Relation of Plasma to Interstitial Fluid Volume in Essential Hypertension

By Robert C. Tarazi, M.D., Harriet P. Dustan, M.D., and Edward D. Frohlich, M.D.

SUMMARY
Extracellular water (radiobromine), plasma volume (radioiodinated human serum albumin), and peripheral plasma renin activity were measured simultaneously in men with uncomplicated, untreated essential hypertension and in normal subjects. The ratio of plasma volume to interstitial fluid volume (PV/IF) was significantly lower in hypertensive patients (0.194 vs. 0.223, P < 0.001). This could not be explained only on the basis of the diminished plasma volume found in hypertensive patients (17.3 ml/cm of body height vs. 18.7 ml/cm, P < 0.05), as three normal subjects with marked plasma volume contraction had normal PV/IF ratios (0.224). This disturbed ratio in hypertensives suggests, therefore, an abnormality in the mechanism regulating the distribution of extracellular water in essential hypertension. Peripheral plasma renin activity correlated inversely with plasma volume, but not with extracellular water volume, suggesting that these two indices of body fluid volume are not always functionally interchangeable.

Additional Indexing Words.
Extracellular fluid volume
Plasma renin activity

VARIOUS STUDIES1-3 have shown that plasma volume is reduced in patients with essential hypertension. This reduction, the cause of which is not apparent, raises the question of whether such patients have an overall contraction of extracellular fluid volume or a selective diminution of its intravascular compartment. The volume of extracellular water (ECW) has been reported to be either expanded4-7 or normal8-12 in uncomplicated hypertension. However, in most of these studies plasma volume was not measured simultaneously, and the types of hypertension were not strictly defined. Yet differences have been reported in extracellular water,12-14 plasma volume,3, 15 and cardiac output16 between essential hypertension and the elevated blood pressure associated with renal parenchymal disease, renoprival states, primary aldosteronism, and renal arterial stenosis. These differences between forms of hypertension that are often similar clinically stress the need for careful definition of the type studied and hence warrant reappraisal of previous conclusions concerning extracellular water. This report summarizes our experiences with simultaneous measurements of extracellular water and plasma volume in men with uncomplicated and untreated essential hypertension.

It became evident during the course of the study that the partition of extracellular fluid into its intravascular and interstitial compartments was altered in hypertensive patients. This raised serious doubts as to the validity of using plasma volume and extracellular fluid volume interchangeably in the study of the renin-angiotensin system, for example.17 Since preliminary results had shown that peripheral plasma renin activity was inversely related to intravascular volume,18 its relation to plasma...
and extracellular fluid volume was studied to determine which compartment correlated better with it and whether extrapolation from one volume index to the other was valid.

Methods

The subjects of this study were 20 men with uncomplicated, untreated, essential hypertension and 26 normal male volunteers. This restriction to men was intended to avoid the possibility of variations of extracellular water within the menstrual cycle. Plasma volume was measured in all 26 normal men; this larger number was obtained by adding as many normals as possible to the previously reported normal group. As simultaneous extracellular water measurements were begun later, only 11 normal volunteers could be studied, and plasma renin activity was determined in nine.

All hypertensive patients were hospitalized but not restricted as to diet or activity; all had renal arteriography performed and determinations of plasma volume (PV), extracellular water (ECW) volume, and peripheral plasma renin activity within the first 5 days. Known secondary causes of hypertension were carefully excluded. None of the patients had either past history or present evidence of cardiac failure or of diminished renal excretory function: blood urea and serum creatinine concentrations and creatinine clearance were normal, and there were no clinical or hemodynamic (cardiac output, Valsalva maneuver) signs of cardiac decompensation. Supine arterial pressure ranged from 140/90 to 175/123 mm Hg (average, 157/108); three patients had fluctuating hypertension while the other 17 always had high blood pressure when off therapy. All had grade 1 to 2 hypertensive funduscopic changes, and none had hemorrhagic or exudative retinopathy. Antihypertensive therapy, including diuretics, was discontinued in all cases for at least 1 month before investigation.

