Long-Term Thiazide Therapy in Essential Hypertension

Evidence for Persistent Alteration in Plasma Volume and Renin Activity

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

SUMMARY

Plasma volume (RIHSA) and peripheral plasma renin activity (Pickens' method) were measured in eight essential hypertensive patients treated with thiazide diuretics alone for periods ranging from 6 to 24 months. Treatment was then stopped and measurements repeated at weekly intervals for a month. During the first week of discontinuance, body weight and plasma volume rose in all ($P < 0.001$ for both), while peripheral plasma renin activity fell from 3.66 to 1.04 ng/ml ($P < 0.005$), and serum sodium concentration was practically unchanged. Over the next 3 weeks, both plasma volume and body weight gradually fell from the high first week “rebound” values to plateau at levels higher than those obtained during treatment (2741 vs. 2567 ml, $P < 0.001$ and 76.1 vs. 74.7 kg, $P < 0.001$, respectively). At the same time, peripheral plasma renin activity remained stable and markedly lower than during treatment ($P < 0.001$), while blood pressure gradually rose. Extracellular water (ECW) was measured serially (radiobromine) in five patients; in all, body weight variations were completely accounted for by changes in ECW, and ratio of plasma to interstitial fluid volume remained stable. These data indicate that blood pressure reduction by long-term thiazide therapy was associated with persistent plasma volume contraction and occurred despite increased peripheral renin activity. There was no evidence for chronic intracellular dehydration, and variations in peripheral renin activity were related to changes in plasma volume and not to serum sodium concentration.

Additional Indexing Words:
Extracellular water Arterial pressure Serum sodium

Chronic thiazide therapy undoubtedly has sustained antihypertensive$^{1-4}$ and weight reducing$^{5,6}$ effects. Various reports have claimed that neither action is associated with persistent reduction in plasma volume,$^{5-7}$ extracellular water,$^{4,5,7}$ exchangeable sodium,$^{4,6,7}$ or cardiac output.$^{8}$ Thus, the chronic blood pressure-lowering effect of thiazides in hypertensive patients has remained unexplained$^{9}$; it has been speculative-ly linked to the sodium ion,$^{9}$ urinary loss of trace metals,$^{6}$ decreased responsiveness to endogenous vasopressor substances,$^{10-12}$ reduction of norepinephrine release by nerve impulses,$^{13}$ or direct action on the vascular system.$^{14}$ The combination of sustained weight loss, reduction in total body water, and normal extracellular fluid volume led to a postulate of chronic intracellular dehydration.$^5$

However, it is common experience that fluid retention with weight gain and often edema occurs whenever chronic diuretic treatment is
Discontinued. This indicates that a potent stimulus for sodium and water reabsorption has been evoked by this treatment, and it seems likely that this stimulus was related to contraction of the extracellular fluid compartment. These considerations, as well as lack of evidence for cellular depletion of sodium\textsuperscript{15, 16} and the conceptual difficulty of ascribing sustained weight reduction to intracellular dehydration in active, normally fed subjects, led to a reexamination of former conclusions. The primary purpose was to study variations in plasma and extracellular water (ECW) volume as chronically treated hypertensive patients discontinued oral diuretic therapy. This allowed correlation of the magnitude and timing of expected increases in extracellular fluid volume with arterial pressure changes. It also avoided difficulties in comparing values obtained before and after long-term treatment when changes in severity of disease and fluid balance may have occurred.\textsuperscript{15} Because of the close relation between peripheral plasma renin activity, intravascular volume,\textsuperscript{17-20} and serum sodium concentration,\textsuperscript{20, 21} this activity was estimated simultaneously with plasma and ECW determinations. Changes in renin activity thus provided an index of the physiologic importance of volume fluctuations, especially as sequential serum sodium measurements showed no significant variation.

