Spectrum of Deranged Sodium Homeostasis in Essential Hypertension

MURRAY EPSTEIN, RODGER LOUTZENHISER, AND ROBERT LEVINSON

SUMMARY Essential hypertension is thought to produce a uniform exaggerated natriuresis and diuresis. Because validation of this formulation in humans is incomplete, the natriuretic and diuretic responses to acute volume expansion were characterized by using water immersion to the neck. This method provides a volume stimulus identical to that induced by 2 L of saline without plasma compositional change. Twenty-seven subjects with essential hypertension were studied on three occasions in the seated posture while in balance on a 10 mEq Na, 100 mEq K diet: during the seated control study, during 4 hours of head-out immersion, and during saline infusion (2 L/2 hours). Four subjects had exaggerated urinary Na excretion in response to neck immersion (Group 3), and 16 had a normal response (Group 2) indistinguishable from that of 15 previously studied normal subjects. The remaining seven subjects (Group 1) had blunted or absent natriuretic responses compared with that in normal subjects (p < 0.005). Similar results were obtained with saline administration; cumulative Na excretion in Group 1 was markedly less than that in Group 2 and the normal subjects. The heterogeneity in Na excretion indicates that an exaggerated natriuresis is not a uniform concomitant of essential hypertension. The significant inverse correlation between basal plasma aldosterone level and peak urinary as well as cumulative Na excretion suggests that plasma aldosterone constitutes a determinant of the differing natriuretic responses. In contrast to findings with urinary Na excretion, the diuretic responses of Groups 1 and 2 were identical. The striking dissociation between renal Na and water handling underscores the specificity of the derangement in renal Na handling.

Key Words • essential hypertension • natriuresis • water immersion • central blood volume

The pivotal role of the kidney in either causing or sustaining hypertension is becoming increasingly clear. It might be anticipated, therefore, that patients with essential hypertension would have alterations in renal sodium handling. For example, classic teaching has been that hypertensive patients manifest an exaggerated natriuresis in response to extracellular fluid volume expansion (ECVE). On the other hand, Hollenberg et al. have observed a functional abnormality characterized by increased renal vascular tone in approximately two thirds of patients with uncomplicated essential hypertension. Since renal perfusion is a determinant of sodium homeostasis through a series of interdependent mechanisms, this might cause an impairment of renal sodium excretion. Thus, countervailing influences on renal sodium handling appear to pertain in hypertensive patients, prompting the present study.

In designing the present study, we selected head-out water immersion as the method for achieving volume expansion. As detailed in several recent reviews, water immersion induces central volume expansion without changing plasma composition. This observation suggests that immersion is a more physiological maneuver than either saline or mannitol administration with which to achieve volume expansion in patients to assess renal sodium handling.

Subjects and Methods

Twenty-seven men with idiopathic hypertension were studied in the Clinical Research Unit of the University of Miami School of Medicine, and their responses were compared with those of 15 normal men studied under identical conditions. Subjects ranged in
SODIUM EXCRETION IN HYPERTENSION/Epstein et al.

age from 19 to 62 years. Permission for the study was obtained from each subject after a detailed description of the procedure and the potential complications. The protocol was approved by the Human Experimentation Committees of the University of Miami School of Medicine and the Miami Veterans Administration Medical Center and was in compliance with the principles outlined in the Declaration of Helsinki. No complications occurred.

Blood pressure was measured with standard cuff and sphygmomanometer with the subjects in both the supine and standing positions every 4 hours throughout the study. Subjects were considered to have hypertension when more than two thirds of their 4-hour blood pressure values exceeded 140/90 mm Hg during the first 2 days of hospitalization (diastolic pressure — phase 5 disappearance of sounds). The administration of all antihypertensive drugs had been discontinued at least 2 weeks before the study. All subjects underwent a thorough inpatient evaluation, which included complete history and physical examination; urinalysis and urine culture; chest roentgenogram, rapid-sequence intravenous pyelogram and electrocardiogram; blood studies for levels of electrolytes, cholesterol and triglycerides, aldosterone, and plasma renin activity (PRA); and measurement of urinary 17-ketosteroids, 17-hydroxycorticosteroids, metanephrine, and vanillylmandelic acid.

In none of the subjects was a known cause of the hypertension, such as primary aldosteronism, pheochromocytoma, renal vascular disease, or Cushing’s syndrome, found. Twenty-three of the subjects were judged to have normal renal function, as evaluated from serum urea nitrogen and creatinine and creatinine clearance (Ccr) values. Four subjects had modest decrements in Ccr, but only one of these was mildly azotemic. None of the subjects had evidence of cardiac failure or liver damage. Three subjects had low renin hypertension, as defined in this clinic, but none had malignant hypertension. Finally, in light of preliminary reports suggesting that athletes who have undergone extensive physical training may manifest an altered natriuretic response during immersion, highly trained subjects and joggers were excluded from the present study.

Subjects were housed throughout the study in a metabolic ward. Each consumed a constant, daily diet containing 10 mEq of sodium, 100 mEq of potassium, and 2000 to 2500 ml of water. For determination of sodium, potassium, and creatinine, 24-hour urine collections were made daily. After a mean of 5 days on the constant diet, at which time urinary sodium excretion was less than 10 mEq/24 hours and weight remained stable, each subject underwent a control study followed several days later by water immersion to the level of the neck in the seated posture. Immersion was performed in a waterproof tank as detailed previously. In addition, 18 subjects underwent saline infusion during the seated posture on Days 11 and 12. The experimental protocols on the three study days were similar and were performed in the following manner.

