Spironolactone as a Nonspecific Treatment for Primary Aldosteronism

By Emmanuel L. Bravo, M.D., Harriet P. Dustan, M.D., and Robert C. Tarazi, M.D.

SUMMARY

Studies were carried out in 14 patients with primary aldosteronism (I°A) to examine the mechanism(s) by which spironolactone reduces arterial pressure. Measures that produced salt and water depletion were found to consistently reduce arterial pressure. Plasma volume and arterial pressure correlated directly and significantly, \( r = +0.509 \) \((P<0.001)\), whether pressure was reduced by spironolactone alone or combined with either hydrochlorothiazide or low dietary sodium, or by rapid sodium depletion alone. With small doses of spironolactone, restricting or liberalizing dietary sodium was associated with decreases or increases, respectively, in arterial pressure and plasma volume.

These results suggest 1) that the antihypertensive action of spironolactone is nonspecific and largely dependent on salt and water balance and 2) that maintenance of reduced plasma volume or extracellular fluid volume (ECFV) is a basic component of the pressure response of I°A to spironolactone therapy.

Additional Indexing Words:
Plasma volume Extracellular fluid volume expansion Diuretics Dietary salt intake
Primary hypertension

ARTERIAL PRESSURE REDUCTION in patients treated with spironolactone has been suggested as a practical test for the diagnosis of primary aldosteronism (I°A).\(^1\) Hypertension caused by excessive production of electrolyte-active steroids responds dramatically to this treatment. However, a substantial proportion of patients with essential hypertension also respond well to spironolactone.\(^2\) Therefore, basic to the proposition that spironolactone allows recognition of hypertension associated with obvious or subtle steroid abnormalities\(^3\) is the question of whether the arterial pressure response represents some “specific effect” or is only a reflection of its natriuretic properties.

This study of 14 patients with proven I°A was undertaken to determine whether arterial pressure response to spironolactone is a “specific effect” or simply a “nonspecific” response to salt and water depletion. The results suggest 1) that the action of spironolactone is nonspecific and largely dependent on salt and water balance in the body and 2) that some function of extracellular fluid volume (ECFV) mediates the associated hypertension of I°A.

Materials and Methods

Patients. Fourteen patients with I°A (seven men, seven women) were the subjects of this study (table 1). The clinical diagnosis was based on 1) hypokalemia, whether unprovoked or provoked by sodium-loading, 2) nonsuppressible aldosterone excretion rates (AER), and 3) low or normal plasma renin activity (PRA) which was not increased by sodium deprivation. All except two were found, either by retrograde adrenal venography or on exploration, to have solitary adenomas. The two exceptions (J.A.W., M.Y.) have not yet been operated upon because their arterial pressures are well controlled by diuretic therapy. Two (L.B., W.L.) are still awaiting surgery. Of the ten who have been operated upon, all have remained normotensive except one (E.H.), who continues to be mildly hypertensive.

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From the Research Division, The Cleveland Clinic Foundation and The Cleveland Clinic Educational Foundation, Cleveland, Ohio.

Supported in part by grants HL 6835 from the National Heart and Lung Institute, National Institutes of Health, and 70-960 from the American Heart Association and 8557 from the Heart Association of Northeastern Ohio (American Heart Association). The study was presented in part at the annual meeting of the American Heart Association, Dallas, 1972.

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Received April 3, 1973; revision accepted for publication May 8, 1973.
Table 1