### Methods

The study included eight hypertensive patients who had been treated with 25 mg twice daily of hydrochlorothiazide (seven patients) or 100 mg per day of chlorthalidone (one patient) alone, for periods ranging from 6 months to 2 years with good to excellent blood pressure control. All had been followed for long periods and were well known to be reliable subjects. Clinical, laboratory, and radiographic examinations, including renal arteriography in seven, failed to reveal any cause for the elevated blood pressure; the eighth patient, a black man with no features suggestive of renal arterial disease and no abnormal findings on rapid sequence intravenous pyelography, was assumed not to have renovascular hypertension. None of the eight had any evidence of cardiac or renal failure; none were hospitalized during the study and all were asked to continue their daily activities and dietary habits unchanged.

The patients came to the laboratory, fasting at about 9 a.m.; after a 30 to 45-min period of supine rest, plasma volume was measured with human serum albumin labeled with 5 \( \mu \)C \( ^{131}I \) or 2.5 \( \mu \)C \( ^{125}I \) using a 10-min equilibration period. When possible, extracellular fluid volume (ECW) was also measured with 30 \( \mu \)C of radiobromine (\(^{82}\)Br) using a 3-hour equilibration period; on these occasions radiobromine was injected intravenously at 8 a.m., and plasma volume was determined 3 hours later after the post-mix

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**Table 1**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Height (cm)</th>
<th>Duration (mo)</th>
<th>Weight (kg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Plasma volume (ml)</th>
<th>Weight (kg)</th>
<th>Blood pressure (mm Hg)</th>
<th>Plasma volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.W.</td>
<td>162</td>
<td>9</td>
<td>64.1</td>
<td>142/96</td>
<td>2175</td>
<td>66.5</td>
<td>140/101</td>
<td>2600</td>
</tr>
<tr>
<td>F.G.</td>
<td>175.5</td>
<td>20</td>
<td>79.1</td>
<td>132/88</td>
<td>2675</td>
<td>82.7</td>
<td>127/77</td>
<td>3450</td>
</tr>
<tr>
<td>S.G.</td>
<td>183</td>
<td>12</td>
<td>88.3</td>
<td>121/82</td>
<td>2813</td>
<td>91.4</td>
<td>116/72</td>
<td>3525</td>
</tr>
<tr>
<td>F.H.</td>
<td>170</td>
<td>10</td>
<td>88.6</td>
<td>157/78</td>
<td>2500</td>
<td>90.9</td>
<td>190/96</td>
<td>2975</td>
</tr>
<tr>
<td>J.S.</td>
<td>178</td>
<td>6</td>
<td>97.5</td>
<td>133/94</td>
<td>3925</td>
<td>98.9</td>
<td>140/102</td>
<td>4120</td>
</tr>
<tr>
<td>E.B.</td>
<td>148</td>
<td>5</td>
<td>50.5</td>
<td>150/96</td>
<td>1775</td>
<td>52.3</td>
<td>172/106</td>
<td>2350</td>
</tr>
<tr>
<td>G.F.</td>
<td>164</td>
<td>29</td>
<td>72.8</td>
<td>133/74</td>
<td>2550</td>
<td>74.7</td>
<td>132/72</td>
<td>2975</td>
</tr>
<tr>
<td>A.B.</td>
<td>162.5</td>
<td>6</td>
<td>56.4</td>
<td>154/103</td>
<td>2125</td>
<td>57.4</td>
<td>154/101</td>
<td>2400</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>74.7</td>
<td>140/88</td>
<td>2567</td>
<td>76.9</td>
<td>146/91</td>
<td>3049</td>
</tr>
</tbody>
</table>

*MD = mean difference from treatment.
†SE = standard error of difference.

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sample had been obtained. Methods and calculations used have been described in detail22 as well as the adequacy of a 3-hour equilibration period for ECW measurement.22,23 Simultaneously with plasma volume determination, blood samples were obtained without stasis for determination of hematocrit by capillary microcentrifugation, of serum sodium, potassium, chloride, and carbon dioxide content by the Technicon method, and of peripheral plasma renin activity by a modified Pickens' procedure.19,24

The initial studies were performed while the patients were under treatment; they were then asked to discontinue medication and return at weekly intervals for 4 weeks. Seven patients measured their brachial arterial pressure twice daily at home, while for the eighth, arterial pressure was taken as the average of three readings obtained at the time of plasma volume determination.

Statistical significance was determined by conventional tests for paired data analysis,25 each patient serving as his own control. The standard error of differences is therefore reported rather than the standard error of mean.

