
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<td>30.4, 13.5</td>
<td>104.0, 42.6</td>
<td>134.0, 66.1</td>
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<td>$FE_{Cl}$ (%)</td>
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<td>0.99</td>
<td>1.65</td>
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<td>Quartiles</td>
<td>0.96, 0.29</td>
<td>1.25, 0.59</td>
<td>2.02, 1.27</td>
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<td>$UV_{K}$ (μmol/min)</td>
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<td>64.1</td>
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<td>Quartiles</td>
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<td>70.8, 39.6</td>
<td>59.1, 35.3</td>
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<td>$FE_{K}$ (%)</td>
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<td>21.0</td>
<td>20.6</td>
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<tr>
<td></td>
<td>Quartiles</td>
<td>23.5, 15.3</td>
<td>21.6, 17.8</td>
<td>27.0, 19.6</td>
</tr>
</tbody>
</table>
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TAELE

2. Plasma aldosterone levels (ng/ml) on immersion in nine patients

All but two of the patients had been receiving steroids (1 mg day\(^{-1}\) kg\(^{-1}\) body weight).

<table>
<thead>
<tr>
<th>Subject</th>
<th>Pre-immersion</th>
<th>Immersion period (h)</th>
<th>Postimmersion</th>
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<td>75</td>
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<td>80</td>
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</tr>
<tr>
<td>Z</td>
<td>50</td>
<td>40</td>
<td>30</td>
</tr>
<tr>
<td>Median</td>
<td>91</td>
<td>80</td>
<td>65</td>
</tr>
<tr>
<td>Quartiles</td>
<td>118, 53</td>
<td>93, 40</td>
<td>76, 25</td>
</tr>
<tr>
<td>Mean</td>
<td>98.7</td>
<td>71.4</td>
<td>61.2</td>
</tr>
<tr>
<td>SEM</td>
<td>25</td>
<td>11.6</td>
<td>8.9</td>
</tr>
</tbody>
</table>

- Osmolar excretion (\(U_{\text{osm.V}}\))
  - This increased during immersion and reached a maximum in the fourth hour (\(P < 0.04\)), decreasing sharply in the postimmersion hour.

- Osmolar clearance (\(C_{\text{osm}}\))
  - There was a rapid increase of \(C_{\text{osm}}\) during immersion to a maximum value in the fourth hour (\(P < 0.01\)) and a sharp decrease in the postimmersion hour.

- Free water clearance (\(C_{\text{H2O}}\))
  - This increased from negative values of \(-0.49\) ml/min in the pre-immersion hour to a peak of \(+0.56\) ml/min in the first hour (\(P < 0.001\)), then decreased to negative values during the remainder of immersion and the post-immersion hour.

- Urine sodium excretion (\(U_{\text{NaV}}\))
  - This increased steadily from a control pre-immersion median value of \(26.3\) \(\mu\)mol/min to a maximum of \(173.1\) \(\mu\)mol/min at the end of the fourth hour (\(P < 0.0025\)) and then decreased to \(55.2\) mol/min in the postimmersion hour.

- Fractional excretion of sodium (\(FE_{\text{Na}}\))
  - This was initially \(0.58\%\) pre-immersion, and increased throughout immersion (\(P < 0.005\)) reaching a peak in the fourth hour, and fell rapidly in the postimmersion hour.

- Urinary potassium excretion (\(U_{\text{K}}V\))
  - There was a sharp rise from the control value of \(27.5\) \(\mu\)mol/min in the pre-immersion hour to a maximum value of \(61.4\) \(\mu\)mol/min in the first hour of immersion (\(P < 0.04\)), falling to pre-immersion levels in the hour after immersion.

- Fractional excretion of potassium
  - This did not change significantly on immersion or in the postimmersion period.

- Glomerular filtration rate (GFR)
  - Inulin clearance did not change significantly throughout immersion when compared with control values, although the median GFR in the first hour of immersion was significantly increased above pre-immersion values (\(P < 0.01\)).

- Plasma aldosterone levels
  - Nine patients had plasma aldosterone levels measured in the pre-immersion hour, during \(4\) h of immersion and after immersion, while seated. They had all received an intake of \(50\) mmol of sodium daily. Results are given in Table 2. Aldosterone levels fell significantly from a median pre-immersion value of \(91\) ng/100 ml to the second hour immersion value of \(60\) ng/ml (\(P < 0.005\)). Only two of the nine patients tested had elevated plasma levels of aldosterone before immersion. There was no statistically significant
correlation between sodium/chloride excretion parameters and plasma aldosterone levels. No significant change was found in the pulse or blood pressure of any patient during immersion.