After 10 hours of overnight fluid restriction, the subject awoke at 0700, voided, and sat quietly for 1 hour. At 0720, an oral water load of 400 ml was administered, followed at 0750 by an additional 300 ml. At 0800 the subject voided again. Immediately after voiding, a 20-gauge ½-in Teflon catheter with an accompanying Teflon stylet was inserted into a forearm vein, permitting sequential sampling of blood without the use of an anticoagulant or an intravenous infusion. Immediately after insertion, venous blood was drawn using a prechilled 10-ml polystyrene disposable syringe and an aliquot was collected for renin and aldosterone measurements in a prechilled Vacutainer tube containing ethylenediaminetetraacetic acid (EDTA). In addition, venous blood was obtained for determination of serum electrolyte and creatinine concentration. After the sample was obtained, a sterile stylet was inserted into the catheter. After voiding and completely emptying his bladder, the subject once again assumed the seated position for 6 hours (0800–1400) for the control, immersion, and saline studies. During the control and saline studies, the subject sat quietly outside the immersion tank for 6 hours. During the immersion study, the subject sat in the tank, immersed in water to the neck for 4 hours (0900–1300); immersion was preceded and followed by 1 hour of quiet sitting outside the tank (prestudy and recovery hours, respectively). Saline infusions consisted of 2 L of 0.9% NaCl in water containing KCl, 5 mEq/L, infused at a constant rate (17 ml/min) from 0900 to 1100; this represented an average infusion volume of 2.6 ± 0.1% body weight.

Each subject stood briefly to void spontaneously at hourly intervals during the study. To maintain adequate urine flow, 200 ml of water was administered orally every hour during the study. Sodium, potassium, and creatinine concentrations were measured in aliquots of the hourly urine collections. All subjects were weighed every morning at 0700 after voiding and before and after each study.

The PRA was measured by radioimmunoassay according to the method of Haber et al.21 Plasma aldosterone (PA) was measured by a radioimmunoassay technique. Analytic methods for sodium, potassium, and creatinine determinations have been reported previously.22 The Ccr was calculated by conventional formulas. In the presentation of the data, mean values are followed by the standard error of the mean (SEM) as an index of dispersion. Data were evaluated statistically using Student’s t test for paired values or, where appropriate, by two-factor analyses of variance for experiments having repeated measurements on the same subject.23 If a significant effect was detected, the Newman-Keuls test was used to determine which treatment means were significantly different. Differences with a p value less than 0.05 were considered significant.

