Role of Reactive Hyperreninemia in Blood Pressure Changes Induced by Sodium Depletion in Patients with Refractory Hypertension

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SUMMARY Sixteen patients with refractory hypertension were submitted to rigorous sodium depletion while cardiovascular homeostasis was monitored with measurements of hormonal and hemodynamic parameters and repeat saralasin tests. This regimen resulted in a negative sodium balance by an average of 300 mEq. The loss of sodium closely correlated to the decrease of body weight (r = 0.70, p < 0.005). Blood pressure (BP) decreased from 176/116 ± 8/3 to 155/109 ± 6/3 mm Hg. There was a significant correlation between percent increments in plasma renin activity (PRA) and the rise in plasma norepinephrine (r = 0.68, p < 0.05) and a close negative correlation between percent increase in PRA and the ratio of fall in mean blood pressure (MAP) per unit of weight loss (r = -0.73, p < 0.005). Thus, patients with the least percent increase in PRA demonstrated the greatest fall in BP per unit of weight loss, indicating that relative rather than absolute elevation of renin may be the factor limiting antihypertensive efficacy of sodium depletion. Sodium depletion induced increase in peripheral resistance and decrease in cardiac output, both mostly attributable to relative hyperreninemia. Indeed, the adverse hemodynamic changes were reversed by angiotensin inhibition, during which BP normalized. It is concluded that vigorous sodium depletion complemented by angiotensin blockade or suppression with sympatholytic agents improves management of otherwise refractory hypertension. (Hypertension 3: 441-447, 1981)

KEY WORDS • sodium depletion • hyperreninemia • refractory hypertension • saralasin • plasma renin activity • hemodynamics • angiotensin blockade • sympatholytic agents • cardiac index • norepinephrine

A NUMBER of experimental1-4 and clinical studies in the last few years have demonstrated a reciprocal relationship between the renin-angiotensin system and the sodium ion in the pathophysiology of hypertension. Clinical observations supported the thesis that one likely cause for the failure of the blood pressure (BP) to respond to chronic treatment with diuretics may respond to the reactive hyperreninemia observed in these patients. This is strongly suggested by the fact that, following salt depletion, the BP often remains unchanged but becomes renin-dependent, as has been repeatedly shown with the use of specific inhibitors of the renin-angiotensin system.1-4 However, a close inspection of the diuretic-induced changes in plasma renin activity (PRA) reported in a clinical study with several weeks' follow-up6 revealed that the absolute increase in renin levels measured in those patients was, in fact, much higher in the responders to diuretics than in the non-responders, an apparently paradoxical reaction. The following study was designed to explore the changes in PRA, norepinephrine, and aldosterone occurring with protracted sodium depletion as well as the effect of this treatment on blood volume and cardiac hemodynamics, and to assess the potential usefulness of this approach to treating refractory hypertension. Our hypothesis was that elimination of a critical amount of sodium associated with sustained suppression of the renin-angiotensin system should lead to normalization of BP.
Methods

Sixteen patients with refractory hypertension participated in this study (table 1). Criterion of "refractoriness" was resistance of BP to ceiling doses of at least one diuretic and one sympatholytic agent administered on an outpatient basis; the BP studied were the mean of four to five daily determinations. Control values were those obtained on the 4th day of hospitalization and bed rest. The experimental nature of this study was explained to all subjects and informed consent obtained. Previous antihypertensive therapy was withdrawn at least 2 weeks before the patients were admitted to the Metabolic Ward. The patients were maintained on an isocaloric diet throughout, and for the first 3 days their daily diet contained 100 mEq of sodium (Na) and 80 mEq of potassium (K). From the 4th day on, the patients underwent sodium depletion using a daily diet of 10 mEq of Na and either 100 mg hydrochlorothiazide or, if the patient had evidence of renal insufficiency, 80 to 200 mg furosemide. (The latter was administered to Patients 3 and 15 respectively.) After 6 to 14 days (9 ± 1, mean ± SEM), when the patients had a daily urinary sodium output equal to the intake, they had a saralasin test. Eight patients (Patients 1–5, 12, 13, and 16) who still had a slightly pressor response or lack of response to saralasin were then placed on a second period of salt depletion during which spironolactone (100–300 mg daily) was added to the above regimen for 4–16 days (average, 10 ± 2). In most cases this period was long enough to achieve equalization of the daily urinary sodium excretion with the sodium intake. Saralasin infusion was repeated at this time in all but one of these patients. Upon completion of the protocol, since chronic angiotensin inhibition was not available at the time, patients were discharged on a combination of the above diuretics with a sympatholytic antihypertensive agent, and 10 of them were followed at monthly intervals as outpatients.

