Importance of the Renin System for Determining Blood Pressure Fall With Acute Salt Restriction in Hypertensive and Normotensive Whites

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Abstract—Hypertensive (n=93) and normotensive (n=39) white individuals were given a high sodium intake of \( \approx 350 \) mmol/d for 5 days followed by a low sodium intake of 10 to 20 mmol/d for 5 days. With this acute and large reduction in salt intake, no significant change was seen in blood pressure in the normotensive individuals, but blood pressure decreased in the hypertensive individuals. Compared with normotensive subjects, hypertensive patients had a 7/7-mm Hg greater fall in blood pressure (\( P<0.05 \) for systolic and \( P<0.01 \) for diastolic, adjusted for age), with similar changes in urinary sodium excretion. From the high-salt to low-salt diet, plasma renin activity rose from 0.90 to 5.99 ng · mL\(^{-1} \) · h\(^{-1} \) in normotensives, whereas in hypertensives it rose from 0.73 to only 3.14 ng · mL\(^{-1} \) · h\(^{-1} \) (\( P<0.05 \) between hypertensives and normotensives). Plasma aldosterone rose by 1396 pmol/L in normotensive subjects and by 511 pmol/L in hypertensive patients (\( P<0.05 \)). Significant inverse correlations were obtained for all subjects between the fall in blood pressure from the high-salt to low-salt diet and the rise in plasma renin activity and aldosterone that occurred in addition to the absolute level on the low-salt diet. These results demonstrate that the larger fall in blood pressure with an acute reduction in salt intake in hypertensives compared with normotensives is, at least in part, due to a less-responsive renin-angiotensin-aldosterone system in the hypertensive patients. (Hypertension. 2001;38:321-325.)

Key Words: renin-angiotensin system ■ blood pressure ■ sodium ■ diet, sodium-restricted ■ hypertension, essential ■ normotension

Substantial evidence suggests that an acute and large reduction in salt intake causes a significant fall in blood pressure (BP) in patients with essential hypertension, whereas a smaller or no change in BP appears to occur in normotensive subjects. The mechanism for this difference is not fully understood. Some studies have suggested that the fall in BP with a reduction in salt intake is related to blunting of the renin response that occurs in many patients with essential hypertension. In white subjects (93 with essential hypertension and 39 with normal BP), we studied the difference in BP response to an acute and large reduction in salt intake to elucidate further the mechanism of BP fall. All participants were studied on their usual diet period for measurement of electrolytes, creatinine, plasma renin activity, and aldosterone levels were measured.

Methods

Ninety-three patients with essential hypertension (systolic BP \( \geq 140 \) mm Hg and/or diastolic BP \( \geq 90 \) mm Hg) and 39 subjects with normal BP (systolic BP <140 mm Hg and diastolic BP <90 mm Hg) were studied. Patients with high BP either had not received previous treatment or had not received treatment for \( \geq 3 \) months before the study. The study group included 46 male and 47 female hypertensives (mean age, 50 years; range, 19 to 70 years) and 25 male and 14 female normotensives (mean age, 28 years; range, 19 to 62 years). All subjects gave informed consent. The study was approved by the local hospital ethics committee.

Subjects were studied on a high sodium intake of \( \approx 350 \) mmol/d for 5 days followed by a low sodium intake of 10 to 20 mmol/d for 5 days. High sodium intake was achieved by supplementing the sodium diet was provided by the metabolic unit kitchen. Potassium intake was not altered for either diet.

BP was measured in each subject in the same arm by nurses who used semiautomatic ultrasound sphygmomanometers (Arteriosonde) with attached recorders. Therefore, measurements were free from observer bias. Supine BP were the mean of 5 readings taken at 1- to 2-minute intervals. Two 24-hour urine samples were collected during the last 2 days of each dietary period for measurement of sodium, potassium, and creatinine. Blood was also taken at the end of each diet period for measurement of electrolytes, creatinine, plasma renin activity, and aldosterone.

Results are reported as mean\( \pm \)SEM. Changes in continuous variables within each group were analyzed by paired \( t \) tests. Comparisons between hypertensives and normotensives at baseline (on the normal diet) were made with unpaired \( t \) tests for continuous variables and \( \chi^2 \) test for categorical data. Because of the significant

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difference between hypertensives and normotensives in age, we used a multiple linear regression model for comparison between the 2 groups in changes in BP and other continuous variables while adjusting for age. All statistical analyses were performed by use of Statistical Package for Social Science (SPSS) software.

Results

Baseline Characteristics

Table 1 shows results obtained on the final day of the usual salt intake (before alteration of salt intake) for hypertensive and normotensive subjects. Hypertensives were older and slightly heavier than normotensives. Average BP for subjects on the normal diet was 170/106 ± 2.4/1.2 mm Hg and 116/74 ± 6.1/1.2 mm Hg in the hypertensive and normotensive individuals, respectively. Plasma renin activity was significantly lower in the hypertensives than normotensives. No significant difference was seen between hypertensives and normotensives in levels of plasma sodium, potassium, and creatinine, and urinary sodium, potassium, creatinine, and volume.