Clinical Characteristics of Patients on Initial Examination

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>Serum electrolytes</th>
<th>Arterial pressure*</th>
<th>Plasma volume</th>
<th>Renin activity</th>
<th>Aldosterone excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Na</td>
<td>K</td>
<td>Cl</td>
<td>CO₂</td>
<td>BUN</td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td>mEq/Liter</td>
<td>mg/dl</td>
<td>mg/dl</td>
<td>mm Hg</td>
<td>ml/cm</td>
</tr>
<tr>
<td>L.B.</td>
<td>47</td>
<td>143</td>
<td>3.1</td>
<td>104</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>Em.H.</td>
<td>52</td>
<td>146</td>
<td>2.8</td>
<td>104</td>
<td>32</td>
<td>12</td>
</tr>
<tr>
<td>P.H.</td>
<td>41</td>
<td>141</td>
<td>2.6</td>
<td>104</td>
<td>27</td>
<td>10</td>
</tr>
<tr>
<td>W.L.</td>
<td>39</td>
<td>140</td>
<td>3.0</td>
<td>100</td>
<td>28</td>
<td>19</td>
</tr>
<tr>
<td>P.P.</td>
<td>47</td>
<td>144</td>
<td>2.9</td>
<td>103</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>D.M.</td>
<td>47</td>
<td>143</td>
<td>2.6</td>
<td>106</td>
<td>26</td>
<td>17</td>
</tr>
<tr>
<td>J.W.</td>
<td>63</td>
<td>141</td>
<td>3.1</td>
<td>100</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>Mean</td>
<td>48</td>
<td>142.6</td>
<td>2.9</td>
<td>103</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>ss</td>
<td>±2.9</td>
<td>±0.78</td>
<td>±0.08</td>
<td>±0.85</td>
<td>±0.8</td>
<td>±1.7</td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>E.F.</td>
<td>29</td>
<td>143</td>
<td>3.0</td>
<td>105</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>M.F.</td>
<td>38</td>
<td>142</td>
<td>2.3</td>
<td>97</td>
<td>26</td>
<td>13</td>
</tr>
<tr>
<td>E.L.H.</td>
<td>58</td>
<td>147</td>
<td>2.1</td>
<td>105</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>L.R.</td>
<td>39</td>
<td>142</td>
<td>2.7</td>
<td>106</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>J.A.W.</td>
<td>33</td>
<td>138</td>
<td>3.3</td>
<td>102</td>
<td>21</td>
<td>13</td>
</tr>
<tr>
<td>D.W.</td>
<td>40</td>
<td>141</td>
<td>3.0</td>
<td>102</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>M.Y.</td>
<td>35</td>
<td>139</td>
<td>3.6</td>
<td>107</td>
<td>25</td>
<td>8</td>
</tr>
<tr>
<td>Mean</td>
<td>39</td>
<td>142</td>
<td>2.9</td>
<td>103</td>
<td>29</td>
<td>12</td>
</tr>
<tr>
<td>ss</td>
<td>±3.5</td>
<td>±1.10</td>
<td>±0.2</td>
<td>±1.2</td>
<td>±1.2</td>
<td>±1.1</td>
</tr>
</tbody>
</table>

*3-5 day averages of pretreatment supine arterial pressures taken four times a day in the hospital.

Abbreviations: BUN = blood urea nitrogen; Cr = creatinine; Fundi (K-W-B) = (Keith-Wagner-Barker), C = control.
All of them had been thoroughly investigated for renal, cardiovascular, and other adrenal causes of hypertension.

**Short-term studies: rapid sodium depletion.** Three patients (E.L.H., I.R., W.L.) underwent rapid sodium depletion in the hospital where metabolic studies were done. All antihypertensive medications, including diuretics, had been stopped at least a month prior to these studies. After two to three days of unrestricted sodium intake, each patient received a diet containing 9 mEq of sodium and 80 mEq of potassium for four to six days. Mercuhydrin, 2 cc intramuscularly, was given on the first and third days of the sodium restriction period. The following measurements were taken: four times daily; supine and standing brachial arterial pressure; three-day averages of supine pressures were determined; daily: body weight (before breakfast and after voiding), serum concentrations of sodium, potassium, chloride, carbon dioxide, creatinine, and 24-hour urinary excretion rates of sodium, potassium, creatinine, and aldosterone. Total blood and plasma volume and PRA at the end of control period and after four days of sodium depletion were obtained. Urine was collected in 24-hour lots and kept refrigerated until analysis.

**Long-term studies of arterial pressure and plasma volume responses during treatment periods with spironolactone alone, or in combination with either thiazide diuretic or low dietary sodium.** Eleven patients were followed in the outpatient clinic for periods ranging from six weeks to six years. Brachial arterial pressure was measured at home twice daily in the supine and standing position. Weekly averages for pretreatment and treatment periods were obtained. Plasma volume (PV), PRA, AER, serum concentrations of sodium, potassium, chloride, carbon dioxide, creatinine, blood urea nitrogen and 24-hour excretion rates of sodium, potassium, and creatinine were measured at appropriate periods during scheduled visits to the outpatient clinic. Visits varied from monthly (during the initial period) to every three to six months in subsequent follow-up periods. Except where indicated, no diet restrictions were imposed during these studies.

Two patients (J.A.W., M.Y.) received spironolactone alone. The initial dose was 200 mg per day and this was gradually reduced to 50–100 mg per day depending on arterial pressure responses.

Six patients (L.B., P.H., W.L., J.W., E.F., M.F.) were treated identically: after at least two weeks of control home blood pressure readings, spironolactone (50 mg q.i.d.) was given alone for two weeks, then hydrochlorothiazide (25 mg b.i.d.) was added. In addition, the arterial pressure response to decreasing amount of spironolactone was studied in one patient (L.B.) over a one-year period while the dose of hydrochlorothiazide was held constant.