Extracellular Water

Extracellular fluid volume was determined with radiobromine (\textsuperscript{82}Br) as described by Moore’s group. Following intravenous injection of sodium radiobromide (30 to 35 microcuries in 50 ml saline), multiple samples of peripheral venous blood were obtained over a period of 3 to 5 hours at intervals varying from 20 min to 1 hour. The final sample was drawn the following morning (8 to 9 a.m.) about 18 hours after the injection. Urine voided during the initial postinjection period (first 3 to 5 hours) was collected separately from that voided from then until the final sample of blood was obtained (18 hours after injection). These samples provided a measure of the amount of radioactivity excreted during each equilibration period, thus avoiding unwarranted extrapolations of isotope excretion from overnight to afternoon periods. Gastrointestinal secretions were not taken into account since none of the patients had vomiting or diarrhea. Blood was withdrawn into tubes containing dry heparin; 2-ml aliquots of plasma and urine were pipetted into tubes of fixed size and counted in duplicate in an automatic gamma-ray scintillation counter. Standards were similarly counted in quadruplicate, using a 1:100 dilution of the radiobromine solution injected. In some cases, counting was done with a discriminator set at the previously determined peak for radiobromine emission while in others no discriminator was used. In six sets of samples from six patients, both methods used concurrently gave similar results. Time of counting varied from 2 to 5 min (nonselective counting) to 100 min (selective counting) to obtain at least 4,000 counts per sample per period.

Bromide space was calculated as: \[
\frac{Q - E}{C_1 - C_2}
\]

when \(Q\) = total counts per minute injected
\(E\) = total counts per minute excreted during the period of equilibration
\(C_1\) = counts per minute per ml of postmix plasma sample
\(C_2\) = counts per minute per ml of premix plasma sample.

Extracellular water was then calculated from the bromide space by correcting for red cell uptake, serum water, and Donnan equilibrium factor:

\[
ECW = \frac{Br_{sp} - PV - 0.6 \times RCM}{1.11} + 0.92 \times PV
\]

Where \(Br_{sp}\) = bromide space
\(PV\) = plasma volume
\(RCM\) = red cell mass, calculated from plasma volume and large vessel hematocrit after correction of the latter for its difference from total body hematocrit.

Equilibration Time for Extracellular Water Determination

In both normal and hypertensive subjects, injected radiobromine achieved a stable level of dilution within 3 hours. Its equilibration curve was practically flat from the third to the 18th hour, as demonstrated by the small variations between bromide spaces calculated from the different samples (table 1). These results agree with those derived from seven patients by Rovner and Conn. There was no significant difference between normotensive and hypertensive subjects.
EXTRACELLULAR FLUID IN HYPERTENSION

in equilibrium time or in the bromine equilibration curve either in its later (3 to 18 hours) or earlier (20 min to 3 hours) parts. The values for ECW reported below have all been calculated from the 18-hour samples, as these were obtained at the time plasma volume and renin activity were determined.

Plasma Volume

Plasma volume (RISA) was measured in the morning immediately after withdrawing the last postmix sample for the radiobromide equilibration curve. As previously described, the patient was allowed to rest in the supine position for at least 30 to 45 min before the injection of 5 microcuries of radioiodinated ($^{131}$I) human serum albumin. Plasma volume was computed directly by the Volcmeteron from plasma samples obtained 10 min after injection; simultaneous counting of the premix and postmix plasma samples insured proper cancellation of residual $^{82}$Br radioactivity. The accuracy of this instrument for plasma volume determination from separated plasma was verified in three patients by comparing results obtained both with it and with deep well counting. Total blood volume was calculated from plasma volume and venous hematocrit; the latter was determined in duplicate by means of capillary microcentrifugation from four samples of blood drawn without stasis. No correction factor was used for plasma trapping, but the large vessel hematocrit was corrected for its difference from total body hematocrit.

$$TBV = \frac{PV}{1 - 0.91CV}$$

where $TBV = \text{total blood volume}$

$CV = \text{large vessel hematocrit}$

$0.91 = \text{ratio of total body hematocrit to large vessel hematocrit}$

Plasma volume was expressed in ml/cm of body height as this index allows comparison between groups of different ages and body constitution.

