Session IV. Demographic Modifiers of Salt–Blood Pressure Relation

Salt Sensitivity and Resistance of Blood Pressure
Age and Race As Factors in Physiological Responses

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To identify characteristics that may contribute to salt sensitivity, we conducted studies of normal subjects who are at risk for hypertension, namely blacks, subjects older than 40 years of age, and first-degree relatives of subjects with essential hypertension. We also formulated definitions for salt sensitivity and resistance with a short-term volume expansion and contraction protocol and additionally from data derived from studies of long-term reduced dietary salt intake. We examined the effects of augmented potassium and calcium intake and also those of sodium as the chloride or the bicarbonate salt. Finally, we sought genetic markers that are associated with salt sensitivity. We found that salt sensitivity is a function of age and is more common in blacks than whites. These groups also have relatively delayed acute salt excretion compared with controls. We were unable to identify effects of gender. Haptoglobin phenotypes (HP 1-1) may facilitate identification of salt-sensitive individuals. A high potassium intake may make individuals less salt sensitive. Sodium chloride and sodium bicarbonate differ in their effects on blood pressure. Sodium chloride augments urinary calcium excretion, but sodium bicarbonate does not. Differences between susceptible and nonsusceptible groups, together with improved knowledge of electrolyte interactions, may facilitate our understanding of salt-sensitive hypertension. (Hypertension 1991;17[suppl I]:I-102–I-108)

Epidemiological data and information from intervention trials suggest that dietary salt (NaCl) intake may be related to the development of hypertension1 and may provide an avenue for dietary intervention, at least in some hypertensive individuals.2–3 Similar compelling observations for potassium4 and calcium have been made.5,6 A common thread among these electrolytes has been suggested7 but not demonstrated. We have studied the effect of administration or restriction of NaCl and have identified racial, genetic, and age-related differences that may be relevant to the heterogeneity in blood pressure responses (salt sensitivity and salt resistance) to dietary NaCl restriction.8–9 Other investigators have found that gender may also be a factor that predicts such responses.9,10 The data underscore the interrelations of NaCl, potassium, and calcium concomitant with both genetic and acquired influences.

Methods

We used four different protocols in the following studies. In the first, large numbers of normotensive and hypertensive white and black men and women were admitted to our clinical research unit, given a fixed NaCl- and calcium-intake diet, and subjected to volume expansion and contraction.8,9 Some of these individuals were monozygotic and dizygotic twins.11 In one study, the protocols were conducted under the condition of either an increased potassium or calcium intake.15 On the first day, the subjects received a 150 mmol sodium intake in the diet and were given an additional 308 mmol sodium i.v. as chloride in the form of 2 l normal saline over 4 hours from 8:00 AM to noon. This procedure in previous studies has markedly and rapidly suppressed the renin–aldosterone axis.16–17 Urine was collected in timed aliquots during and after the NaCl load. On the first day, the subjects received a 150 mmol sodium intake in the diet and were given an additional 308 mmol sodium i.v. as chloride in the form of 2 l normal saline over 4 hours from 8:00 AM to noon. This procedure in previous studies has markedly and rapidly suppressed the renin–aldosterone axis. Urine was collected in timed aliquots during and after the NaCl load. The next day the subjects received a 10 mmol NaCl diet and were given 40 mg furosemide by mouth at 8:00 AM, noon, and 4:00 PM, which markedly stimulated...
the renin-aldosterone system.\textsuperscript{8} Timed aliquots of urine were again measured. At specific intervals, blood pressure was measured and blood collected to determine electrolyte values, renal function, and plasma concentration of renin activity (PRA), aldosterone (ALD), and norepinephrine (NE).

In the second protocol, white and black normotensive men were asked to ingest NaCl at levels of 10, 300, 600, 800, 1,200, and 1,500 mmol/day for times sufficient to achieve sodium and chloride balance. All urine was collected. The aforementioned plasma values and blood pressure were obtained on the balance days.\textsuperscript{18} Some of these white and black subjects were restudied under conditions that prevented potassium loss during NaCl loading.\textsuperscript{18}

For the next two studies, families with monozygotic twin children were recruited. All families were instructed to reduce their dietary NaCl intake to values 50% of those (150 mmol/24 hr) considered normal in Indiana.\textsuperscript{22-26} These families were successful in lowering their NaCl excretion to less than 75 mmol/24 hr for 12 weeks. Their children were then randomly assigned to receive either placebo or NaCl capsules sufficient to replenish their dietary NaCl intake to baseline values. Blood pressure was measured at regular intervals with a Hawksley random-zero sphygmomanometer (Hawksley, England). In similar family studies, the parents and their children were given supplements of potassium to double baseline intake or placebo formulations. The accompanying anion of potassium in these studies was one other than chloride.

In the fourth study, normotensive and hypertensive black and white men and women were given a 60 mmol/24 hr NaCl diet.\textsuperscript{21} In random order, they then received either NaCl or sodium bicarbonate (NaHCO\textsubscript{3}) in the form of mineral water (Staatliche Fachingen, Mainz, FRG) for 7 days, which was sufficient to increase their intake to 120 mmol/24 hr. Blood specimens were obtained and all urine was collected. Blood pressure was measured by an automated method. A preallotted recovery period of at least 1 month elapsed before the subjects were assigned to the alternative regimen.