One patient (D.M.) received a combination of spironolactone (50 mg q.i.d.) and furosemide (40 mg q.i.d.) during a relatively short observation period of six weeks.

Two patients were followed for extended periods while on spironolactone and varying limitations on dietary sodium intake: P.P. for six years and E.m.H. for three years. Both were thoroughly instructed on the appropriate diet and periodic checks for 24-hour urine collections for sodium and potassium were made to determine their adherence to it.

**Analytical methods.** Serum and urine were analyzed for sodium and potassium by flame photometry with lithium as the internal standard. Blood for the estimation of PV and PRA was drawn together in the morning under fasting conditions after at least 30-45 min of supine rest. PV was measured from the volume of distribution of 2.5 μCi of 125I human serum albumin with the use of a 10-min equilibration period as previously described. Values are expressed as ml per cm of height to minimize individual differences in body fat and as percent of normal to allow inclusion of values for both men and women. PRA was estimated using a basic processing procedure described by Pickens et al. as modified by Dusman, Tarazi, and Frohlich, followed by pressor bioassay or radioimmunoassay of angiotensin I. Urinary aldosterone was determined by measurement of the 24-hour excretion of the acid-labile conjugate of the hormone utilizing a gas-liquid chromatographic method described previously. The normal values for PV, PRA, and AER as measured in this laboratory are shown in table 2.

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

### Table 2

**Values for Normal Subjects as Determined by Our Laboratory**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Sodium intake (mEq per day)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unrestricted</td>
<td>Low (4th day)</td>
<td>High (3rd day)</td>
</tr>
<tr>
<td></td>
<td>(9 mEq/day)</td>
<td>(3.9 mEq/kg/day)</td>
<td></td>
</tr>
<tr>
<td>Plasma volume (ml/cm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>18.4 ± 0.33</td>
<td>8.9 ± 1.76</td>
<td>1.22 ± 0.32</td>
</tr>
<tr>
<td>Females</td>
<td>15.3 ± 0.25</td>
<td>6.5 ± 1.0</td>
<td>4.0 ± 0.68</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/4 hrs)</td>
<td>(0.4 – 2.7)</td>
<td>(3.3 – 20.0)</td>
<td>(0.23 – 3.5)</td>
</tr>
<tr>
<td>Aldosterone excretion (μg per 24 hrs)</td>
<td>(2.1 – 16.2)</td>
<td>(22 – 122)</td>
<td>(2.0 – 7.0)</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± se; numbers in parentheses represent the normal range.

_Circulation, Volume XLVIII, September 1973_
Results

Short-term studies: rapid sodium depletion. Restriction of dietary sodium and administration of a mercurial diuretic caused in all cases 1) weight loss, 2) a decrease in PV, and 3) significant reduction in arterial pressure (table 3). Changes in arterial pressure were evident within a 24-48 hour period and correlated significantly with PV (P < 0.02). Serum sodium concentration remained virtually unchanged. PRA increased significantly in one; AER increased in one in spite of suppressed PRA and further decreases in serum potassium concentration. All of them had good renal conservation of sodium; in two, serum potassium concentration increased during sodium restriction as usually occurs in 1°A. Failure of the one patient to regain normal serum potassium concentration probably indicates depleted body stores of potassium at the start of the study since she was in positive potassium balance during the period of sodium deprivation.

Long-term studies: arterial pressure and PV responses during treatment periods with spironolactone alone or in combination with either thiazide diuretics or low dietary sodium. Arterial pressure and plasma volume correlated directly and significantly in patients under either means used to reduce pressure. This correlation was obtained both in data derived from one patient (P.P.) followed over a six-year period prior to removal of an aldosteronoma (fig. 1), and also in data derived from ten patients (six men, four women). Both diastolic (fig. 2) and systolic (fig. 3) arterial pressure correlated directly with PV (P < 0.001 for both relations).

In two patients treated with spironolactone alone (200 mg per day), arterial pressure was reduced to normal within four to five weeks. Once arterial pressure was reduced, it was possible to decrease the dose of spironolactone to 100 mg per day without significant increases in arterial pressure.

Figure 4 presents data on six patients who received combined spironolactone-hydrochlorothiazide therapy. The mean systolic and diastolic arterial pressures were not different from control during the administration of spironolactone alone. With the addition of hydrochlorothiazide therapy, arterial pressure decreased significantly (systolic, P < 0.02; diastolic, P < 0.05). Arterial pressure was definitely within normal limits after two weeks of combined therapy. A notable feature of this response was the dissociation between the effects on potassium balance and arterial pressure. In each

![Figure 1](image)

Figure 1

Relationship between diastolic arterial pressure (DBP) and plasma volume (PV) during chronic diuretic therapy in a patient prior to removal of an aldosteronoma. Data were obtained over a six-year follow-up period. (This figure, as well as figure 2, were reproduced in a review of our work in Circulation Research, in press).