Plasma Renin Activity

Plasma renin activity was estimated by the method of Dustan and associates, as modified by Dustan and co-workers, from peripheral blood samples obtained at approximately the same time in the morning along with the plasma volume determination, the patient having rested in the supine position for at least 30 to 45 min.

$$ECW = 1.236 + 0.046 \times \text{(height)} + 0.142 \times \text{(weight)} + 0.003 \times \text{(age)}$$

$F = 9.338$ $P < 0.01$ for the F test

$$ECW = 0.721 + 0.043 \times \text{(height)} + 0.142 \times \text{(weight)}$$

$F = 14.87$ $P < 0.01$ for the F test

Table 1

<table>
<thead>
<tr>
<th>Sampling time (hr)</th>
<th>Number of subjects</th>
<th>Bromide space*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>92.2 (±0.8)</td>
</tr>
<tr>
<td>2</td>
<td>23</td>
<td>96.1 (±0.7)</td>
</tr>
<tr>
<td>3</td>
<td>37</td>
<td>98.2 (±0.9)</td>
</tr>
<tr>
<td>5</td>
<td>8</td>
<td>99.5 (±1.4)</td>
</tr>
<tr>
<td>Extrapolation to zero time</td>
<td>26</td>
<td>89.6 (±1.4)</td>
</tr>
</tbody>
</table>

* Expressed as a per cent of 18-hour space ± 1 standard error of mean.

Statistical analysis was performed by accepted methods for calculating correlation coefficients ($r$), regression analysis, and significance tests.

Results

The volume of extracellular water of normal subjects and of hypertensive patients was not significantly different (tables 2 and 3). However, the hypertensive patients were heavier (88.1 kg vs. 75.1 kg) and, therefore, were expected to have less ECW per unit of body weight than normal controls. To determine whether the insignificant difference between the two groups represented a relative increase of ECW in the hypertensives, eight patients and eight normal subjects matched for body weight were compared (table 4); their ECW volumes were practically identical. Furthermore, as compared with normal values derived from published regression equations based on total body water, the ECW volume of both normals and hypertensives was within the expected normal range (table 3).

Age was not found to be a significant factor influencing ECW values; its introduction into, or omission from, the regression equation for ECW did not alter either the correlation coefficient ($r$) or the $F$ value. In the following equations, height is expressed in centimeters, weight in kilograms, age in years, and ECW in liters:
### Table 2

**Plasma Volume, Extracellular Water, and Peripheral Plasma Renin Activity in Normal and Essential Hypertensive Subjects**

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>PV (L)</th>
<th>ECW (L)</th>
<th>PV/IF</th>
<th>Renin (ng/ml/4 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>73.5</td>
<td>171</td>
<td>2.85</td>
<td>15.2</td>
<td>0.231</td>
<td>0.44</td>
</tr>
<tr>
<td>2.</td>
<td>87</td>
<td>180</td>
<td>3.30</td>
<td>18.1</td>
<td>0.223</td>
<td>2.0</td>
</tr>
<tr>
<td>3.</td>
<td>74</td>
<td>175</td>
<td>3.00</td>
<td>16.5</td>
<td>0.223</td>
<td>1.5</td>
</tr>
<tr>
<td>4.</td>
<td>65.5</td>
<td>176.5</td>
<td>2.85</td>
<td>16.1</td>
<td>0.216</td>
<td>1.8</td>
</tr>
<tr>
<td>5.</td>
<td>67</td>
<td>171</td>
<td>3.05</td>
<td>16.7</td>
<td>0.223</td>
<td>1.0</td>
</tr>
<tr>
<td>6.</td>
<td>80</td>
<td>188</td>
<td>3.60</td>
<td>21.1</td>
<td>0.206</td>
<td>0.54</td>
</tr>
<tr>
<td>7.</td>
<td>72.2</td>
<td>163.7</td>
<td>3.40</td>
<td>18.8</td>
<td>0.221</td>
<td>—</td>
</tr>
<tr>
<td>8.</td>
<td>77.5</td>
<td>169.4</td>
<td>3.05</td>
<td>15.8</td>
<td>0.239</td>
<td>1.2</td>
</tr>
<tr>
<td>9.</td>
<td>66.4</td>
<td>170</td>
<td>2.55</td>
<td>13.9</td>
<td>0.224</td>
<td>2.5</td>
</tr>
<tr>
<td>10.</td>
<td>77</td>
<td>186.7</td>
<td>3.50</td>
<td>18.7</td>
<td>0.230</td>
<td>0.4</td>
</tr>
<tr>
<td>11.</td>
<td>85.5</td>
<td>193</td>
<td>3.73</td>
<td>21.4</td>
<td>0.211</td>
<td>—</td>
</tr>
</tbody>
</table>