Results

Clinical Features

Table 1 shows the clinical and laboratory findings in the subjects. Fifteen subjects were white, and 12 were
<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Age (yr)</th>
<th>Race</th>
<th>Blood pressure (mm Hg)</th>
<th>Creatinine</th>
<th>24-hour clearance</th>
<th>PRA (ng ANG I/ml/hr)</th>
<th>PA (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (blunted natriuretic response to immersion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>W</td>
<td>135/83</td>
<td>133/93</td>
<td>1.3</td>
<td>85</td>
<td>10.2</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>W</td>
<td>147/91</td>
<td>148/90</td>
<td>1.1</td>
<td>86</td>
<td>26.0</td>
</tr>
<tr>
<td>3</td>
<td>31</td>
<td>B</td>
<td>145/92</td>
<td>146/106</td>
<td>1.7</td>
<td>102</td>
<td>8.2</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>B</td>
<td>153/90</td>
<td>148/96</td>
<td>1.1</td>
<td>152</td>
<td>14.1</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>B</td>
<td>130/86</td>
<td>142/96</td>
<td>0.9</td>
<td>127</td>
<td>8.6</td>
</tr>
<tr>
<td>6</td>
<td>54</td>
<td>W</td>
<td>134/91</td>
<td>136/95</td>
<td>1.0</td>
<td>115</td>
<td>20.3</td>
</tr>
<tr>
<td>7</td>
<td>40</td>
<td>B</td>
<td>142/95</td>
<td>145/104</td>
<td>1.1</td>
<td>106</td>
<td>21.4</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>31 ± 5</td>
<td></td>
<td>141 ± 3/90 ± 2</td>
<td>143 ± 2/97 ± 2</td>
<td>1.2 ± 0.1</td>
<td>110 ± 9</td>
<td>15.5 ± 2.7</td>
</tr>
<tr>
<td>Group 2 (appropriate natriuretic response to immersion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>28</td>
<td>B</td>
<td>137/96</td>
<td>136/100</td>
<td>1.1</td>
<td>98</td>
<td>5.0</td>
</tr>
<tr>
<td>9</td>
<td>28</td>
<td>W</td>
<td>117/83</td>
<td>128/96</td>
<td>1.2</td>
<td>101</td>
<td>9.1</td>
</tr>
<tr>
<td>10</td>
<td>26</td>
<td>W</td>
<td>144/106</td>
<td>121/106</td>
<td>1.2</td>
<td>109</td>
<td>3.7</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>B</td>
<td>145/98</td>
<td>140/98</td>
<td>1.0</td>
<td>67</td>
<td>6.9</td>
</tr>
<tr>
<td>12</td>
<td>34</td>
<td>B</td>
<td>148/112</td>
<td>154/119</td>
<td>1.3</td>
<td>118</td>
<td>12.8</td>
</tr>
<tr>
<td>13</td>
<td>31</td>
<td>W</td>
<td>140/94</td>
<td>137/102</td>
<td>1.1</td>
<td>150</td>
<td>1.4</td>
</tr>
<tr>
<td>14</td>
<td>48</td>
<td>W</td>
<td>155/101</td>
<td>154/101</td>
<td>2.2</td>
<td>62</td>
<td>15.1</td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>B</td>
<td>136/105</td>
<td>143/109</td>
<td>1.5</td>
<td>75</td>
<td>4.6</td>
</tr>
<tr>
<td>16</td>
<td>20</td>
<td>B</td>
<td>123/97</td>
<td>127/113</td>
<td>1.3</td>
<td>124</td>
<td>2.8</td>
</tr>
<tr>
<td>17</td>
<td>43</td>
<td>W</td>
<td>158/107</td>
<td>149/114</td>
<td>1.0</td>
<td>111</td>
<td>8.4</td>
</tr>
<tr>
<td>18</td>
<td>58</td>
<td>B</td>
<td>176/100</td>
<td>178/108</td>
<td>1.2</td>
<td>85</td>
<td>11.5</td>
</tr>
<tr>
<td>19</td>
<td>32</td>
<td>B</td>
<td>171/111</td>
<td>191/116</td>
<td>1.2</td>
<td>105</td>
<td>20.6</td>
</tr>
<tr>
<td>20</td>
<td>57</td>
<td>W</td>
<td>137/101</td>
<td>144/110</td>
<td>1.0</td>
<td>111</td>
<td>3.3</td>
</tr>
<tr>
<td>21</td>
<td>62</td>
<td>W</td>
<td>116/85</td>
<td>125/92</td>
<td>1.1</td>
<td>108</td>
<td>12.0</td>
</tr>
<tr>
<td>22</td>
<td>38</td>
<td>W</td>
<td>129/100</td>
<td>136/108</td>
<td>1.0</td>
<td>109</td>
<td>5.2</td>
</tr>
<tr>
<td>23</td>
<td>29</td>
<td>W</td>
<td>147/92</td>
<td>146/96</td>
<td>1.0</td>
<td>122</td>
<td>3.1</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>38 ± 3</td>
<td></td>
<td>142 ± 4/99 ± 2</td>
<td>144 ± 5/105 ± 2</td>
<td>1.2 ± 0.1</td>
<td>103 ± 6</td>
<td>7.8 ± 1.3</td>
</tr>
<tr>
<td>Group 3 (exaggerated natriuretic response to immersion)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>59</td>
<td>W</td>
<td>160/109</td>
<td>170/120</td>
<td>1.2</td>
<td>105</td>
<td>4.8</td>
</tr>
<tr>
<td>25</td>
<td>19</td>
<td>W</td>
<td>128/80</td>
<td>128/85</td>
<td>1.2</td>
<td>132</td>
<td>1.8</td>
</tr>
<tr>
<td>26</td>
<td>50</td>
<td>B</td>
<td>149/114</td>
<td>141/110</td>
<td>1.2</td>
<td>103</td>
<td>8.0</td>
</tr>
<tr>
<td>27</td>
<td>39</td>
<td>W</td>
<td>160/114</td>
<td>154/102</td>
<td>1.0</td>
<td>127</td>
<td>1.8</td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>42 ± 9</td>
<td></td>
<td>149 ± 8/104 ± 8</td>
<td>148 ± 9/104 ± 7</td>
<td>1.2 ± 0.1</td>
<td>117 ± 7</td>
<td>4.1 ± 1.5</td>
</tr>
</tbody>
</table>

PRA = plasma renin activity; ANG I = angiotensin I; PA = plasma aldosterone.

The subjects were classified as either Group 1, 2, or 3 on the basis of their natriuretic response during immersion (see Table 1). Group 1 had a significantly lower diastolic pressure (both supine and upright) than Group 2. An examination of the PRA and PA values of the three groups disclosed that mean PRA of Group 1 exceeded that of both Groups 2 (p < 0.01) and 3 (p < 0.05). Mean PA values of Group 1 tended to exceed the corresponding values of both Groups 2 and 3, although this difference never attained statistical significance. Neither age, race, serum creatinine concentration, nor 24-hour endogenous Cr, differed among groups.

