Definitions and Characteristics of Sodium Sensitivity and Blood Pressure Resistance

MYRON H. WEINBERGER, JUDY Z. MILLER, FRIEDRICH C. LUFT, CLARENCE E. GRIM, AND NAOMI S. FINEBERG

SUMMARY Sensitivity and resistance to the effects of sodium were evaluated in normotensive and hypertensive humans by two approaches. Blood pressure was measured after an intravenous infusion of 2 L of normal (0.9%) saline and after sodium and volume depletion induced by a low sodium diet and furosemide administration in 378 normal volunteers and 198 subjects with essential hypertension. Those in whom mean arterial blood pressure decreased by at least 10 mm Hg after sodium and volume depletion were considered sodium-sensitive, and those with a decrease of 5 mm Hg or less (including an increase in pressure) were considered sodium-resistant. The second study utilized the blood pressure response to modest dietary sodium restriction in 74 normotensive subjects to identify sodium sensitivity and resistance. In both studies the responses were heterogeneous. In the first study significantly more hypertensive subjects were sodium-sensitive, as compared with those in the normotensive group (p<0.001). Plasma renin activity (low, normal, or high) did not predict sodium responses. In both groups sodium-sensitive individuals were significantly older (p<0.001) and had lower baseline renin values than sodium-resistant subjects. Factors related to the change in mean arterial blood pressure after sodium and volume depletion included baseline pressure (r = −0.54, p<0.001) and age (r = −0.16, p = 0.002 in the normotensive group; r = −0.28, p<0.001 in the hypertensive group). The response to dietary sodium restriction was also correlated with baseline pressure (r = 0.61, p<0.001) and the initial urinary sodium excretion (r = 0.27, p<0.01). These two different studies demonstrate that sensitivity and resistance exist in normotensive as well as hypertensive subjects and that this phenomenon may be associated with the change in blood pressure with age.

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KEY WORDS • hypertension • salt • race • age • renin

SUBSTANTIAL epidemiological evidence implicates sodium indirectly in the prevalence of hypertension and its cardiovascular sequelae.

Although the beneficial effects of severe sodium restriction in the treatment of hypertension have long been recognized, evidence of blood pressure reduction with modest degrees of sodium restriction is relatively recent. Considerable debate has been engendered regarding the role of sodium in the pathogenesis, maintenance, and treatment of hypertension.

Studies in normotensive subjects have demonstrated a blood pressure rise with massive sodium loading and a decrease in blood pressure with a modest reduction in sodium intake, indicating that the blood pressure response to sodium is heterogeneous. The concepts of sodium sensitivity and resistance of blood pressure have been advanced by several investigators using different techniques and studying different populations. However, the characteristics and mechanisms involved in these responses remain unclear.

We have utilized a standardized protocol of rapid intravascular volume expansion and contraction for clinical and investigative purposes in a large population of normotensive and hypertensive subjects. In addition, we have examined the effect of modest dietary sodium restriction in a number of normotensive families. These two studies provided a unique opportunity to examine sodium sensitivity and resistance of blood pressure in different ways in a large number of carefully characterized normotensive and hypertensive subjects.
Methods

All studies described below were approved by the Indiana University School of Medicine Human Use and Clinical Research Center Committees. Informed consent was duly documented. The designs of the studies have been described in detail previously.15,21-30 The rapid volume expansion and contraction protocol was performed in 378 normotensive subjects and in 198 subjects with essential hypertension in whom secondary forms of hypertension had previously been excluded.21,22 Antihypertensive medications had been withdrawn for 2 weeks or more, and oral contraceptives or estrogens (in normal volunteers) for at least 3 months. All normotensive subjects had blood pressure readings under 140/90 mm Hg at every outpatient visit and throughout hospitalization. All hypertensive subjects had three or more readings above that level, including at least one while they were hospitalized.