High Salt to Low Salt Intake

Figure 1 shows distribution of change in mean arterial pressure with acute salt restriction in normotensive (A) and hypertensive (B) individuals. In 24-hour urinary sodium excretion, the hypertensives had a greater fall in BP and smaller rise in plasma renin activity and aldosterone compared with normotensives. The reduction in body weight with acute salt restriction was smaller in hypertensives than in normotensives. No significant differences were seen between hypertensives and normotensives in changes in supine pulse rate, plasma sodium, potassium, creatinine, urinary sodium, potassium, creatinine, and volume.

Correlations Between BP Response and Other Variables

Taking all subjects together, the fall in mean arterial pressure with the low-salt diet was significantly correlated with age ($r=0.47, P<0.001$). A significant inverse correlation also occurred between the fall in mean arterial pressure with salt restriction and (1) plasma renin activity (log-transformed values) on the low-salt diet ($r=-0.35, P<0.001$) (Figure 2); (2) rise in plasma renin activity from the high-salt to the low-salt diet ($r=-0.33, P<0.001$); (3) plasma aldosterone on low-salt diet ($r=-0.42, P<0.001$); and (4) rise in plasma aldosterone ($r=-0.42, P<0.001$). Correlation analyses also were performed in hypertensives and normotensives separately. Subgroup analyses showed that most significant inverse correlations between changes in BP and plasma renin activity were seen between hypertensives and normotensives in changes in arterial pressure with acute salt restriction.
activity or aldosterone were present in hypertensives alone, but no significant correlations were found in the normotensives alone.

To further investigate the quantitative relationship between the change in BP and the renin system, we performed a multiple linear regression analysis. \( R^2 \) was 0.21 when the change in mean arterial pressure was entered as a dependent variable and the changes in plasma renin activity and aldosterone levels and absolute levels on the low-salt diet were entered as independent variables. \( R^2 \) changed to 0.29 when the status (hypertensive = 1, normotensive = 0) was added to the independent variables. \( R^2 \) changed little (0.31) when changes in body weight, urinary sodium, and potassium excretion were added to the independent variables. These results also demonstrate the importance of the renin-angiotensin system in determining the fall in BP with acute salt restriction.

### Comparisons Between Hypertensives and Normotensives in Changes in BP and Plasma Renin Activity in 34 Subjects Matched for Age and Sex

Age is an important confounding factor in the present study due to the fact that hypertensive patients were significantly older than normotensive subjects, and the finding that age was significantly correlated with the fall in BP with the low-salt diet. To exclude further potential bias due to the age difference, we matched a subgroup of normotensives and hypertensives by age and gender. A total of 34 subjects were matched (17 normotensives and 17 hypertensives). Average age was 35 ± 3 and 36 ± 3 years for the normotensives and hypertensives, respectively. Each group had 10 men and 7 women.

Figure 3 shows change in systolic BP, plasma renin activity, and urinary sodium excretion from high-salt to low-salt diet in age- and sex-matched normotensive and hypertensive individuals. With a similar reduction in salt intake, the hypertensive patients had a 9/6-mm Hg greater fall in BP compared with that of the normotensive subjects \((P<0.05\) for both systolic and diastolic BP). Plasma renin activity rose from 0.77 ± 0.20 to 6.12 ± 0.91 ng · mL\(^{-1}\) · h\(^{-1}\) in normotensive subjects, whereas in hypertensive patients it only rose from 0.89 ± 0.17 to 3.94 ± 0.53 ng · mL\(^{-1}\) · h\(^{-1}\) \((P<0.05 \)hypertensives versus normotensives). Results for the other measurements in these matched subjects also were similar to those observed in the larger number of subjects.
In the age- and sex-matched individuals, a significant correlation was seen between the fall in mean arterial pressure and the change in plasma renin activity with salt restriction \( r = -0.41, P < 0.05 \). However, the fall in BP was not significantly associated with change in plasma aldosterone or with absolute levels of plasma renin activity or aldosterone on low-salt diet.

**Discussion**

Several studies have investigated responses of BP to acute manipulation of sodium and volume balance in humans. However, in some of these studies, a nonphysiological protocol was followed to achieve sodium depletion, including administration of furosemide.\(^{14-16}\) Although the study by Weinberger et al\(^6\) showed congruence of 2 different approaches for the assessment of BP response to salt, controversy still exists.\(^{17}\) Among the studies that used a dietary approach, most were performed in hypertensive patients and some in normotensive individuals, and few were done simultaneously. The present study demonstrates that with a similar acute reduction in salt intake, hypertensive patients have a greater fall in BP with smaller rises in plasma renin activity and aldosterone. The fall in BP with salt restriction was significantly related to the plasma renin activity and aldosterone on the low-salt diet and to the rise in plasma renin activity and aldosterone ongoing from the high-salt to the low-salt diet. These results suggest that the greater fall in BP with salt restriction in hypertensive patients is, at least in part, due to a decreased responsiveness of the renin-angiotensin-aldosterone system in hypertensives.