Urinary Sodium and Potassium Excretion
Cumulative sodium excretion following imposition of dietary sodium restriction was assessed in all subjects. Sodium excretion of Group 1 (267 ± 38 mEq) was not different from that of either Group 2 (255 ± 24 ± 58 mEq). Black did not differ from whites with respect to age (35 ± 3 SE vs 39 ± 4; p > 0.4), PRA (10.4 ± 1.7 vs 8.4 ± 1.0 ng angiotensin l/ml/hr; p > 0.4), PA level (222 ± 39 vs 280 ± 44 pg/ml; p > 0.2), or blood pressure (p > 0.2).
TABLE 2. Urinary Excretory Patterns of 27 Subjects During Control and Immersion Studies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Presudy</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>V (ml/min)</td>
<td>1.9±0.3</td>
<td>2.3±0.2</td>
<td>2.4±0.2</td>
<td>2.4±0.2</td>
<td>2.5±0.2</td>
<td>1.8±0.2</td>
</tr>
<tr>
<td>Immersion</td>
<td>2.0±0.3</td>
<td>5.0±0.3*</td>
<td>6.0±0.4*</td>
<td>4.4±0.3*</td>
<td>4.0±0.3*</td>
<td>0.8±0.1*</td>
</tr>
<tr>
<td>UNaV (µEq/min)</td>
<td>4.8±1.2</td>
<td>4.1±0.9</td>
<td>4.0±0.9</td>
<td>3.6±0.9</td>
<td>3.0±0.8</td>
<td>2.2±0.8</td>
</tr>
<tr>
<td>Immersion</td>
<td>3.4±0.8</td>
<td>14.5±3.0*</td>
<td>22.3±4.2*</td>
<td>25.7±4.5*</td>
<td>31.4±5.2*</td>
<td>8.0±1.8*</td>
</tr>
<tr>
<td>UNaV + UKV (µEq/min)</td>
<td>43±5</td>
<td>46±5</td>
<td>46±5</td>
<td>48±5</td>
<td>50±5</td>
<td>44±5</td>
</tr>
<tr>
<td>Immersion</td>
<td>45±4</td>
<td>86±6*</td>
<td>108±8*</td>
<td>99±8*</td>
<td>90±8*</td>
<td>32±4*</td>
</tr>
<tr>
<td>CCT (ml/min)</td>
<td>126±7</td>
<td>120±6</td>
<td>114±6</td>
<td>117±6</td>
<td>116±6</td>
<td>106±6</td>
</tr>
<tr>
<td>Immersion</td>
<td>132±6</td>
<td>137±6*</td>
<td>133±6*</td>
<td>127±5</td>
<td>131±6†</td>
<td>101±6</td>
</tr>
<tr>
<td>FE Na (%)</td>
<td>0.026±0.006</td>
<td>0.029±0.006</td>
<td>0.025±0.005</td>
<td>0.025±0.007</td>
<td>0.018±0.005</td>
<td>0.020±0.007</td>
</tr>
<tr>
<td>Immersion</td>
<td>0.019±0.004</td>
<td>0.081±0.017*</td>
<td>0.133±0.028*</td>
<td>0.153±0.027*</td>
<td>0.187±0.031*</td>
<td>0.060±0.013*</td>
</tr>
<tr>
<td>UNaV + UKV (µEq/min)</td>
<td>48±5</td>
<td>51±5</td>
<td>50±5</td>
<td>52±5</td>
<td>53±5</td>
<td>46±5</td>
</tr>
<tr>
<td>Immersion</td>
<td>49±5</td>
<td>101±7*</td>
<td>131±9*</td>
<td>125±10*</td>
<td>122±10*</td>
<td>41±5</td>
</tr>
</tbody>
</table>

Values are means ± SE. V = urine flow rate; UNaV = urinary sodium excretion rate; UKV = urinary potassium excretion rate; CCT = creatinine clearance; FE Na = fractional excretion of sodium.

*p < 0.005, †p < 0.05, compared with control values.

38 mEq) or 3 (285 ± 77 mEq). Similarly, the weight loss incurred during the attainment of sodium balance mirrored the changes in cumulative sodium loss. There were no significant differences in weight loss (Group 1, -1.0 ± 0.4; Group 2, -1.2 ± 0.2; Group 3, -1.7 ± 0.5 lb), although the loss in Group 3 tended to exceed that in the other two groups.

The effects of 4 hours of water immersion on urinary sodium and potassium excretion of the entire group of 27 subjects are shown in Table 2. During quiet sitting (control), the rate of sodium excretion (UNaV) ranged from 2.2 to 4.8 µEq/min. Immersion resulted in a highly significant increase in the mean UNaV compared with control values, beginning with the initial hour of immersion. During the final hours of immersion UNaV was on average 10-fold greater than it was during the corresponding control period (p < 0.005). Recovery was associated with a prompt return toward prestudy values (p < 0.001 for recovery compared with Hour 4 of immersion).

Examination of the individual natriuretic responses of the 27 subjects disclosed a continuum of markedly different responses (Figures 1 and 2). Despite the stimulus of 4 hours of immersion, Subjects 1, 2, 7, 14, 15, 21, and 23 manifested a sluggish or barely discernible increase in UNaV compared with prestudy values (see Figure 1). Furthermore, mean UNaV of Group 1 was less than that of 15 normal control subjects during Hours 2 to 4 of immersion. These seven subjects were classified arbitrarily as Group 1. Sixteen subjects manifested an appropriate natriuretic response, which did not differ from normal sodium-depleted subjects undergoing an identical study (designated Group 2). The remaining four subjects, designated Group 3, manifested a profound natriuresis, which exceeded the 34 ± 7 µEq/min seen in 15 normal subjects during an identical sodium diet (see Figure 2). As can be seen in Figure 3A, mean UNaV for Group 2 patients exceeded that of Group 1 during all 4 hours of immersion, while
mean $U_{NaV}$ for Group 3 exceeded the corresponding values for both Groups 1 and 2 as well as for normal subjects during every hour of immersion.

Fractional excretion of sodium ($FE_{Na}$; $C_{Na}/C_G \times 100$) remained constant during control, ranging from 0.18 to 0.29% for the entire group. Immersion resulted in an increase, from $0.019 \pm 0.004\%$ to $0.187 \pm 0.031\% \ (p < 0.05)$. Cessation of immersion was associated with a prompt decrease to $0.060 \pm 0.013\%$. The responses of the individual subgroups tended to parallel the pattern observed for $U_{NaV}$.