Briefly, after a 1-day period of hospital acclimatization, subjects underwent blood sampling, blood pressure measurement, and urine collection beginning at 0800. At that time, they received an intravenous infusion of 2 L of normal (0.9%) saline at a rate of 500 ml/hr.21 At the end of the saline infusion (noon), blood was again sampled, urine collection terminated, and a new collection begun, which lasted until midnight. A third urine collection occurred during the sleep period and ended at 0800 the following morning. On the day after the saline suppression maneuver, sodium and volume depletion was induced by a 10-mEq sodium diet and three doses of oral furosemide (40 mg) given at 1000, 1400, and 1800.22 The stimulatory effect of sodium and volume depletion was assessed in blood samples obtained at 0800 the following morning, after 2 hours of ambulation. The normotensive subjects served as age-, race-, and sex-matched controls for the hypertensive subjects. The protocol also permitted subdivision of the hypertensive group on the basis of plasma renin activity (PRA) as follows: high renin (PRA ≥2.5 ng/ml/3 hr after saline), low renin (PRA ≤4.0 ng/ml/3 hr after sodium and volume depletion and upright posture), and normal renin (normal suppression and stimulation of PRA). Subjects with primary aldosteronism were identified by failure of plasma aldosterone to be suppressed normally (≤10 ng/dl) after saline infusion,21 as well as failure of PRA to be stimulated normally (≥4 ng/ml/3 hr) after the sodium and volume depletion maneuver.22 Trained and certified nurses measured blood pressure.

The purpose of the second study, conducted in normotensive volunteer families, was to examine the feasibility of, and blood pressure response to, modest dietary sodium restriction (=80 mEq/day) in ambulatory subjects living at home. The details of subject recruitment28 and dietary instruction31 have been described previously. In brief, during a baseline period of 1 month, 74 adults each collected five 24-hour urine samples and subsequently received individualized dietary instruction from a research dietician. During the next 3 months, their adherence to dietary sodium restriction was evaluated by 24-hour urine collections every 2 weeks. Blood pressure was measured in the home by trained and certified individuals on the days of urine collection, during the baseline and sodium restriction phases. At each visit three measurements were made while the subjects were seated; an average of the second and third measurements was used for data analysis.

PRA,32 aldosterone,31 and norepinephrine34 were measured by radioassay techniques. Sodium, potassium, and creatinine were measured by established automated techniques. After coding, entry into a computer, and verification, data were analyzed with paired and unpaired t tests, chi-square comparisons, repeated measures analysis of variance and covariance, and multiple regression analysis. Differences were considered to be significant at the level of p < 0.05, except when a two-tailed paired t test was used, in which case p < 0.1 was considered to be significant.

Results

The mean blood pressure responses to the saline infusion and to the sodium and volume depletion maneuver in hypertensive and normotensive subjects are depicted in Figure 1. Although a significant increase in mean arterial blood pressure (MABP) after saline infusion was seen in both groups (p < 0.001), there was no significant difference in the magnitude of the response between normal and hypertensive subjects. As seen in Figure 1, both groups had a decrease in blood pressure after sodium and volume depletion. The response of the hypertensive group was significantly (p < 0.001) greater than that of the normotensive group.

For purposes of further investigation, the MABP at the end of the saline infusion was compared with that observed during upright posture the morning after the sodium and volume depletion maneuver. Individuals with a decrease in MABP of at least 10 mm Hg were designated as sodium-sensitive, and those with less than a 5 mm Hg decrease (including those with an increase in MABP) were considered to be sodium-resistant. Individuals with an intermediate change in
MABP (<10 mm Hg but ≥5 mm Hg) were considered to have indeterminate sodium sensitivity. Figure 2 shows the distribution of normotensive and hypertensive individuals on the basis of their MABP response to rapid expansion and contraction of sodium and extracellular fluid balance. Data in both groups demonstrated a Gaussian distribution. The curves were significantly different (p < 0.001) when compared by the Kolmogorov-Smirnov test. The hypertensive subjects were more sensitive to sodium than the normotensive subjects, but striking heterogeneity was evident in both populations. Table 1 indicates the proportionate responsiveness in the two groups. More than half the normotensive subjects demonstrated sodium resistance, and one fourth were sodium-sensitive. Half the hypertensive subjects were sodium-sensitive, and one third were sodium-resistant. The same proportion (16%) of both groups had an indeterminate response.