Body weight was determined daily during hospitalization, and BP and pulse rate checked manually four times daily in the supine position. Blood samples for PRA and plasma aldosterone determination were drawn in the upright position through an indwelling catheter on the third day of admission, as described previously. After 3 hours after discontinuation of the infusion, until the BP had returned to the preinfusion level.

In five patients, the following hemodynamic studies were carried out: blood volume and cardiac output were measured before and during the saralasin test on the third day of admission, and again at the end of the first salt depletion phase. Blood volume was determined by the radioiodinated (125I) serum albumin method and cardiac output by the indocyanine green (Cardiogreen) dilution technique, using a Colson 103 densitometer. Total peripheral resistance (TPR) was calculated according to the formula, TPR (dyn/sec/cm²) = mean blood pressure (mm Hg)/cardiac output (1/min) × 79.9.

Urine was collected daily in 24-hour samples for electrolyte determination, and cumulative Na balance was calculated. Fecal losses were not taken into account, and skin losses were assumed to be negligible since the patients were maintained in an air-conditioned environment. The PRA was determined by radioimmunoassay of generated angiotensin I and expressed as ng/ml/hr. Plasma aldosterone was also measured by radioimmunoassay and plasma norepinephrine by radioenzymatic assay utilizing the phenylethanolamine-N-methyl transferase (PNMT) method. Normal range for our laboratory is between 0.200 and 0.400 ng/ml after 30 seconds of recumbency. The patients were classified in low, normal, or high renin subgroups according to the renin-sodium index on the third day of admission, as described previously. Routine blood chemistries were determined by autoanalyzer, and urine electrolytes by flame photometry. Data were analyzed by the Student’s paired t test, and the regression lines were calculated using the method of least squares.

Results

Sixteen hypertensive patients, 32 to 61 years of age (average age, 46 ± 2 years), were included in this study. Fourteen were black and two white; 10 were men and six women. Two (patients 1 and 3) were diagnosed as having primary aldosteronism (one chose to remain on conservative treatment after this study, whereas the other was operated on 1 year later and had an aldosterone-producing adenoma removed from the right adrenal gland), and the remainder had essential hypertension. Blood urea nitrogen ranged from 9 to 36 mg/100 ml (17.5 ± 1.7). Original renin-profiling revealed that three had elevated, seven normal, and six suppressed PRA (table 1).

During the first period of salt depletion, the weight of all patients decreased from 81.5 ± 3.6 to 78.9 ± 3.4 kg (p < 0.001); the BP from 176/116 ± 8/3 to 155/109 ± 6/3 mm Hg (p < 0.001 for the systolic, p < 0.05 for the diastolic); and the PRA increased from 8.64 ± 4.3 to 33.51 ± 8.9 ng/ml/hr (p < 0.01) (table 1). The cumulative loss of Na for the whole group averaged 296 ± 42 mEq and correlated, as expected, with the decrease in body weight (r = 0.7, p < 0.005). Salt losses also correlated with the percent increases in PRA (r = −0.75, p < 0.001). No significant correlation was found between the control PRA (on a logarithmic scale) and the changes in weight (r = 0.27, p > 0.05) and in MAP (r = −0.27, p > 0.05); nor between the weight loss and the MAP drop (r = −0.21, p > 0.05). The effect of the reduction of total body sodium on plasma aldosterone and
TABLE 1. Clinical Data Before and After the First Phase of Sodium Depletion

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<tr>
<th>Patient</th>
<th>Age, Sex</th>
<th>Diagnosis</th>
<th>Wt</th>
<th>BP</th>
<th>PRA (ng/ml/hr)</th>
<th>BUN (mg/100 ml)</th>
<th>Wt</th>
<th>BP</th>
<th>PRA (ng/ml/hr)</th>
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<td>8.9</td>
<td>2.9</td>
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</table>

*Patients followed subsequently for 4 to 6 months as outpatients.