To examine the determinants of the differing natriuretic responses, we compared the changes in $FE_{Na}$ in the three study groups. As shown in Figure 4, the major determinant of the natriuretic responses of Groups 2 and 3 was an increased tubular rejection of sodium. In contrast, $FE_{Na}$ was essentially unchanged in Group 1. Group 2 manifested a 10-fold increase in $FE_{Na}$ (from 0.02 to 0.20 $\pm 0.03\%$) during immersion. Group 3 manifested a marked and striking increase, which was twofold greater than that manifested by Group 2 (from $0.04 \pm 0.01$ to $0.42 \pm 0.08\%; \ p < 0.005$). Thus, the changes in $FE_{Na}$ paralleled those in $U_{NaV}$.

The rate of potassium excretion ($U_{K^+}$) did not vary significantly during control, ranging from 43 to 50 $\mu$Eq/min. Immersion was associated with a kaliuresis compared with control during all 4 hours of immersion. Recovery was associated with a prompt decrement in $U_{K^+}$ to $32 \pm 4 \mu$Eq/min, a value significantly less than the corresponding value during the control study. In contrast to the spectrum of markedly differing individual natriuretic responses, there was a striking similarity in the individual kaliuretic responses for all 3 groups (Figure 3B).

![Figure 2](image-url)  **Figure 2.** Effect of water immersion on rate of urinary sodium excretion ($U_{NaV}$) in Group 3 ($n = 4$). Shaded area represents means $\pm$ SE for 15 normal subjects undergoing an identical immersion study. All subjects manifested a natriuretic response equaling or exceeding that seen in normal subjects; Subjects 5 and 27 manifested a natriuresis that exceeded 100 $\mu$Eq/min.

![Figure 3](image-url)  **Figure 3.** Effect of water immersion on (A) the rate of urinary sodium excretion ($U_{NaV}$), (B) the rate of urinary potassium excretion ($U_{K^+}$), and (C) the diuretic response (urine flow rate, V) in 27 hypertensive subjects and 15 normal controls (shaded area). Group 3 subjects manifested an exaggerated natriuresis which exceeded that of both normal control and Group 2 subjects. In contrast to the marked differences in renal sodium handling, the kaliuresis and diuresis of all three groups were identical. Results are means $\pm$ SE.
The sum of $U_{Na}V + U_{K}V$ as an index of distal delivery was also assessed. A comparison of the hourly excretory rates for $U_{Na}V + U_{K}V$ disclosed that the excretory response for Groups I and 2 did not differ during each hour of immersion. A comparison of the cumulative sodium and potassium excretion during the 4 hours of immersion disclosed that cumulative excretion was similar for Groups I and 2 ($24 \pm 3$ vs $27 \pm 2$ mEq/4 hours; $p > 0.4$). In contrast, cumulative excretion in Group 3 ($42 \pm 2$ mEq/4 hours) exceeded that in both Groups 1 and 2 ($p < 0.005$ and $p < 0.01$, respectively).

Urine Flow Rate and Creatinine Clearance

Urine flow rate (V) during control ranged from 1.8 to 2.5 ml/min (see Table 2). Despite identical water intake during control and immersion studies, V throughout the 4 hours of immersion exceeded those observed during control ($p < 0.005$). Mean $V$ increased from a prestudy level of $2.0 \pm 0.3$ to a peak of $6.0 \pm 0.4$ ml/min during Hour 2 of immersion. Recovery was associated with a prompt decrease ($p < 0.001$, compared with prestudy values).

In contrast to the spectrum of markedly differing individual natriuretic responses, there was a striking similarity in the diuretic responses in two of the three subgroups. The temporal profile and magnitude of diuretic responses for Groups 1 and 2 were identical (Figure 3C) and did not differ from that of 15 normal subjects undergoing an identical study. Although the diuresis in Group 3 tended to exceed that of Groups 1 and 2, it did not attain statistical significance. Similarly, the response of Group 3 did not differ from that of normal subjects.

In addition to assessing the effects of immersion on V, we also compared cumulative urine volume during the 4 hours of immersion. An examination of the mean cumulative water excreted disclosed that Groups 1 and 2 excreted identical volumes ($1082 \pm 77$ vs $1083 \pm 78$ ml/4 hours), while excretion in Group 3 ($1554 \pm 181$ ml/4 hours) exceeded that of both Groups 1 and 2 ($p < 0.05$, compared to Groups 1 and 2).

Mean $C_{cr}$ for all 27 subjects remained constant throughout control. Immersion did not alter $C_{cr}$ as compared with the prestudy hour. Recovery was associated with a mean decrease in $C_{cr}$ of 30 ml/min for recovery compared with both prestudy values and Hour 4 of immersion ($p < 0.001$).

In light of the differing natriuretic responses, it was of interest to examine the individual $C_{cr}$ responses during immersion. As shown in Figure 4, $\Delta C_{cr}$ (the absolute change from the preimmersion hour) was unaltered during immersion in Groups 1 and 2. In contrast, Group 3 manifested a marked increase in $C_{cr}$ by Hour 3 of immersion, $\Delta C_{cr}$ was $24 \pm 9$ ml/min greater than during the prestudy hour. Recovery was associated with a striking decrease in $C_{cr}$ for all three groups ($-30 \pm 9$, $-25 \pm 7$, $-48 \pm 14$ ml/min for Groups 1, 2, and 3, respectively). This decrease differed from the response of the normal control subjects.

Saline Administration

In addition to undergoing immersion studies, saline was administered to 18 subjects. We anticipated that such a comparison of the effects of two different (but hemodynamically equivalent) volume expansive maneuvers would elucidate further the contribution of factors other than changes in extracellular fluid volume in mediating the natriuretic and diuretic effects of immersion. Thus, we also compared cumulative sodium excretion during 4 hours of immersion and saline in
these 18 subjects and found that the values were similar (5.2 ± 1.1 vs 5.4 ± 1.3 mEq; NS). Similarly, the natriuresis in Group 1 was blunted as assessed during immersion and saline (0.8 ± 0.4 vs 1.0 ± 0.6 mEq; NS). Thus, regardless of the manner in which renal sodium handling was assessed, the natriuresis of immersion correlated with renal sodium handling during saline administration.