The sodium-sensitive and sodium-resistant subgroups within each population were compared on the basis of various characteristics, shown in Table 2. In both groups sodium-sensitive subjects were significantly older than those in whom MABP was resistant to sodium (p < 0.001). Sodium-sensitive subjects within both populations had significantly lower PRA values at baseline (p < 0.01). Since neither PRA nor plasma aldosterone values were normally distributed, a square root transformation was utilized before analysis to provide a more normal distribution and to facilitate data analysis. After the saline infusion, the magnitude of PRA suppression did not differ between the sodium-sensitive and sodium-resistant normotensive subjects, but sodium-resistant hypertensive individuals had significantly higher PRA values at every measurement than did their sodium-sensitive counterparts (p < 0.001). After stimulation of the renin-aldosterone system by sodium and volume depletion, significantly lower PRA was seen in sodium-sensitive subjects, whether normotensive (p < 0.05) or hypertensive (p < 0.001), than in those who were sodium-resistant.

To examine the relationship between age, PRA, and sodium sensitivity or resistance, we performed an analysis of covariance, as well as matching subjects in...
Both groups for age. After adjustment for age in the normotensive group, there was no difference in PRA. However, when the sodium-sensitive and sodium-resistant subgroups were separated into those 40 years of age or under and those who were over 40, the sodium-sensitive subjects in the older group had significantly lower PRA (p < 0.001). In the hypertensive group, correction for age did not change the significant difference (p < 0.001) in PRA.

Although differences in PRA were observed between the sodium-sensitive and sodium-resistant groups, no differences in plasma aldosterone levels were discernible, at baseline or after the suppressive or stimulatory maneuvers. Sodium-resistant hypertensive subjects had higher baseline serum creatinine values in normotensive subjects. At baseline, sodium-resistant normotensive subjects had lower levels of plasma norepinephrine (p < 0.05) than those who were sodium-sensitive. Such differences were not observed after saline suppression or volume depletion or in the hypertensive subjects. Urinary norepinephrine excretion did not differ among any of the groups at any point in the study.

To determine whether demographic characteristics influenced sodium sensitivity or resistance, subjects were subdivided on the basis of race and sex. The results of this analysis are shown in Figure 3. Among normotensive subjects, there were no differences in the responses of any group during the study. Among hypertensive subjects, black women had a significantly greater blood pressure increase with saline infusion than did white women (p < 0.05), but no other differences were seen. Hypertensive subjects were noted to have a significantly greater change in blood pressure after the sodium and volume depletion maneuver than the normotensive subjects (p < 0.001), except for black women (who had the greatest change in blood pressure among the normotensive subgroups), in whom the difference was of borderline significance (p = 0.07, see Figure 3). Sensitivity of blood pressure to sodium was more likely to be observed among hypertensive subjects than among their race- and sex-matched normotensive counterparts (p < 0.025, Table 3). There were significant differences in the distributions of sodium-sensitive and sodium-resistant subjects in the four demographic groups, as shown in Table 3. Among whites, normotensive subjects were more apt to be sodium-resistant, whereas sensitive and resistant responses were more evenly distributed among hypertensive subjects. Among blacks, however, those with hypertension were more frequently sodium-sensitive.