F = female; M = male; PA = primary aldosteronism; EH = essential hypertension; Wt = weight (kg); BP = blood pressure (mm Hg); PRA = plasma renin activity (ng/ml/hr); BUN = blood urea nitrogen (mg/100 ml).

norepinephrine was checked in 10 patients. Aldosterone levels increased from 22.3 ± 7.5 to 115.3 ± 29.4 ng/100 ml (p < 0.01), and norepinephrine levels from 0.332 ± 0.09 to 0.740 ± 0.12 ng/ml (p < 0.01).

The MAP changes induced by salt depletion did not correlate with the concomitant increase of PRA expressed either in absolute value or in percent (r = 0.13, p > 0.05, and r = 0.39, p > 0.05 respectively). However, when the changes in MAP were divided by the changes in body weight, a close negative correlation appeared between the percent increase in PRA and the ratio of these two parameters (r = 0.73, p < 0.005) (fig. 1). In other words, patients who had the least percent increase in PRA were the ones to demonstrate the greater drop in MAP per unit of weight loss.

Some other interrelationships between various parameters emerged during the first salt depletion period: a very close correlation was observed between the level of PRA achieved after sodium depletion and the MAP fall induced by saralasin at that point (r = -0.89, p < 0.001) (fig. 2). Interestingly, the percentage of increment in PRA was directly correlated with the changes in plasma norepinephrine levels (r = 0.68, p < 0.05) (fig. 3 left), as well as with the absolute values of norepinephrine measured after salt depletion (r = 0.66, p < 0.05) (fig. 3 right), indicating a tendency to parallel changes of these parameters.

![Figure 1](http://hyper.ahajournals.org/DownloadedFrom.png)
Figure 4 illustrates the hemodynamic effects induced by sodium depletion in five patients. As would be expected, blood volume decreased. Total peripheral vascular resistance increased despite the fall in MAP, and there was a decrease in cardiac output and cardiac index. Saralasin infusion before sodium depletion caused a pressor reaction and a fall in cardiac index; on the contrary, repeat saralasin after sodium depletion had a vasodilator effect, with a fall in peripheral resistance and elevation of cardiac index. Resting heart rate increased following salt depletion (from 68 ± 4 beats/min to 79 ± 4, p < 0.05) but did not change during competitive blockade of the renin angiotensin system with saralasin.

Eight patients underwent a second period of salt depletion. The addition of spironolactone to the low sodium diet and to the previous natriuretic agent resulted in an additional negative Na balance of 346 ± 70 mEq and an additional weight loss of 1.96 ± 0.2 kg (p < 0.001). The PRA rose further from 24.95 ± 13.7 to 44.55 ± 22.1 ng/ml/hr (p < 0.05) and plasma aldosterone levels from 89.9 ± 35.6 to 159.7 ± 34.9 ng/100 ml (p > 0.05). During this step the MAP decreased from 168/113 ± 7/3 to 151/105 ± 5/2 mm Hg (p < 0.05 for the systolic, p < 0.05 for the diastolic BP). However, in two of these patients (Patients 15 and 16) BP levels failed to decrease further despite the additional weight loss. In all the patients except Patient 16 who had very high renin levels, the effect of saralasin infusion on BP was studied again after the additional decreases in total body sodium. A very close correlation was found between the saralasin-induced BP change at the end of the first salt depletion and that measured under similar conditions following the second salt depletion (r = 0.91, p < 0.001). In other words, the more the BP had become renin-dependent at the end of the first phase, the more it fell during saralasin infusion after the additional salt depletion. Interestingly, all the patients, even those with primary aldosteronism, responded with a BP drop to saralasin infusion following the two-step salt depletion, whereas in five of them saralasin had still produced an increase in BP at the end of the first salt depletion period.