Results

Plasma volume (PV) was significantly lower and peripheral plasma renin activity (PRA) significantly higher during chronic thiazide therapy than 4 weeks following its discontinuance (tables 1 and 2). PRA was considerably greater than would be expected in untreated patients with uncomplicated essential hypertension.19 In five patients, PV values were available from determinations performed just before thiazide treatment was begun; in all five plasma volume was reduced during therapy and in four out of five it increased 4 weeks after discontinuance of treatment to within 100 ml of pre-treatment values (table 3). The fifth patient (G.F.) followed the same trend but post-treatment plasma volume was 385 ml greater than the pre-treatment value.

In the first week without therapy, body weight and plasma volume rose significantly ($P < 0.001$) and PRA fell from 3.66 to 1.04 ng/ml ($P < 0.005$). In the subsequent 3 weeks of the study, both weight and plasma volume slowly declined from the first week's rebound values but never returned to treatment levels so that at the end of 4 weeks plasma volume and body weight were still significantly higher than during therapy (15.2 vs 17.0 ml/cm, $P < 0.001$ and 74.7 vs. 76.1 kg, $P < 0.025$, respectively). Plasma renin activity remained reduced with insignificant fluctuations. Arterial pressure rose slowly in all patients after treatment was discontinued and did not fluctuate as did weight and plasma volume (fig. 1).

Extracellular water volume was determined in five patients just before treatment was stopped. In three this measurement was repeated twice, 1 week and again 4 weeks.
following discontinuance of therapy. In the remaining two patients only one additional ECW determination was made in one patient at the end of the first week and in the other, at the end of the fourth. In all but one of these determinations ECW was higher after therapy was stopped than during treatment (table 4). In all patients, changes in weight were entirely accounted for by ECW variations. Plasma and interstitial fluid volume (calculated as ECW-PV) varied in parallel fashion as shown by the insignificant variations in their computed ratio.

**Discussion**

Prolonged thiazide therapy in these essential hypertensive patients was associated with reduced plasma volume and increased peripheral plasma renin activity. Body weight,
Table 3

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before treatment (ml)</th>
<th>During treatment (ml)</th>
<th>After treatment (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C.W.</td>
<td>2325</td>
<td>2175</td>
<td>2425</td>
</tr>
<tr>
<td>F.G.</td>
<td>3000</td>
<td>2675</td>
<td>2925</td>
</tr>
<tr>
<td>S.G.</td>
<td>3100</td>
<td>2813</td>
<td>3066</td>
</tr>
<tr>
<td>E.B.</td>
<td>2200</td>
<td>1775</td>
<td>2125</td>
</tr>
<tr>
<td>G.F.</td>
<td>2700</td>
<td>2550</td>
<td>3085</td>
</tr>
</tbody>
</table>

extracellular fluid, and plasma volume fluctuated from low levels during treatment to rebound peaks in the first week of discontinuance and then to intermediate levels thereafter. Fluctuations of body weight were almost completely accounted for by variations in extracellular water (radiobromine space) (table 4). Inasmuch as measurements obtained 4 weeks after discontinuance of all medication represent the characteristics of untreated patients, it can be concluded that plasma and extracellular fluid volume are chronically contracted by persistent thiazide therapy.

These results are in agreement with those of Hansen who found a significant fall in total blood volume and exchangeable sodium after 3 months of treatment with hydrochlorothiazide. As can be calculated from his published figures, the loss of water associated with fall in body sodium accounted for his patients' weight loss. Similar results were reported by Winer with shorter (6 to 8 weeks) therapy, suggesting a maintained diuretic-induced loss of isotonic extracellular fluid with no evidence of intracellular dehydration. Wilson and Freis initially found that plasma volume was reduced by 8% and extracellular fluid by 2.5 L after 6 months of treatment. Their later studies demonstrated a gradual but uneven return toward normal of these indices; however, some reduction was evident in ECW (P < 0.01) at 6 months and in PV (P < 0.05) at 12 months though the latter was not statistically significant at 6 months.