Discussion

The physiological changes in normal man induced by immersion up to the neck in 1-3 m of water at 34°C can be summarized as: (1) central hypervolaemia, (2) suppression of plasma vasopressin and aldosterone levels, (3) increase in urinary prostaglandin E excretion in sodium-deprived individuals, (4) mixed water and sodium diuresis [1–7, 12]. There is, in addition, a variable degree of sweating induced by contact of skin surfaces with a water temperature of 34°C, but which is limited by the swelling of the stratum corneum of the skin so that sweat loss of sodium and water progressively decreases until it disappears after about 3-5 h [13].

Epstein and colleagues have reported a series of careful investigations of the pathophysiology of water immersion up to the neck in normal control subjects and in patients suffering from cirrhosis of the liver [7, 9]. Because of similarities in the pathophysiology of hypoproteinaemic oedema in both nephrotic syndrome and in cirrhosis of the liver, the effects of water immersion in nephrotic syndrome were investigated in five patients. The physiological changes in these patients included an overall weight loss of about 2 kg, 1-2 litre of hypotonic urine being excreted in 4 h containing about 35 mmol of chloride and of sodium [10, 14]. In the present paper the chloride, sodium and water handling in the nephrotic subject on immersion were investigated. The rapid rise in urine volume and the elaboration of a urine hypotonic to plasma may be explained, as in the normal subject and the cirrhotic patient, by inhibition of vasopressin secretion due to the probable presence of ADH secretion. The fraction of distally delivered chloride, which is reabsorbed distally \( C_{H_2O}/C_{H_2O} + C_{Cl} \) cannot be utilized to analyse the kinetics of chloride reabsorption here because \( C_{H_2O} \) was positive only in a few patients, its median value being positive just in the first hour of immersion, indicating some distal chloride reabsorption. This does not exclude the possibility of distal tubular chloride reabsorption in the subsequent hours, but the experimental design prevents us drawing any firm conclusions. \( FE_{Cl} \) values increase throughout immersion indicating a reduced reabsorption of chloride in the renal tubule independent of changes in GFR.

The increase in urinary sodium excretion and urinary chloride excretion could not be attributed to increases in the GFR, for two reasons: (a) there was no overall increase in GFR during the four immersion hours, (b) \( FE_{Na} \) and \( FE_{Cl} \) increased during immersion and they normalize GFR changes by definition (see the Appendix). Conversely, although \( U_K \) increased significantly during the entire immersion period, there was no significant increase in \( FE_K \), supporting the view that some of the changes in potassium handling may have been due to the increase in GFR in the first hour of immersion; GFR subsequently fell to control levels.

The role of aldosterone in the chloruresis or natriuresis associated with immersion is undecided by the present data. Thus, seven out of nine patients had normal or low plasma aldosterone levels initially, and normal or low aldosterone levels have been observed in nephrotic patients [15, 17]. There was, however, a significant fall in plasma aldosterone levels in the immersion period compared with the pre-immersion hour. There was, however, no correlation between initial or subsequent aldosterone levels and the extent of immersion natriuresis or chloruresis. Moreover, the rapid onset of chloruresis and natriuresis is unlike that associated with switching off aldosterone secretion in which there is usually a considerable delay, often more than 1 h. This delay between the lowering of aldosterone levels in plasma and
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the subsequent renal tubular effects on sodium handling makes statistical evaluation of the simultaneous plasma aldosterone and urine sodium excretion data questionable. Thus, the failure to find a significant correlation may be entirely due to analysing simultaneous plasma and urine samples rather than plasma samples with urine samples passed 1 or more h later. Epstein and his colleagues have demonstrated in normal man that the chlorouresis and natriuresis of immersion are associated with a parallel increase in the urinary excretion of prostaglandin E [12]. Prostaglandin levels have not yet been measured in the urine of nephrotic patients treated by neck immersion in water.