**Patients with Essential Hypertension**

<table>
<thead>
<tr>
<th>No.</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>PV (L)</th>
<th>ECW (L)</th>
<th>PV/IF</th>
<th>Renin (ng/ml/4 hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>86.1</td>
<td>177.5</td>
<td>2.9</td>
<td>18.5</td>
<td>0.186</td>
<td>0.44</td>
</tr>
<tr>
<td>2.</td>
<td>88.3</td>
<td>185</td>
<td>3.10</td>
<td>20.4</td>
<td>0.179</td>
<td>0.2</td>
</tr>
<tr>
<td>3.</td>
<td>69.5</td>
<td>170.2</td>
<td>2.4</td>
<td>15.2</td>
<td>0.187</td>
<td>—</td>
</tr>
<tr>
<td>4.</td>
<td>108</td>
<td>185</td>
<td>3.05</td>
<td>23.5</td>
<td>0.149</td>
<td>1.5</td>
</tr>
<tr>
<td>5.</td>
<td>83.6</td>
<td>194</td>
<td>2.98</td>
<td>17.3</td>
<td>0.207</td>
<td>1.3</td>
</tr>
<tr>
<td>6.</td>
<td>82.7</td>
<td>165.5</td>
<td>2.6</td>
<td>15.8</td>
<td>0.197</td>
<td>0.42</td>
</tr>
<tr>
<td>7.</td>
<td>106</td>
<td>186</td>
<td>3.75</td>
<td>22.5</td>
<td>0.200</td>
<td>0.2</td>
</tr>
<tr>
<td>8.</td>
<td>78.1</td>
<td>173</td>
<td>3.48</td>
<td>20.9</td>
<td>0.200</td>
<td>0.42</td>
</tr>
<tr>
<td>9.</td>
<td>77</td>
<td>183</td>
<td>3.25</td>
<td>18.9</td>
<td>0.208</td>
<td>1.7</td>
</tr>
<tr>
<td>10.</td>
<td>78</td>
<td>170</td>
<td>3.35</td>
<td>17.4</td>
<td>0.238</td>
<td>0.4</td>
</tr>
<tr>
<td>11.</td>
<td>120</td>
<td>183</td>
<td>3.48</td>
<td>23.9</td>
<td>0.170</td>
<td>0.86</td>
</tr>
<tr>
<td>12.</td>
<td>97</td>
<td>188</td>
<td>3.1</td>
<td>21.8</td>
<td>0.166</td>
<td>0.93</td>
</tr>
<tr>
<td>13.</td>
<td>81</td>
<td>177</td>
<td>2.85</td>
<td>17.1</td>
<td>0.201</td>
<td>0.9</td>
</tr>
<tr>
<td>14.</td>
<td>86</td>
<td>178</td>
<td>2.6</td>
<td>18.8</td>
<td>0.161</td>
<td>1.5</td>
</tr>
<tr>
<td>15.</td>
<td>85</td>
<td>166</td>
<td>3.5</td>
<td>17.9</td>
<td>0.243</td>
<td>0.6</td>
</tr>
<tr>
<td>16.</td>
<td>63.5</td>
<td>165.3</td>
<td>2.16</td>
<td>13.4</td>
<td>0.193</td>
<td>—</td>
</tr>
<tr>
<td>17.</td>
<td>101</td>
<td>180</td>
<td>3.25</td>
<td>21.8</td>
<td>0.175</td>
<td>0.5</td>
</tr>
<tr>
<td>18.</td>
<td>65.9</td>
<td>160</td>
<td>3.0</td>
<td>15.8</td>
<td>0.235</td>
<td>0.4</td>
</tr>
<tr>
<td>19.</td>
<td>106.8</td>
<td>185.4</td>
<td>3.15</td>
<td>22.2</td>
<td>0.164</td>
<td>0.6</td>
</tr>
<tr>
<td>20.</td>
<td>98</td>
<td>178</td>
<td>3.6</td>
<td>21.0</td>
<td>0.207</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Abbreviations: PV = plasma volume; ECW = extracellular water; PV/IF = ratio of plasma volume to interstitial fluid.*