**Determinants of Sodium Excretion**

**Blood Pressure**

To assess the relationship between resting blood pressure and renal sodium handling, we examined the relationship between sodium excretion (both peak \( U_{NaV} \) and cumulative sodium excretion during 4 hours of immersion) and blood pressure in all 27 subjects immediately before the study began. Figure 5 summarizes cumulative sodium excretion during immersion and in the recumbent, seated, and standing postures. Examination of the data discloses a striking dissociation between blood pressure at the time of study and the observed natriuresis. For example, Subject 7, with a blunted natriuretic response, manifested elevations in blood pressure that were similar to those seen in Subjects 27 and 5, who manifested an exaggerated natriuresis. Conversely, Subject 8 tended to manifest only a modestly elevated blood pressure despite a striking natriuresis. When the blood pressure at the time of study was correlated with the corresponding natriuresis during immersion for the entire group, the natriuresis varied independently of blood pressure levels (Table 3).

An examination of the relationship between race and renal sodium handling failed to disclose a significant difference. Peak \( U_{NaV} \) during immersion of the white subjects was similar to that manifested by the 12 black subjects (38 ± 8 vs 30 ± 7 μEq/min; \( p > 0.4 \)). An assessment of cumulative sodium excretion during the 4 hours of immersion showed that the values did not differ between white and black subjects (6.1 ± 1.5 vs 5.0 ± 1.2 mEq/4 hours; \( p > 0.5 \)).

**Age**

Since earlier reports have suggested that age may constitute a determinant of the exaggerated natriuresis, we examined the relationship between sodium excretion (both peak \( U_{NaV} \) and cumulative sodium excreted during 4 hours of immersion) and age in all 27 subjects. Neither peak \( U_{NaV} \) (\( r = 0.30, p > 0.10 \)) nor cumulative sodium (\( r = 0.36, p > 0.05 \)) correlated with increasing age.

**Discussion**

During the past 3 decades much attention has been focused on the kidney’s role in causing and sustaining hypertension. The results of many studies indicate that patients with essential hypertension (as compared with normotensive persons) manifest an exaggerated natriuretic and diuretic response to rapidly administered infusions of hypertonic saline, mannitol, dextrose and water, and isotonic saline. As a consequence of such investigations, it has been accepted as a truism that hypertensive patients manifest an exaggerated natriuresis in response to ECVE. A review of many of these studies suggests that the exaggerated natriuresis may be attributable in part to the experimental conditions rather than to the hypertension per se. The observations of Hollenberg et al., demonstrating an increased renal vascular tone in the majority of patients

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Systolic</th>
<th>Cumulative sodium</th>
<th>Diastolic</th>
<th>Cumulative sodium</th>
<th>Mean</th>
<th>Cumulative sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Supine</td>
<td>0.36</td>
<td>0.39</td>
<td>0.44*</td>
<td>0.44*</td>
<td>0.42*</td>
<td>0.43*</td>
</tr>
<tr>
<td>Seated</td>
<td>0.01</td>
<td>0.07</td>
<td>-0.14</td>
<td>-0.04</td>
<td>-0.09</td>
<td>0.01</td>
</tr>
<tr>
<td>Standing</td>
<td>0.42*</td>
<td>0.50*</td>
<td>0.36</td>
<td>0.37</td>
<td>0.39*</td>
<td>0.43*</td>
</tr>
</tbody>
</table>

\( *p < 0.05 \).
with uncomplicated essential hypertension, have raised the possibility that an exaggerated natriuresis may not necessarily occur during all conditions of study. The results of the present investigation demonstrate that an exaggerated natriuretic response to ECVE is not necessarily an accompaniment of hypertension. We found that many subjects with essential hypertension manifest either an appropriate or a blunted natriuresis in response to the ECVE attained by water immersion.

Effects related to the experimental design other than ECVE might explain the observed alterations in the renal handling of sodium. Although both diurnal variation and posture are known to influence renal function and renin-aldosterone levels, all subjects were studied in a similar seated position and at the same time of day. Since changes in plasma volume are critical determinants of renal sodium handling, all three studies were performed during identical sodium balance and the volume of the administered water load was kept constant during all three studies.

Previous studies have raised the possibility that a low sodium intake may obliterate significant differences between hypertensive and normotensive subjects in the amount of sodium excreted. However, this formulation does not appear to constitute a tenable explanation for the failure of many of our subjects to manifest an exaggerated natriuresis, since other studies have reached opposite conclusions. For example, Papper et al.23 compared the response of hypertensive and normotensive subjects to intravenous sodium loading under rigidly controlled conditions at three different levels of dietary salt ingestion and found that the apparent exaggerated response of subjects with essential hypertension persists at each level of salt consumption. Despite the findings in the latter study, we believe that the low sodium intake in our subjects may have contributed to the observed changes in sodium excretion. Conceivably, increased levels of aldosterone may play a more prominent role in promoting sodium retention.