When the hypertensive subjects were compared on the basis of their PRA values (Figure 4), the low-renin group was found to have a significantly greater blood pressure response to saline infusion (p < 0.02) and to sodium and volume depletion (p < 0.05) than the normal- or high-renin subgroups. However, as shown in Table 4, sensitivity of blood pressure to sodium was also observed among individuals in the normal- and high-renin hypertensive subgroups, and resistance was seen in some subjects in the low-renin group. Significantly more hypertensive subjects in the low-renin group were sodium-sensitive than in the other two groups (p < 0.01), when compared by chi-square analysis. Conversely, fewer hypertensive subjects in the low-renin group were sodium-resistant than in the other two groups. No differences were observed between the distributions of sodium-sensitive and sodium-resistant subjects in the normal- and high-renin subgroups.

### Table 2. Differences between Sodium-Sensitive and Sodium-Resistant Subjects

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Normotensive</th>
<th>Hypertensive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitive</td>
<td>Resistant</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>35.3 ± 1.8</td>
<td>26.9 ± 0.8*</td>
</tr>
<tr>
<td>PRA (ng/ml/3 hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.3 ± 0.09</td>
<td>2.6 ± 0.06†</td>
</tr>
<tr>
<td>Suppressed</td>
<td>1.1 ± 0.04</td>
<td>1.2 ± 0.03</td>
</tr>
<tr>
<td>Stimulated</td>
<td>4.7 ± 0.19</td>
<td>5.2 ± 0.11‡</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>5.4 ± 0.2</td>
<td>5.4 ± 0.1</td>
</tr>
<tr>
<td>Suppressed</td>
<td>1.8 ± 0.1</td>
<td>1.7 ± 0.04</td>
</tr>
<tr>
<td>Stimulated</td>
<td>7.7 ± 0.3</td>
<td>7.6 ± 0.2</td>
</tr>
<tr>
<td>Serum creatinine (mg/dl, baseline)</td>
<td>1.02 ± 0.02</td>
<td>1.01 ± 0.01</td>
</tr>
<tr>
<td>Plasma norepinephrine (µg/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.32 ± 0.04</td>
<td>0.22 ± 0.02‡</td>
</tr>
<tr>
<td>Suppressed</td>
<td>0.14 ± 0.02</td>
<td>0.14 ± 0.01</td>
</tr>
<tr>
<td>Stimulated</td>
<td>0.59 ± 0.08</td>
<td>0.45 ± 0.03</td>
</tr>
</tbody>
</table>

Values are means ± SEM. PRA = plasma renin activity.

*p < 0.001, †p < 0.01, ‡p < 0.05.
The relationship between baseline (supine) MABP and the change in blood pressure after furosemide-induced sodium and volume depletion was similar \((r = -0.54, p < 0.001)\) in the hypertensive and normotensive groups. The relationship with age was weaker but highly significant for both normotensive subjects \((r = -0.16, p = 0.002)\) and hypertensive subjects \((r = -0.28, p < 0.001)\). In the hypertensive group the most important predictor of the magnitude of blood pressure change after sodium and volume depletion was baseline PRA \((p < 0.002)\).