### Table 3

**Extracellular Water in Normal and Essential Hypertensive Men**

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Weight (kg)</th>
<th>ECW (% body weight)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Determined*</td>
<td>Predicted†</td>
</tr>
<tr>
<td>Normal subjects</td>
<td>11</td>
<td>75.1</td>
<td>23.3 (±0.69)</td>
</tr>
<tr>
<td>Essential hypertensives</td>
<td>20</td>
<td>88.1</td>
<td>21.9 (±0.38)</td>
</tr>
</tbody>
</table>

* Average ± 1 standard error of mean.
† Predicted according to published regression equations.

**Ratio of Plasma Volume to Interstitial Fluid**

Plasma volume averaged 18.7 ± 0.42 ml/cm of body height; this figure is lower than the one (19.6) previously reported and agrees more closely with the findings (18.3) of Chien's group. This probably reflects a better
representation of normal range by the larger sample.

Nevertheless, hypertensive patients still had lower plasma volumes than normal subjects (17.3 ± 0.49 vs. 18.7 ± 0.42, \( P < 0.05 \)).

The ratio of plasma volume to interstitial water (calculated as \( \text{ECW} - \text{PV} \)) was determined for those individuals in whom both values were available from simultaneous determinations (11 normals and 20 hypertensives); it averaged 0.223 in normal subjects and 0.194 in hypertensive patients \( (P < 0.001) \) (table 5). Since hypertensive patients had lower plasma volumes than normal subjects, it could be inferred that this reduction was the cause of their diminished PV/IF ratio. This, however, did not seem to be the case since several of the 11 normal subjects in whom ECW and plasma volume were measured simultaneously had low plasma volume, resulting in an average for that group of 17.9 ml/cm. In three who had some of the lowest plasma volumes of the entire normal group (15.1, 16.1, and 16.1 ml/cm), the PV/IF ratio measured 0.224, 0.216, and 0.231, respectively.

### Table 4

<table>
<thead>
<tr>
<th>Group</th>
<th>Weight (kg)</th>
<th>ECW*</th>
<th>PV/IF†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal subjects</td>
<td>75.7</td>
<td>23.4 (±0.81)</td>
<td>0.222 ± 0.0037</td>
</tr>
<tr>
<td>Essential hypertensives</td>
<td>75.9</td>
<td>22.8 (±0.72)</td>
<td>0.196 ± 0.0085</td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td>&gt;0.5</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

* ECW = extracellular water expressed in % of body weight ± 1 standard error of mean.
† PV/IF = ratio of plasma volume to interstitial fluid ± 1 standard error of mean.

Whatever their plasma volume, therefore, and this ranged from 15.1 to 20.8 ml/cm, normal subjects had a stable PV/IF ratio, a fact reflected in the close and highly significant relation of their plasma volume to extracellular water \( (r = 0.971, P < 0.001) \). In contrast, the wider variation of this ratio among hypertensive patients reflected itself in the less close relationship between their plasma and extracellular water volume \( (r = 0.694, P < 0.01) \) whether expressed in absolute figures or as percentage of body weight (figs. 1 and 2).

### Table 5

**Plasma Volume/Interstitial Fluid Ratio (PV/IF)** in Normal and Essential Hypertensive Men

<table>
<thead>
<tr>
<th>Group</th>
<th>Number</th>
<th>Average</th>
<th>SD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal men</td>
<td>11</td>
<td>0.223</td>
<td>0.010</td>
<td>0.003</td>
</tr>
<tr>
<td>Essential hypertensives</td>
<td>20</td>
<td>0.194</td>
<td>0.026</td>
<td>0.058</td>
</tr>
<tr>
<td>( t )-value</td>
<td>4.46</td>
<td></td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>( P )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* SD = standard deviation.
† SE = standard error of mean.