Blood urea nitrogen levels were increased from 17.5 ± 7 to 25.2 ± 2.9 mg/100 ml (p < 0.001) during the first sodium depletion. The changes in this parameter were more pronounced following salt depletion in...
patients with the higher control levels ($r = 0.65$, $p < 0.001$). During the spironolactone-induced additional volume contraction, pre-renal azotemia became more pronounced and blood urea nitrogen levels increased from 22.8 ± 3.8 to 31.9 ± 6.3 mg/100 ml, ($p > 0.05$).

Sympatholytic agents (mostly the same one to which the patient had been previously unresponsive, i.e., propranolol, methyldopa, or clonidine) were added to diuretics after discharge from the hospital. Ten patients (table 1) were followed thereafter at monthly intervals during at least 4 to 6 months. With the combined therapy, their ambulatory BP was lower than that achieved with salt depletion alone during hospitalization (139/96 ± 4/3 vs 155/108 ± 6/3 mm Hg) respectively. The increase in body weight from 82.4 ± 3.5 to 83.3 ± 3 kg during the 4–6 month follow-up was not statistically significant. At this time the weight was still markedly lower, however, than that measured before starting salt depletion (82.4 ± 3.5 vs 86.3 ± 3.3 kg respectively, $p < 0.05$).

Discussion

Sixteen patients with refractory hypertension were submitted to aggressive sodium depletion by low sodium diet and diuretics. This regimen resulted in the loss of variable amounts of salt accompanied by a loss of body weight, a contraction of intravascular fluid volume, increases in heart rate and peripheral vascular resistance, and a fall in cardiac index. The decrease in total body sodium induced significant increments in PRA, plasma norepinephrine, and plasma aldosterone. (During these maneuvers, the BP was normalized ($\leq 140/90$ mm Hg) in only one patient). Repeat saralasin tests at various points indicated that hypertension could be converted to a renin-dependent type after sodium depletion, even in patients with primary aldosteronism. Tests also indicated that the undesirable hemodynamic changes observed with salt depletion, i.e., increase in peripheral vascular resistance and decrease in cardiac index, were due to renin stimulation and could be easily reversed by angiotensin blockade. The pre-renal azotemia ob-
served during the course of this treatment was probably due to decreased renal flow. This can partly be attributed to hyperreninemia, and to this extent it may be expected to respond to chronic blockade of the renin-angiotensin system. Actually, angiotensin-converting enzyme inhibitors have been shown experimentally to exert a preferential vasodilatory effect on the renal vasculature. Effective renal plasma flow increases even in non-salt-depleted hypertensive patients, but after sodium depletion, angiotensin blockade causes a striking increase in glomerular filtration rate, as well. Clinical studies with teproside in hypertensive patients have demonstrated an increase in creatinine clearance following angiotensin-converting enzyme inhibition, and studies with captopril have shown an increase in renal blood flow and decrease in filtration fraction during chronic angiotensin blockade.

During the first period of sodium depletion, the average cumulative sodium loss was approximately 300 mEq, which led to a small decrease but not normalization of BP. For half of the patients, this amount was sufficient to convert their arterial pressure to renin dependence, as indicated by the clearly depressed response to saralasin. The other half required additional sodium loss of another 350 mEq on the average, which led to conversion of BP to renin dependence, but, with one exception, again, failed to normalize it. Thus, a critical amount of sodium had to be eliminated, which varied widely from patient to patient, before the BP became manageable (i.e., responsive to a combination of diuretics and sympatholytic agents, to which it had previously been resistant). In most cases, this could be achieved only after an aldosterone antagonist was added to the diuretic regimen, presumably because secondary hyperaldosteronism limited the diuretic efficacy of thiazides.

Several theories have been advanced to explain the mechanism by which excessive sodium accumulation may render the arterial pressure difficult to control. These include expansion of intravascular fluid volume, stimulation of humoral vasopressor substances, heightened vascular wall sensitivity to vasopressors, and structural alteration of the arteriolar wall due to local accumulation of sodium and retention of fluid (waterlogging) that may lead to increased peripheral vascular resistance. Several investigators in the past have studied the capacity of diuretics to decrease BP or potentiate the vasodepressor effect of sympatholytic agents. However, they have mostly focused on the volume aspect of this maneuver, attributing the antihypertensive effect to contraction of plasma or extracellular fluid volume, whereas we believe that sodium per se may activate other vasopressor substances.