Table 3

<table>
<thead>
<tr>
<th>Subject</th>
<th>Procedure</th>
<th>Arterial Pressure* mm Hg</th>
<th>Plasma Volume % N</th>
<th>Serum Na mEq/liter</th>
<th>Renin activity ng/ml</th>
<th>Uinary aldosterone µg/d</th>
<th>Body Weight kg</th>
<th>Cumulative Na loss mEq</th>
</tr>
</thead>
<tbody>
<tr>
<td>El.H</td>
<td>Control</td>
<td>167/108</td>
<td>129</td>
<td>140</td>
<td>3.6</td>
<td>2.7</td>
<td>33</td>
<td>-1.4</td>
</tr>
<tr>
<td></td>
<td>Na depletion†</td>
<td>131/96</td>
<td>105</td>
<td>138</td>
<td>4.9</td>
<td>9.2</td>
<td>52</td>
<td>-1.7</td>
</tr>
<tr>
<td>I.R.</td>
<td>Control</td>
<td>200/118</td>
<td>110</td>
<td>139</td>
<td>2.9</td>
<td>0.1</td>
<td>132</td>
<td>-2.4</td>
</tr>
<tr>
<td></td>
<td>Na Depletion</td>
<td>124/84</td>
<td>93</td>
<td>139</td>
<td>2.6</td>
<td>1.3</td>
<td>229</td>
<td>-1.7</td>
</tr>
<tr>
<td>W.L.</td>
<td>Control</td>
<td>171/118</td>
<td>102</td>
<td>141</td>
<td>3.5</td>
<td>2.7</td>
<td>45</td>
<td>-2.4</td>
</tr>
<tr>
<td></td>
<td>Na Depletion</td>
<td>148/102</td>
<td>87</td>
<td>138</td>
<td>3.8</td>
<td>3.6</td>
<td>49</td>
<td>-2.4</td>
</tr>
</tbody>
</table>

*Arterial pressure values represent three-day averages of supine arterial pressures taken four times a day.
†Accomplished by 9 mEq Na diet and the administration of Mercuhydrin (2 cc i.m.) every other day.

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Serum added.

In patients on a sodium-restricted diet, arterial pressure was reduced by dosages of spironolactone usually considered inadequate. This response occurred within a week, about two to three weeks earlier than has been reported previously with doses of 400-600 mg per day.\textsuperscript{1,2} In P.P. (fig. 6) it was possible to decrease the dosage of spironolactone to 25 mg per day without a significant increase in arterial pressure as long as dietary sodium was restricted. Additional studies demonstrating the dependence of the antihypertensive effect of spironolactone on salt and water balance can be seen in figure 7. In this patient increasing dietary

one-year period, arterial pressure could be adequately controlled with as little as 50 mg per day of spironolactone as long as conventional doses of hydrochlorothiazide were maintained.

Relationship between diastolic arterial pressure (DBP) and plasma volume (PV) in ten patients with primary aldosteronism during long-term treatment periods, with spironolactone alone or in combination with either thiazide diuretics or low dietary sodium. Data were obtained over a period of six weeks to six years. Plasma volume is expressed in percent of normal because of naturally occurring sex differences.

Figure 2

patient there was a significant increase in serum potassium concentration as early as the first week of therapy ($P < 0.005$), a rise which was not altered by the addition of hydrochlorothiazide. On the other hand, there was usually little or no decrease in arterial pressure until hydrochlorothiazide was added. Serum sodium fell only slightly. In four of the six patients PV was measured serially; in each, arterial pressure reduction was associated with PV contraction. In one patient (fig. 5) studied over a

one-year period, arterial pressure could be adequately controlled with as little as 50 mg per day of spironolactone as long as conventional doses of hydrochlorothiazide were maintained.

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one-year period, arterial pressure could be adequately controlled with as little as 50 mg per day of spironolactone as long as conventional doses of hydrochlorothiazide were maintained.
Arterial pressure response to decreasing doses of spironolactone during treatment with conventional doses of hydrochlorothiazide in one patient (L.B.). Each bar represents the weekly average of supine arterial pressure readings taken at home.

Figure 5

Arterial pressure response to decreasing doses of spironolactone during treatment with conventional doses of hydrochlorothiazide in one patient (L.B.). Each bar represents the weekly average of supine arterial pressure readings taken at home.