Urinary Na+/K+ ratios rose throughout the period of immersion. This was perhaps due to the reduction in plasma aldosterone levels, even though they were initially normal or low in seven out of nine patients. It may be that nephrotic patients are hypersensitive even to normal plasma aldosterone levels and conserve sodium in its presence more efficiently than control subjects with these levels. The major cause of the increase in Na+/K+ ratio was the steady increase in sodium excretion and a much smaller increase in potassium excretion on immersion, the latter being due to changes in GFR as demonstrated by the lack of change in FEK on immersion. We did not find that reduced aldosterone levels caused a decreased urinary potassium excretion due to increased potassium reabsorption.

To indicate quantitative changes in delivery of sodium chloride into the distal tubule and reabsorption from the ascending loop of Henle, we have employed ‘chloride’ clearance rather than ‘sodium’ clearance in calculations, chloride being preferable to sodium in the case of a bicarbonate diuresis [18] which is found on water immersion in both normal man [19] and in the nephrotic patient (G. M. Berlyne, unpublished work).

The therapeutic implications of neck immersion in nephrotic patients are uncertain. There is a brisk diuresis and an increased sodium chloride excretion of about 35 mmol after 4 h of immersion. However, the depth and temperature of the bath are critical. A standard domestic bath is not suitable, because the water depth is insufficient to cause a diuresis, there being inadequate hydrostatic pressure to entrain the onset of a diuresis. In addition, the dangers of slipping on entering a deeper bath are obvious and the danger of drowning, as a result of syncope in the bath, presents an ever-present hazard in the nephrotic patient.

There were no significant changes in the blood pressure or pulse rate of the seated patient during immersion. Immersed patients had the tendency to feel sleepy during immersion, but this could not be differentiated from the soporific results of a warm bath in normal man.

References


APPENDIX

The data are markedly non-normal and consequently non-parametric methods including tests of significance and data display are used throughout. Location is denoted by median and dispersion by the interquartile range [1].

Median

If the observations $X_1, X_2, \ldots, X_k$ are ranked in increasing order and denoted $X_{(1)}, X_{(2)}, \ldots, X_{(k)}$ then: (1) $k$ odd, i.e. $k = 2n + 1; \text{median} = X_{(n+1)}$ and (ii) $k$ even, i.e. $k = 2n; \text{median} = 1/2[X_{(n)} + X_{(n+1)}]$.

The median rather than the mean is chosen because the median does not give as much weight to outliers.

Interquartile range

This is defined to contain half of the observations, e.g.:

$$Q_1 = 1/2[X_{(3)} + X_{(4)}]; Q_2 = X_{(6)} = \text{median}; Q_3 = 1/2[X_{(8)} + X_{(9)}] \text{ and the interquartile range } = (Q_1, Q_3).$$

The interquartile range is used because of Chebyshev's theorem.

Chebyshev's theorem

For any sample drawn from a distribution for which a second moment exists at least $[1 - (1/N^2)] \times 100\%$ of the measurements lie within $N$ standard deviations of the average of the measurements, e.g. mean $\pm 1 \text{ sd}$ is guaranteed to contain $[1 - (1/1^2)] \times 100\% = 0\%$ of the measurements and mean $\pm 2 \text{ sd}$ is guaranteed to contain $[1 - (1/2^2)] \times 100\% = 75\%$ of the measurements.

If the underlying distribution were normal, these values would be 68\% (mean $\pm 1 \text{ sd}$) and 95\% (mean $\pm 2 \text{ sd}$). Since our distribution is not normal, the mean $\pm 1 \text{ sd}$ does not guarantee to include any data points, whereas by definition the interquartile range $(Q_1, Q_3)$ includes 50\% of the measurements; the latter is to be preferred.

Fractional excretion of sodium

$$FE_{Na} = 1 - TR_{Na}$$

$$= \frac{1 - GFR \, P_{Na} - U_{Na}V}{GFR \, P_{Na}}$$

$$= \frac{GFR \, P_{Na} - (GFR \, P_{Na} - U_{Na}V)}{GFR \, P_{Na}}$$

$$= \frac{U_{Na}V}{GFR \, P_{Na}} = \frac{C_{Na}}{GFR}$$

where $FE_{Na}$ = fractional excretion of sodium, $TR_{Na}$ = tubular reabsorption of sodium, $GFR$ = glomerular filtration rate, $P_{Na}$ = plasma sodium concentration, $U_{Na}V$ = urinary excretion of sodium per minute and $C_{Na}$ = clearance of sodium.

Reference