Another possible explanation for the different natriuretic responses is that cumulative sodium excretion to achievement of balance differed between groups. Thus, one might argue that the blunted natriuresis of Group 1 was a consequence of the greater cumulative sodium loss before balance was achieved and thus a greater degree of volume contraction. A similar formulation might have provided an explanation for the higher levels of PRA and PA in this group. The finding that cumulative sodium excretion and weight loss to balance were similar for all three groups militates against this possibility.

Since “trained” subjects (as opposed to “sedentary” subjects) may manifest a relatively blunted or absent natriuretic and diuretic response during immersion (S. K. Hong, unpublished observations, 1985), highly trained subjects and joggers were excluded.

Finally, in view of the well-known hemodynamic alterations affecting hypertensive humans,26 it is conceivable that head-out water immersion failed to in-
duce similar central volume expansion in all subjects. The current finding that despite widely differing changes in renal sodium handling all the subjects manifested a diuresis indicates that this was not the case and that acute central hypervolemia was indeed achieved. The current observations, therefore, must represent markedly differing responses in sodium excretion in response to water immersion.

The observation of a dissociation between renal sodium and water handling merits comment. Previous investigators have suggested that, in addition to the exaggerated natriuresis, patients with essential hypertension manifest an exaggerated diuresis following volume expansion. In contrast, we were unable to confirm these findings: Groups 1 and 2 manifested identical diuretic responses during immersion despite markedly different natriuretic responses. These findings suggest the presence of independent mechanisms mediating renal sodium and water handling. Previous studies from our laboratory demonstrating dissociations of renal sodium and water handling during immersion are consistent with such a formulation.

An attractive formulation to explain the similar diuretic responses in the face of differing natriuretic responses is a difference in the degree of central compartmentalization in response to immersion. Thus, it is conceivable that immersion induced differing degrees of central hypervolemia in the three groups. Despite such differences, the magnitude of the cephalad augmentation was sufficient in all three groups to produce a uniform suppression of arginine vasopressin with a resultant diuresis. In contrast, if the threshold necessary to affect afferent traffic to the central nervous system centers that modulate renal sympathetic traffic is greater than that necessary to affect vasopressin release and differed among the three groups, one can postulate that this threshold was attained in Group 1, and not in Group 3.

The concept that not all hypertensive persons manifest an exaggerated natriuresis in response to acute volume expansion is not nearly as iconoclastic as it may seem. A review of the available literature discloses several studies in which a lack of uniformity of renal sodium handling was observed. For example, Cottier et al. noted marked variability in the natriuretic responses of five severely hypertensive subjects receiving an intravenous sodium load. Whereas three of the subjects manifested an exaggerated natriuresis, the remaining two manifested responses not differing from that of normal subjects. Green et al. studied renal sodium and water handling in 26 nonhypertensive controls and 53 patients with hypertension and observed that the hypertensive patients could be divided into a "normal sodium-excreter" group and a "high sodium-excreter" group (n = 18). During the saline infusion test, the high sodium-excreter group excreted sodium at a mean rate of 535 ± 182 μEq/min, a level approximately threefold greater than that of the normal sodium-excreter hypertensive subjects. Similarly, Lowenstein et al. demonstrated that of nine essential hypertensive patients who underwent hypertonic saline loading, three manifested an "appropriate" natriuresis, which did not differ from that of normal control subjects.

More recently, Kawasaki et al. have provided additional support for the concept that patients with essential hypertension constitute a markedly heterogeneous group with regard to both the blood pressure and the sodium excretory response to chronic volume expansion. They demonstrated that in response to dietary sodium loading (249 mEq/day) nine patients increased their average mean blood pressure by 10% or more ("salt-sensitive" group), whereas the blood pressure in the remaining 10 patients did not change or increased by less than 10% ("non-salt-sensitive" group). Of interest, the salt-sensitive patients gained more weight and excreted less sodium than did the non-salt-sensitive patients. Thus, essential hypertensive patients exhibit heterogeneity with regard to the natriuretic response to both acute and chronic salt loading.

The determinants of the differing sodium excretory responses in hypertension have been a subject of continuing controversy. Several lines of evidence suggest that the enhanced sodium excretion in patients with essential hypertension may relate to the level of blood pressure elevation. For example, Vaamonde et al. demonstrated that the elevation of blood pressure induced by metaraminol infusion in normal control subjects caused an exaggerated natriuresis. Eisinger demonstrated a similar effect in the dog. In contrast, Hollander and Judson were unable to demonstrate a high degree of correlation between the level of the blood pressure and the natriuretic response to saline administration. Our results are in agreement with those of Hollander and Judson, suggesting that, in addition to the arterial pressure, other factors must be operating to enhance sodium excretion in patients with essential hypertension. Nevertheless, since methodological considerations precluded blood pressure measurements during immersion, immersion-induced changes in blood pressure might have contributed to the variable natriuretic responses. We believe that this possibility is unlikely, however, since previous studies from our laboratory have failed to discern a change in blood pressure in normal subjects undergoing immersion.

Recent studies have suggested that an alteration of control of vascular resistance during salt loading may be relevant to the observed results. Takeshita et al. determined the venous pressure—distensibility relationship in hypertensive patients placed on low and high salt diets. Patients were arbitrarily divided into two groups based on blood pressure response to salt loading: those whose mean blood pressure increased by more than 10% while on the high salt diet as compared with those on the low salt diet (salt-responsive patients) and those whose mean blood pressure did not increase by more than 10% (salt-nonresponsive patients). Venous pressure—volume curves were not different between salt-responsive and salt-nonresponsive patients while on the low salt diet. High salt intake shifted the venous pressure—volume relationship toward the pressure axis for salt-responsive patients. (p <
0.05) but not for salt-nonresponsive patients. If salt loading (or volume expansion) decreases venous distensibility, such a change might contribute to redistribution of venous blood from the periphery to the cardiopulmonary circulation. Thus, alterations in venous distensibility might constitute a determinant of the central hypervolemia induced by immersion and the resultant natriuresis. To the extent that alterations in venous distensibility differed among members of the present study population, this may have contributed to the spectrum of widely differing natriuretic responses.