Discussion

The present study provides clear evidence that, during treatment of the hypertension accompanying 1°A, good arterial pressure control is dependent on sodium to 200-250 mEq per day resulted in increased arterial pressure even though spironolactone was maintained at previously “effective” doses.

Effect of increasing sodium intake on arterial pressure while maintaining “effective” doses of spironolactone in one patient (Em.H.). Other explanations as in figure 5.

Em. H. 52 YRS. W.M. ALDOSTERONOMA

Figure 7

Effect of increasing sodium intake on arterial pressure while maintaining “effective” doses of spironolactone in one patient (Em.H.). Other explanations as in figure 5.
Sodium depletion may influence catecholamine metabolism and the neurogenic control of arterial pressure.\textsuperscript{13} Changes in the cellular distribution of water or electrolytes may be responsible for vascular smooth muscle relaxation.\textsuperscript{14} Finally, it is possible that total ECF\textsuperscript{27} and the ratio of plasma to interstitial fluid volume may play important roles.\textsuperscript{18} In any event, these findings suggest that maintenance of PV contraction is a basic component of the pressure response to 1\textdegree A to diuretic therapy and focus attention on the importance of intravascular volume as a determinant of arterial pressure in this and other types of fluid volume-dependent hypertension.

Because spironolactone has little or no effect on the arterial pressure of secondary aldosteronism, it has been widely held that its striking effectiveness in 1\textdegree A depends on a specific mineralocorticoid blockade rather than a nonspecific diuretic effect.\textsuperscript{3} Indeed, the differential response to the thiazide diuretics and spironolactone has been advocated as distinguishing patients with "normokalemic" 1\textdegree A from those with essential hypertension. Gwinup and Steinburg\textsuperscript{19} reported that arterial pressure is reduced by either spironolactone or thiazide diuretics in essential hypertensives while patients with 1\textdegree A respond only to spironolactone.

This study provides conclusive evidence that the ability of spironolactone to reduce arterial pressure in 1\textdegree A is largely dependent on salt and water balance and not to any specific antagonism of the effects of electrolyte-active steroids. First, when salt intake was restricted, very small amounts of spironolactone were needed to sustain normal arterial pressure (fig. 6); in fact arterial pressure fell as early as the first week of therapy. When salt intake was increased, arterial pressure rose in spite of continued administration of previously effective doses of spironolactone (fig. 7). Further, low doses of spironolactone, in combination with hydrochlorothiazide, achieved arterial pressure responses similar to those obtained with large doses (400-600 mg) of spironolactone alone,\textsuperscript{1, 2} and rapid sodium depletion alone was similarly effective in reducing arterial pressure to normal (table 2). Spark and Melby\textsuperscript{1, 3} reported that on conventional doses of 100 mg of spironolactone per day, patients with 1\textdegree A gain weight and become hypertensive again. They suggested that higher doses of spironolactone were needed to provide adequate blockade of electrolyte-active steroid(s). An alternative explanation is that positive sodium balance had occurred with re-expansion of blood volume. This possibility is clearly illustrated in two of the patients reported here. The first patient, despite urinary aldosterone excretions exceeding 500\textsuperscript{g} per 24 hours, was normotensive with restricted dietary sodium and 25 mg of spironolactone per day (fig. 6). In the second patient (fig. 7) it could be clearly shown that his arterial pressure responses to spironolactone therapy were largely dependent on sodium intake.

Finally, we have confirmed work of others\textsuperscript{1, 2, 10} showing that spironolactone is effective therapy for patients with aldosteronism and is particularly useful as a potassium-sparing agent when a potent natriuretic agent is being used as part of a regimen for treatment of the associated hypertension. In addition, we have shown that small doses are just as effective when combined with either sodium restriction or with conventional doses of hydrochlorothiazide. In view of these observations it is no longer advisable to use large doses of spironolactone as the treatment of choice in 1\textdegree A. The therapeutic regimen suggested here has proved far superior to existing modes of medical therapy; it is much less expensive, predictable, rapid, and has none of the side effects (i.e., painful gynecomastia and decreased libido in the male, and menstrual irregularities and nausea in the female) commonly encountered in patients taking large doses of spironolactone. The therapeutic approach outlined in these studies has been found to be particularly useful in the preoperative preparation of the patient for surgery, and in the long-term management of cases not suitable for surgery.

Acknowledgment

We are indebted to Mrs. Ann Molyneaux, Mrs. Mirka Kukla and Mrs. Shirley Bartunek for their excellent technical assistance and to Mrs. Betty Libby for secretarial help.

References

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Circulation. 1973;48:491-498
doi: 10.1161/01.CIR.48.3.491
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

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