Our findings of different responses of BP and renin system to an alteration of dietary salt intake between hypertensives and normotensives are in agreement with the findings by Weinberger et al,\(^5\) who studied 378 normal volunteers and 198 patients with essential hypertension by use of rapid sodium and volume expansion (saline infusion) and contraction maneuvers (low-salt diet and furosemide administration). In their study, after acute sodium and volume depletion, hypertensive patients had a larger fall in mean arterial pressure compared with normotensives. They also found that subjects who had greater BP response to sodium depletion (ie, more sodium sensitive) had lower plasma renin activity at baseline and less rise in plasma renin activity after sodium and volume depletion. Overlack et al\(^5\) investigated BP responses to 1 week of low sodium (20 mmol/d) and high sodium (300 mmol/d) intake in 163 normotensive whites. With the alteration of sodium intake, no significant change was seen in average BP. However, individual BP response was heterogeneous, which was related to plasma renin activity at baseline and during low-salt and high-salt diets. More recently, Krekels et al\(^6\) studied interrelationships among cumulative sodium loss, renin activation, and BP changes during moderate sodium restriction (55 mmol/d) in 55 patients with untreated essential hypertension. They found that the change in BP with the alteration of salt intake was also related to the response of the renin system but not to the change in sodium balance. Our results support this conclusion, given that the weight loss with salt reduction was not related to the fall in BP.

When comparing 2 different tests for assessment of BP responses to sodium in the same individuals, Weinberger et al\(^6\) demonstrated that increases in plasma renin activity with sodium and water depletion induced by the low-salt diet and furosemide in the first study predicted (correlated with, \(P < 0.001\)) the BP response to the low-salt diet in the second study, which was conducted 3 months later. Our previous study\(^7\) with the use of the angiotensin II antagonist saralasin showed that the fall in BP with saralasin was inversely correlated with the fall in BP with salt restriction. These results indicated that subjects who had the biggest fall in BP with salt restriction had the least fall in BP with saralasin when salt was restricted and that those subjects who had little change in BP with salt restriction had a bigger fall in BP with saralasin when salt was restricted. This relationship provides direct evidence that the fall in BP with salt restriction is, at least in part, mediated by reactivity of the renin-angiotensin system.

In the present study, the major components of the renin-angiotensin-aldosterone system and their responsiveness explained 21% of the variability of BP responses to acute salt restriction. The combination of the components and responsiveness of the renin-angiotensin-aldosterone system with patient status (hypertensives versus normotensives) and changes in body weight, urinary sodium, and potassium excretion explained 29% of the variability of BP responses to acute salt restriction. Therefore, a large percentage of the variability of BP responses to acute salt restriction is due to other mechanisms that merit further studies. The recent study
by Morris et al.\textsuperscript{18} suggests that potassium intake has a
significant effect on BP response to a dietary salt loading. In
the present study, potassium intake was not altered. However,
with acute salt restriction there was a small reduction in
24-hour urinary potassium excretion (4.6 mmol in normoten-
sives, \( P=0.236 \); and 8.8 mmol in hypertensives, \( P<0.001 \)).
These small changes in urinary potassium excretion may have
some confounding effects on the BP responses to salt restric-
tion. However, they are unlikely to account for the difference
between hypertensives and normotensives in BP responses to
alteration of salt intake, given that neither the urinary potas-
sium excretion nor plasma potassium was significantly dif-
ferent between hypertensives and normotensives either at
baseline or from the high-salt to low-salt diet. Other studies
have suggested that the sympathetic nervous system,\textsuperscript{19,20} the
kallikrein-kinin system,\textsuperscript{21} the NO system,\textsuperscript{22} and many eico-
sanoids\textsuperscript{23} also may contribute to the BP responses to acute
alteration of salt intake. How far these changes are integrated
into the response of the renin-angiotensin system is not clear,
although much evidence suggests a complex feedback system
between activity of the sympathetic nervous system and
activity of the renin-angiotensin-aldosterone system.

In conclusion, our results demonstrate that with an acute
reduction in salt intake, hypertensive patients have a greater
fall in BP compared with normotensive subjects. This greater
fall in BP is, at least in part, due to decreased responsiveness
of the renin-angiotensin-aldosterone system in hypertensives.
Our findings reinforce the accumulating evidence that, at
least in the short-term (5 days), changes in BP with a
reduction in salt intake are, at least in part, modulated by
reactivity of the renin-angiotensin-aldosterone system.

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