The preliminary results of the second study, which measured the blood pressure response to dietary sodium restriction in normotensive adults, have been re-
There were no significant differences between the two groups. The mean age of the sodium-sensitive group compared the blood pressure changes when sodium intake was changed from 9 mEq/day to 249 mEq/day in hypertensive subjects, and arbitrarily separated them into sodium-sensitive and sodium-resistant responses. They observed less sodium excretion during the high-sodium intake in the sodium-sensitive subjects than in the sodium-resistant group. They did not examine normotensive subjects in a similar fashion. Neither did they identify characteristics associated with sodium sensitivity or resistance. Many studies have demonstrated that dietary sodium restriction lowers blood pressure in hypertensive persons, but the heterogeneous nature of responses to sodium restriction has only recently been emphasized, by Longworth et al. They and associates have reported previously. Figure 5 depicts the distribution of the change in MABP for the study population. We have reexamined the heterogeneous blood pressure responses observed in that study and devised an arbitrary definition of blood pressure sensitivity and resistance to sodium, in order to compare responses to dietary sodium restriction with those to saline infusion and volume depletion. We defined sodium sensitivity as a decrease in MABP of at least 3 mm Hg after dietary sodium restriction, and resistance as an increase of at least 3 mm Hg. Although these changes in blood pressure are small, the multiple precise measurements made in the home, by the same observer using the same Hawksley (Lancing, England) Random Zero sphygmomanometer, and compared by repeated measures analysis of variance provide confidence in the significance of even small changes in MABP. The sodium-sensitive subjects (n = 31) had a significantly higher (p<0.001) baseline MABP (89.01 ± 1.5 [SEM] mm Hg) than did those resistant to sodium restriction (n = 13, MABP = 74.5 ± 1.4 mm Hg). The mean age of the sodium-sensitive group (39.8 ± 1.5 yr) was not significantly different from that of the sodium-resistant group (36.3 ± 1.5 yr). There were no significant differences between the two groups in weight or in sodium or potassium excretion — increased age and decreased renal function, as judged by serum creatinine levels, between the two groups.

### Discussion

These studies represent two novel approaches to the assessment of sodium sensitivity and resistance of blood pressure in humans. Kawasaki and colleagues compared the blood pressure changes when sodium intake was changed from 9 mEq/day to 249 mEq/day in hypertensive subjects, and arbitrarily separated them into sodium-sensitive and sodium-resistant responses. They observed less sodium excretion during the high-sodium intake in the sodium-sensitive subjects than in the sodium-resistant group. They did not examine normotensive subjects in a similar fashion. Neither did they identify characteristics associated with sodium sensitivity or resistance. Many studies have demonstrated that dietary sodium restriction lowers blood pressure in hypertensive persons, but the heterogeneous nature of responses to sodium restriction has only recently been emphasized, by Longworth et al. They and associates have reported previously. Figure 5 depicts the distribution of the change in MABP for the study population. We have reexamined the heterogeneous blood pressure responses observed in that study and devised an arbitrary definition of blood pressure sensitivity and resistance to sodium, in order to compare responses to dietary sodium restriction with those to saline infusion and volume depletion. We defined sodium sensitivity as a decrease in MABP of at least 3 mm Hg after dietary sodium restriction, and resistance as an increase of at least 3 mm Hg. Although these changes in blood pressure are small, the multiple precise measurements made in the home, by the same observer using the same Hawksley (Lancing, England) Random Zero sphygmomanometer, and compared by repeated measures analysis of variance provide confidence in the significance of even small changes in MABP. The sodium-sensitive subjects (n = 31) had a significantly higher (p<0.001) baseline MABP (89.01 ± 1.5 [SEM] mm Hg) than did those resistant to sodium restriction (n = 13, MABP = 74.5 ± 1.4 mm Hg). The mean age of the sodium-sensitive group (39.8 ± 1.5 yr) was not significantly different from that of the sodium-resistant group (36.3 ± 1.5 yr). There were no significant differences between the two groups in weight or in sodium or potassium excretion — increased age and decreased renal function, as judged by serum creatinine levels, between the two groups.

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levels than sodium sensitivity. This suggests that more sodium-resistant hypertensive persons have intrinsic renal disease, with the associated increased renin release and vasoconstrictor predominance of angiotensin II affecting their blood pressure elevation. Alternatively, it is conceivable that mild renal impairment, manifested by the modest increase in serum creatinine, prevented these individuals from responding to furosemide appropriately. The efficacy of furosemide in patients with moderate renal impairment makes the latter possibility unlikely.