Contrasting with the results of this study and of others suggesting different degrees of PV and ECW contraction, Gifford and associates and Lauwers and Conway found that plasma volume returned to pretreatment levels after 1 month of treatment. Neither the latter two groups nor Wilkins and co-workers could demonstrate a reduction in extracellular fluid with chronic thiazide therapy. Since body weight remained reduced with chronic thiazide therapy, Lauwers and Conway postulated an intracellular loss of fluid to explain the weight loss despite normalization of ECW. It is difficult to reconcile the discrepancies between these results. Some can partly be explained by such differences as additional medications given to some of the patients investigated. Since neural blocking agents influence venomotor activity and increase plasma volume and interfere with sodium balance, it is difficult to interpret determinations made shortly after discontinuance of these drugs. Methodological variations do not, however, constitute an

Table 4

Effect of Discontinuing Chronic Thiazide Therapy on Extracellular Water (ECW) Volume

<table>
<thead>
<tr>
<th>Patient</th>
<th>Before discontinuing treatment</th>
<th>Following cessation of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>ECW (L)</td>
</tr>
<tr>
<td>---------</td>
<td>--------------</td>
<td>---------</td>
</tr>
<tr>
<td>C.W.</td>
<td>64.1</td>
<td>14.3</td>
</tr>
<tr>
<td>F.H.</td>
<td>88.6</td>
<td>16.02</td>
</tr>
<tr>
<td>S.G.</td>
<td>88.4</td>
<td>17.7</td>
</tr>
<tr>
<td>J.S.</td>
<td>97.5</td>
<td>20.6</td>
</tr>
<tr>
<td>A.B.</td>
<td>56.4</td>
<td>11.1</td>
</tr>
</tbody>
</table>

Average change +1.9 +2.3 +0.005 +1.95 +1.42 +0.002

*PV/IF = ratio of plasma to interstitial fluid volume.
adequate explanation of all the discrepancies reported, even though measurements of extracellular fluid volume are notoriously variable. Subtle differences in mechanisms of hypertension or in patients' cooperation or sodium intake may possibly explain the rest.

Winer\(^{45}\) has shown that addition of 20 g of salt per day was enough to overcome negative sodium balance and the antihypertensive effect of chronic thiazide medication. This could not be achieved by adding only 6 to 12 g. These observations and his blood volume expansion studies\(^ {29}\) suggest that the effect of thiazide on sodium economy is at the root of their antihypertensive action.\(^ {9}\) In the absence of any documented intracellular depletion of sodium,\(^ {9, 15, 16}\) this may be an argument in favor of chronic contraction of the extracellular fluid compartment. Another side of evidence lies in the impressive weight, plasma volume, and ECW changes following cessation of treatment which were also noted by Wilson and Freis.\(^ {31}\) The extracellular fluid expansion and weight gains were obvious to both patient and observer and were always commented upon, sometimes bitterly. The evident puffiness and occasional dependent edema could not represent simple redistribution of water from intracellular to extracellular compartments since they were associated with definite weight increase. This rebound phenomenon seems difficult to explain on the basis of diminished intracellular water postulated by Lauwers and Conway,\(^ {5}\) since any retention of water with stopping of treatment would first replenish the postulated intracellular dehydration. The rapid weight gain can speculatively be linked to chronic ECW contraction, since the latter is a stimulus to increased sodium reabsorption.\(^ {36}\) With continued intake of thiazide effectively blocking this absorption the stimulus is thwarted; when diuretics are discontinued, the stimulus is unmasked and leads to the rebound peak observed.

Arterial pressure in essential hypertension is not dependent on intravascular volume as is the hypertension associated with renal parenchymal disease.\(^ {97}\) This might explain the lack of fluctuations of arterial pressure with variations in plasma volume after cessation of therapy. The contrast between the slow pressure rise and the rapid rebound plasma volume peak does not, therefore, negate the role of volume reduction in the antihypertensive effects of thiazides. On the other hand, even a small reduction in blood volume may have a profound effect on arterial pressure if adequate reflex homeostasis is interfered with.\(^ {15, 38-40}\) Thiazide interference with response to vasopressors\(^ {10-12}\) or to nerve stimulation or both\(^ {14}\) and their sustained decrease of peripheral resistance\(^ {9}\) may well amplify the hypotensive effect of modest reductions in plasma volume noted by many,\(^ {28-31}\) besides ourselves. This does not mean, however, that the blood pressure-lowering effect of thiazides is entirely due to volume reduction, since they often are effective even when given intermittently (5 days a week), and in our experience are thus less potent in maintaining a continuously contracted volume. Patients following this intermittent schedule often complain of weight gain and occasional puffiness during the days without diuretics; plasma volume measured in three subjects on the morning of the third day without thiazides was expanded to near pre-treatment levels.