Discussion

No significant difference was found in the extracellular water volume of normal subjects and men with essential hypertension uncomplicated by exudative retinopathy, cardiac decompensation, or diminution in renal excretory function. The two groups were compar-
able, though the hypertensive patients were on the average somewhat older and heavier than normal controls. No significant age group differences in ECW have been demonstrated by others,\textsuperscript{19} nor was age found to be a significant factor in multiple correlation analysis of ECW in our group. Moreover, Chien and associates\textsuperscript{25} in a careful longitudinal study could find no difference in plasma volume with age. Differences due to body weight are more difficult to evaluate since extracellular water, in common with other aqueous phases of the body, varies inversely with weight when expressed in reference to it.\textsuperscript{19} However, when matched for body weight with normal subjects, the hypertensive patients had normal ECW; furthermore, all hypertensives had ECW well within the normal averages derived from published regression equations based on total body compositional ratios.\textsuperscript{19}

These results are similar to some\textsuperscript{8-12} but at variance with other reports\textsuperscript{4-7} in the literature; this discrepancy between findings of

### Figure 1

*Relation of plasma volume to extracellular water (ECW) in normal men and men with essential hypertension. Most patient points lie below the 95% confidence limits of the regression equation defining this relation in normal subjects. Correlation coefficient (r) equals 0.971 for normal subjects and 0.694 for hypertensives.*

### Figure 2

*Relation of plasma volume to extracellular water (both expressed as a percentage of body weight) demonstrating the abnormal spread of this relation in hypertensive subjects (see text).*

normal and of expanded ECW in hypertension cannot be explained by methodologic differences since both expanded and normal values were reported by workers utilizing the same methods (radiosulfate\textsuperscript{4, 5, 9, 11} and insulin\textsuperscript{6, 8, 10}). The differences probably result from varying criteria for patient selection. Thus, lack of reference to antihypertensive therapy,\textsuperscript{6} inclusion of patients with “minimal cardiac impairment,”\textsuperscript{4} and selection of those with increased exchangeable sodium\textsuperscript{7} are some of the more obvious factors that may influence the results obtained. Treatment with drugs inhibiting autonomic nervous activity has been associated with fluid retention,\textsuperscript{29} expansion of plasma volume, and disturbance of fluid balance.\textsuperscript{30, 31} Extracellular fluid expansion is the rule in cardiac decompensation.

### Table 6

*Relationship of Peripheral Plasma Renin Activity to Plasma and ECW Volumes in Nine Normotensive and 18 Essential Hypertensive Men*

<table>
<thead>
<tr>
<th>Fluid compartment</th>
<th>Correlation coefficient (r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma volume (ml/cm)</td>
<td>-0.629</td>
</tr>
<tr>
<td>ECW (% of body weight)</td>
<td>-0.408</td>
</tr>
</tbody>
</table>

*Circulation, Volume XL, September 1969*
even in the absence of obvious edema.\textsuperscript{9,12} Patients with increased total exchangeable sodium and expanded ECW usually have advanced fundal changes\textsuperscript{5}; this combination of hypertensive retinopathy, expanded ECW, and increased exchangeable sodium correspond to the findings of Hollander and associates in malignant hypertension.\textsuperscript{12}

Possible differences between clinically similar types of hypertension are as relevant, therefore, to explanations of variations in ECW, as obvious factors like body weight, cardiac impairment, or antihypertensive therapy; specific diagnostic investigations, such as renal arteriography, may then be needed to allow as accurate a classification of patients as possible.\textsuperscript{32} Without strict definition of the hypertension studied, accurate evaluation and valid comparison of various reports seem impossible.