At any rate, this study was not designed to investigate mechanisms of sodium action but simply to show that inappropriate accumulation of sodium may be responsible for refractoriness of hypertension, and therefore elimination of a certain critical amount of sodium is necessary before the BP can be controlled.

Interestingly, with sufficient sodium depletion, even the two cases of proven primary hyperaldosteronism became responsive to saralasin and subsequently to combination therapy, which had been ineffective in the past. The reciprocal relationship between the renin-angiotensin system and the sodium ion has been repeatedly demonstrated in the past both in experimental and clinical studies. Although several investigators have commented on the role of reactive hyperreninemia as a limiting factor to the antihypertensive effectiveness of diuretics, our data help to clarify the seemingly paradoxical finding that good responders to salt depletion may develop a far more pronounced increase in PRA than poor responders. It appears that a small renin response to stimulation by sodium depletion may represent a major percent increment for the patients with suppressed baseline PRA in spite of the small absolute numbers. Such patients were shown to exhibit a lesser decrease of BP per unit of weight loss than patients with higher initial PRA who had a proportionately smaller change in their renin levels following salt depletion. Since the patients with low renin levels would probably be expected to have heightened vascular wall reactivity to the renin-angiotensin system, it may be that a small absolute increment in PRA in them represents an important change as perceived by their sensitive arteriolar tree. On the other hand, a larger absolute elevation in PRA induced by salt depletion may represent a less pronounced percent increment in patients with higher baseline PRA and in physiological terms may be less important in the face of a decreased vascular sensitivity to angiotensin II. The rate of increase in PRA during sodium depletion appears in our patients to determine the relative change of BP per unit of weight loss: patients who exhibited the smallest percent of rise in PRA were the ones in whom a small weight loss was associated with a substantial decrement in BP (large ratio), whereas those with the largest percent increments in PRA tended to be the ones who required a large weight loss to achieve a small BP change (fig. 1). Therefore, the vasopressive effect of reactive hyperreninemia cannot be measured using only absolute renin levels; rather, initial renin levels along with the percent of changes in renin secretion should be considered.

Plasma norepinephrine levels are taken to reflect the activity of the sympathetic nervous system. They were recently reported to be similar in normal volunteers and hypertensive patients of the three renin subgroups and to increase after diuretics. It is well established that angiotensin II enhances the synthesis of, and vascular responsiveness to catecholamines; the norepinephrine levels achieved after the maneuver were found to be directly correlated to the increase of percent PRA. This suggests that the plasma levels of one hormonal system may physiologically modulate the levels of the other. The fact that the autonomic nervous system was most stimulated in patients with the highest percentage of increments of PRA, that is, in patients who probably increased the most their
peripheral resistance during salt depletion, suggests that norepinephrine's response may contribute to the hemodynamic modifications induced by salt depletion. Indeed, it is possible that norepinephrine also plays a limiting role in the BP-lowering effect of salt depletion.

Thus, interference with either of the pressor mechanisms at this point may be sufficient to induce BP control. Blockade of the renin system by saralasin at different steps of salt depletion demonstrates that normalization of BP could be obtained in our patients despite increased sympathetic activity. Alternatively, the addition of a sympatholytic agent at the time of discharge, for long-term maintenance, also normalized BP in most patients. However, chronic blockade of the renin system, when routinely available, might prove preferable, since it would be expected to counteract some of the undesirable effects of vigorous sodium depletion, such as decreased cardiac output, increased peripheral resistance, and decreased renal blood flow, as mentioned earlier.

In conclusion, it appears that accumulation of sodium may be the cause for refactoriness of hypertension, since elimination of a critical amount, varying widely between patients, may render a previously resistant BP responsive to treatment with sympatholytic agents. The lack of normalization of BP by diuretics alone is attributed to reactive hyperreninemia: however, it is not the absolute increase in renin that determines the degree of BP lowering per unit of weight loss obtained by sodium depletion, and this is also correlated with a concomitant increase in norepinephrine.

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