Plasma renin activity is closely related to that functional, ill-defined entity called "effective blood volume."\(^ {41}\) Though it is not strictly identical with intravascular volume, since blood distribution and vascular capacity are important factors in its definition, total blood and plasma volume, at least in the supine position, are valid indices of its function, since they have been demonstrated to be significantly related to PRA both in acute experiments\(^ {17, 18, 42}\) and in untreated normal and hypertensive subjects.\(^ {19}\) Thus, simultaneous measurement of PRA and PV may help evaluate the functional significance of a measured variation in the "10-minute albumin space." The increased plasma renin activity during thiazide treatment and its marked reduction in the first week after therapy are probably related to changes in plasma...
volume (tables 1 and 2) and underline their significance.

Brown's group\textsuperscript{20,21} has emphasized the importance of serum sodium in regulation of renin activity, especially when changes in serum sodium and plasma volume occur concomitantly as during thiazide treatment. However, variations in some renin activity are significant.\textsuperscript{29} Plasma volume and serum sodium thus changed in different ways during the first week of discontinuance (fig. 1): PRA fell as expected from plasma volume expansion irrespective of serum sodium changes. These suggestions as to the greater importance of intravascular volume changes than of serum sodium variations in determining plasma renin activity are similar to the conclusions of Newsome and Bartter,\textsuperscript{30} Maebashi and Yoshinaga,\textsuperscript{44} and Meyer and associates.\textsuperscript{42} They confirm our previous findings of a significant negative correlation between total blood volume and PRA in resting untreated normotensive and hypertensive subjects\textsuperscript{19}; no such relationship was found with serum sodium concentration.\textsuperscript{19,45} Changes in total exchangeable sodium similar to those described by Hansen\textsuperscript{28} could have played a role but were not measured in this study.

The experience of Bourgoignie and co-workers\textsuperscript{46} has been different from ours. They found elevated plasma renin levels during the early phase of thiazide treatment only if sodium intake was concurrently reduced and normal renin levels with continued diuretic treatment. This difference may be partly due to the concurrent administration, in 18 of their 32 patients, of other antihypertensive agents known to affect renin release.\textsuperscript{47} Moreover, wide variations in plasma renin activity may be related to circumstances of sampling (such as posture activity) and prevent detection of significant differences.\textsuperscript{29} The half-hour pre-sampling rest secured for our patients may be another reason for differences between the two studies. In contrast, our results confirm former observations by Pickens and Enoch\textsuperscript{18}; Genest and associates\textsuperscript{48} also found that essential hypertensives had high mean PRA ($P < 0.01$) only if patients taking thiazides were included in the study. The finding by Tobian's group\textsuperscript{46} of higher juxtaglomerular counts in normal rats given chlorothiazide for 5 weeks also seems to indicate continued renin stimulation by the diuretic.

The higher plasma renin activity and chronic weight reduction with continued thiazide therapy followed by rapid ECW expansion with discontinuance as well as the continued potentiation of other antihypertensive agents by thiazides\textsuperscript{40} and the reversal of their effects by high salt intake,\textsuperscript{35} all correlate naturally with chronic reduction in plasma volume, extracellular fluid, and total exchangeable sodium as demonstrated in this and other studies.\textsuperscript{28-31} It is not implied that this chronic hypovolemia is solely responsible for long-term hypotensive effect of thiazide in essential hypertension. However, this volume-reducing effect may be particularly important in some hypertensive disease,\textsuperscript{37} and since it may play a role in potentiating other antihypertensive agents\textsuperscript{40,49} it should be taken into consideration when investigating treated patients.

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