In contrast with essential hypertension but like malignant hypertension, the increased blood pressure produced in man by primary aldosteronism or by mineralocorticoid administration is associated with expanded ECW.\textsuperscript{13,14} While the hypertension of chronic parenchymal renal disease without nitrogen retention appears to be characterized by normal body sodium, potassium, and sulfates,\textsuperscript{32} the development of renoprival hypertension seems to depend in part on the degree of ECW expansion.\textsuperscript{33} Dustan and Page\textsuperscript{34} demonstrated a direct parallelism between changes in body weight, presumably representing ECW variations, and changes in blood volume and blood pressure in terminal renal failure before and after bilateral nephrectomy. This was recently confirmed by Blumberg and associates\textsuperscript{35} utilizing radiobromine for direct measurements of extracellular fluid volume.

Various animal studies have confirmed these clinical observations. Braun-Menendez\textsuperscript{26} found that only rats with expanded ECW developed hypertension following subtotal nephrectomy, and similar results were found in dogs.\textsuperscript{37,38} In contrast, plasma volume and ECW remained normal in dogs made hypertensive by renal artery clipping.\textsuperscript{39} Ledingham and Cohen\textsuperscript{40} found that the development of hypertension in rats following clipping of a renal artery was associated with a brief initial period of ECW expansion, but hypertension persisted while ECW returned to normal.

Although total extracellular water volume remained relatively normal in patients with uncomplicated essential hypertension, its distribution between the intravascular and interstitial fluid compartments was altered. Moore\textsuperscript{31} pointed out that the relation of plasma volume to ECW is particularly stable with a high correlation coefficient ($r = 0.83$); a similar relation also obtained in our normals. The PV/IF ratio is an expression of this relation; the ratio (0.223) determined in our normal subjects by tagged albumin and radiobromine is in close agreement with the ratio (0.23) reported by others using Evans blue and radiobromine.\textsuperscript{19} This ratio was similar in all our normal subjects, even in three with a particularly low plasma volume. Thus, contraction of plasma volume was not sufficient by itself to alter the distribution ratio in the extracellular compartment.

In contrast, the partition of ECW in hypertensive patients was significantly altered (PV/IF = 0.194, $P < 0.001$) and the ratio varied widely, measuring more than 0.220 in three patients, 0.200 in six, and less than 0.200 in 11. The lower ratio in hypertensives was not apparently due to their heavier weight: the same difference from normals was found between groups matched for body weight (table 4). In comparing the relation of plasma volume to extracellular water with expected normal regressions (figs. 1 and 2), it would be equally correct to infer that hypertensive subjects either have too low plasma volumes for their extracellular water or relatively expanded ECW for their actual plasma volumes. This altered ratio was also found by Walser and co-workers\textsuperscript{9} who compared total blood volume derived from red cell mass determination to extracellular water. The lack of statistical significance in their results may be ascribed to the inclusion of red cell mass in study of the partition between water compartments, and possibly to the small number of
patients. This alteration in volume distribution between the compartments of ECW in essential hypertensives, their lower plasma volume,1-3 and their greater diuresis following intravenous infusions42 seem to agree with Tobian's suggestion that in hypertension the mechanism regulating extracellular fluid volume is set as though ECW were expanded.43

The normal close correlation between ECW and PV seem to allow the interchangeability of these two indices in considering functions related to them. This conclusion, however, is not valid when the ratio of plasma volume to interstitial fluid is disturbed. Though, as reported elsewhere,27,44 peripheral plasma renin activity was inversely related to plasma volume in hypertensive patients, no relationship was found when ECW was substituted for PV. Unless direct measurements of both volume indices demonstrate a stable PV/IF ratio under the particular conditions investigated, it does not seem valid to extrapolate alterations from ECW to PV or vice-versa, since particular functions may correlate with one and not the other volume.

Acknowledgment
We wish to thank Doctor P. Khairallah for assistance with radioisotope technics and to acknowledge the fine technical work performed by Kathleen Koenig, R.N., and Helen Kleinhenz, R.N., as well as the secretarial assistance of Mrs. A. Raulinaitis and Miss D. Henkin, and the laboratory help of Mrs. M. Kukla and Miss I. Patterson. We are particularly grateful to Prof. C. Berretoni for his help with statistical analysis of the results.

References


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ROBERT C. TARAZI, HARRIET P. DUSTAN and EDWARD D. FROHLICH

Circulation. 1969;40:357-366
doi: 10.1161/01.CIR.40.3.357
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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