Plasma norepinephrine levels did not differ significantly between sodium-sensitive and sodium-resistant normotensive subjects, and both sodium-sensitive and sodium-resistant normotensive and hypertensive subjects had the expected decrease in plasma norepinephrine with saline infusion and the expected increase with sodium and volume depletion, as previously observed. However, sodium-sensitive hypertensive subjects in this study had significantly higher plasma norepinephrine levels at baseline than did those who were sodium-resistant. Since the sodium-sensitive hypertensive subjects had a greater urinary sodium excretion during the saline load, we cannot invoke α-adrenergic-mediated sodium reabsorption as an explanation for the blood pressure response. On the other hand, sodium sensitivity may be associated with a chronic increase in sodium balance, which is consistent with the lower PRA observed in this group. Thus, the subtle increase in sodium balance could have enhanced the pressor effects of norepinephrine and thus contributed to sodium sensitivity. Alternatively, a mechanism of increased norepinephrine activity, similar to that which others have reported in subjects with labile hypertension and which we have found to be associated with an exaggerated natriuretic response to a saline load in such subjects, may also have been operative in the sodium-sensitive hypertensive subjects.

A variety of studies have identified individuals at increased risk for the development of hypertension. Black subjects are more likely to develop hypertension than are whites. We examined both populations on the basis of sex and race to discern any differences in sodium sensitivity or resistance. Among the normotensive subjects, we found no demographic differences in blood pressure responses. Among the hypertensive subjects, black women had a greater increase in blood pressure after saline infusion than did white women. All hypertensive subjects had a greater decrease in blood pressure after sodium and volume depletion than did their normotensive counterparts, except for the black female subjects, who had the greatest blood pressure responses among the normotensive subjects. Furthermore, we observed that sodium sensitivity was more common among the hypertensive subjects in all four demographic groups. Thus, the differences in sodium sensitivity and resistance could not be explained on demographic grounds.

Substantial data from a variety of studies indicate that hypertensive persons with low PRA are more apt to be responsive to diuretic therapy than their counterparts with normal or high PRA. Indeed, some investigators have proposed that the decision to institute antihypertensive therapy be based on a patient’s renin status. Although the present study confirms the increased frequency of sodium sensitivity among hypertensive persons with low renin, it is important to emphasize the heterogeneity of blood pressure responses that we observed in all three renin subgroups. Sodium resistance was seen in hypertensive subjects with low renin, as well as sodium sensitivity in subjects with high or normal renin. Thus, sensitivity of blood pressure to sodium cannot be predicted by renin levels alone.

Although the data from the normotensive adults participating in the 3-month study of dietary sodium restriction are less comprehensive than those obtained with the more rapid protocol, and the number of subjects was considerably smaller, the implications of our observations deserve emphasis. These studies demonstrate compliance with moderate dietary sodium restriction during a 3-month period by normotensive adults living at home. They also demonstrate that modest sodium restriction can lower blood pressure in normotensive persons. The heterogeneity of blood pressure responses observed in this study, which utilized a different intervention, confirms the concept of heterogeneity of blood pressure sensitivity and resistance among normotensive persons. Despite the differences in both the population and the study design, sodium sensitivity was again correlated with age. Within this normotensive population, subjects with higher baseline blood pressure were more apt to be sodium-sensitive than those with lower pressure. These results support the concept that the increase in blood pressure with age, even in the normotensive range, appears to be dependent on sodium.

These observations provide new information concerning two different approaches to the definition of sodium sensitivity and resistance. In addition to confirming previous observations concerning certain subgroups or aspects of the sodium sensitivity phenomenon in hypertension, we have provided new evidence of a spectrum of responses to sodium in normotensive subjects. We have also identified similarities and differences between different populations studied in similar ways, which should be helpful in further investigations. As always, these studies pose myriad questions to be answered. The need for specific markers of sodium sensitivity and resistance is obvious. Their identification would provide a major advance in the investigation, treatment, and ultimate prevention of sodium-sensitive hypertension. Finally, these studies, conducted as long as 12 years ago, provide a new opportunity to examine the contribution of sodium sensitivity or resistance to changes in blood pressure with age.

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