An additional possibility to explain the spectrum of differing natriuretic responses during immersion derives from the studies of Hollenberg and Williams and Rydstedt et al. These investigators identified a substantial subgroup (approximately one-third) of young patients with essential hypertension in whom control of the renal circulation was deranged. This abnormality was characterized by a renal blood supply that was resistant to the influences of dietary sodium restriction. Additional studies demonstrated that renal vascular responsiveness to angiotensin II remained independent of sodium intake. Taken together, these observations strongly suggest that there is a subgroup of patients with essential hypertension who fail to modulate their renal blood flow, aldosterone, andpressor responses to angiotensin II with changes in sodium dietary intake. Similar differences in renal hemodynamic and adrenal changes may contribute to the spectrum of natriuretic responses observed in the present study.

The occurrence of an exaggerated natriuresis has been postulated to correlate inversely with PRA. Kraf koff et al. compared the response to ECVE with isotonic saline in two groups of patients with uncomplicated hypertension (low renin and normal renin groups) and in normotensive subjects. They observed that patients with low renin hypertension manifested a significantly greater natriuretic and diuretic response to ECVE. The authors postulated that the exaggerated response of low renin patients may imply a functionally significant increase of extracellular fluid volume in these subjects. Alternatively, the low renin state may permit greater renal excretion of sodium when sudden increases in extracellular volume occur. The present demonstration of an inverse correlation between basal PRA levels and sodium excretion are consistent with this postulate.

Within the past several years, increasing evidence has accumulated suggesting the presence of a circulating natriuretic factor that normally depresses renal tubular reabsorption in response to ECVE. Recently, Buckalew and Gruber have published a scholarly review summarizing the evidence for the existence of a natriuretic hormone (NH) and the recent developments regarding its characterization. The influence of a natriuretic factor may well be relevant to the explanation of the differing natriuretic responses seen in our subjects. Buckalew and Gruber proposed a model for the participation of NH in hypertension. According to this hypothesis, salt ingestion leads to NH release by expanding the "effective" plasma volume. In hypertensive subjects, the renal response to NH is blunted, causing NH levels to become higher than in normotensive subjects. These pathologically elevated NH levels subsequently further increase blood pressure, either by activating the sympathetic nervous system or by increasing vascular reactivity directly, or both. Thus viewed, hypertension is the result of the need to regulate volume in the presence of a defect in renal sodium excretion. In accordance with this formulation, it is tempting to speculate that the differing natriuretic responses to immersion in our subjects may be attributable to the interplay of differing NH levels.

Finally, it is tempting to invoke atrial natriuretic factor as a major participant in the efferent limb modulation of the differing natriuretic responses during immersion. Since its discovery in 1981, remarkable advances have been accomplished in the identification, purification, and determination of the amino acid sequences of atrial natriuretic and vasoactive peptides and their precursors. Although the central effect of atrial natriuretic factor is to induce a natriuresis, it also exerts potent vasoactive properties tending to lower blood pressure. Thus, differing degrees of central blood volume expansion with corresponding differences in atrial distention may account for the disparate natriuretic responses. Intriguingly, atrial natriuretic factor induces an increase in glomerular filtration rate in addition to its potent natriuretic activity. Thus, the demonstration that Group 3 subjects manifested an increase in glomerular filtration rate during immersion is consistent with the postulate that atrial natriuretic factor release was greatest in these subjects.

In summary, short-term central blood volume expansion induced a spectrum of markedly differing natriuretic responses in 27 hypertensive subjects. Additional studies using saline administration in 18 of the subjects confirmed these differences, underscoring that the differing responses were related to hypertension per se and were not a function of the volume expansion maneuvers selected. Although immersion was associated with an increase in C_{SV} in Group 3 subjects, an examination of the F_{ENPV} changes indicated that natriuresis was attributable to an increased tubular rejection of sodium. The demonstration of an inverse correlation between the prestudy PA levels and the natriuretic response suggests that both an increased distal delivery of filtrate and a lessened mineralocorticoid effect contributed to the exaggerated natriuresis in Group 3. The possibility that differing levels of natriuretic factors or the renal response to such factors may contribute to the observed differences in renal sodium excretion remains to be investigated.

References
T. Renal excretion of water, sodium and chloride. Circulation 1953;7:258–267
20. Li JCR. Introduction to statistical inference. Ann Arbor, MI: Edwards Brothers, 1957
Spectrum of deranged sodium homeostasis in essential hypertension.
M Epstein, R Loutzenhiser and R Levinson

_Hypertension._ 1986;8:422-432
doi: 10.1161/01.HYP.8.5.422

_Hypertension_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1986 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on
the World Wide Web at:
http://hyper.ahajournals.org/content/8/5/422

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally
published in _Hypertension_ can be obtained via RightsLink, a service of the Copyright Clearance Center, not
the Editorial Office. Once the online version of the published article for which permission is being requested
is located, click Request Permissions in the middle column of the Web page under Services. Further
information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to _Hypertension_ is online at:
http://hyper.ahajournals.org//subscriptions/