The statistical analysis of data from these investigations relied on repeated-measures and two- and three-way analysis of variance (ANOVA), regression analysis, linear and nonlinear curve fitting,\textsuperscript{18} and previously described twin analyses.\textsuperscript{11}

Results

Volume Expansion and Contraction Protocol

The baseline observations in the 351 normotensive subjects are tabulated in Table 1. The 24-hour sodium excretion of the described subject groups was not different at baseline. Plasma electrolyte levels and creatinine clearance measurements were not different between blacks and whites (p>0.05). In Figure 1, the natriuretic responses of white and black subjects are compared for awake (8:00 AM-10:00 PM) and asleep (10:00 PM-8:00 AM) periods during volume expansion with saline administration and volume contraction with furosemide administration. During the saline day, whites excreted more sodium than blacks (p<0.05). During that night, blacks excreted more sodium than whites (p<0.05). However, for the 24-hour period (day plus night), whites excreted more sodium than blacks (p<0.05). During furosemide administration, blacks excreted the sodium that they had retained; for that day, sodium excretion of blacks exceeded that of whites (p<0.05).

In Figure 2, similar data are shown for subjects separated by age. During the saline day, the younger subjects were more facile at sodium elimination than older subjects (p<0.05). During the night, the pattern was reversed (p<0.05). With furosemide, older subjects excreted more of their sodium at night.
TABLE 1. Baseline Observations of Normotensive Subjects

<table>
<thead>
<tr>
<th></th>
<th>≤40 Years</th>
<th></th>
<th>≥40 Years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>White</td>
<td>Black</td>
<td>White</td>
<td>Black</td>
</tr>
<tr>
<td>n</td>
<td>240</td>
<td>64</td>
<td>69</td>
<td>17</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>22.2±6.4</td>
<td>24.9±6.3</td>
<td>52.4±8.8</td>
<td>49.2±6.2</td>
</tr>
<tr>
<td>Urinary Na (mmol/24 hr)</td>
<td>153±48</td>
<td>168±50</td>
<td>161±62</td>
<td>154±38</td>
</tr>
<tr>
<td>Urinary K (mmol/24 hr)</td>
<td>60±19</td>
<td>42±12</td>
<td>62±18</td>
<td>46±19</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/3 hr) Baseline</td>
<td>7.8±5.6</td>
<td>6.8±4.2</td>
<td>5.9±5.5</td>
<td>4.0±4.5</td>
</tr>
<tr>
<td>Postsaline</td>
<td>1.5±1.1</td>
<td>1.5±1.0</td>
<td>1.3±1.2</td>
<td>0.8±0.5</td>
</tr>
<tr>
<td>Postfurosemide</td>
<td>32.3±20.3</td>
<td>24.4±12.6</td>
<td>22.2±15.5</td>
<td>10.6±11.0</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl) Baseline</td>
<td>34.0±22.2</td>
<td>31.6±21.8</td>
<td>28.3±17.9</td>
<td>17.9±9.4</td>
</tr>
<tr>
<td>Postsaline</td>
<td>3.2±2.1</td>
<td>4.6±2.8</td>
<td>3.7±2.2</td>
<td>3.8±2.1</td>
</tr>
<tr>
<td>Postfurosemide</td>
<td>73.1±52.8</td>
<td>62.2±44.9</td>
<td>55.1±32.0</td>
<td>39.0±32.2</td>
</tr>
<tr>
<td>Plasma norepinephrine (ng/ml) Baseline</td>
<td>0.23±0.15</td>
<td>0.23±0.11</td>
<td>0.33±0.15</td>
<td>0.44±0.19</td>
</tr>
<tr>
<td>Postsaline</td>
<td>0.13±0.08</td>
<td>0.11±0.05</td>
<td>0.17±0.07</td>
<td>0.16±0.08</td>
</tr>
<tr>
<td>Postfurosemide</td>
<td>0.45±0.27</td>
<td>0.44±0.18</td>
<td>0.68±0.55</td>
<td>0.83±0.45</td>
</tr>
</tbody>
</table>

Values are mean±SD.

compared with younger subjects (p<0.05). The similarities between black subjects and older ones compared with white subjects and younger ones is readily apparent. Although older subjects had lower creatinine clearance values than younger ones, no differences in creatinine clearance were observed between whites and blacks. These analyses were repeated with corrections for body weight and body surface area. Such corrections did not influence the results. In separate analyses, the decrease in creatinine clearance with age was greater in black subjects compared with whites.

PRA values in black subjects were lower compared with whites and were stimulated to a lesser degree by the low sodium diet and furosemide (p<0.05) (Table 1). A similar pattern of lower PRA values was also found in older compared with younger subjects (Table 1). No consistent differences were identified when ALD and NE values were analyzed. In other such investigations summarized in Table 2, we found that whites had higher erythrocyte sodium-lithium countertransport values than blacks. We have not yet studied enough older subjects to determine differences between younger and older persons regarding this variable.

The monozygotic and dizygotic twin analyses showed that body weight, height, body surface area, and blood pressure were influenced by genetic variance in addition to neurohumoral factors, including PRA, ALD, NE, creatinine clearance, sodium, and potassium excretory responses.

Figure 2. Bar chart showing natriuretic responses to furosemide and saline (asleep, awake, and 24-hour periods) of younger and older subjects in terms of sodium excretion.
We also examined our subject population in terms of salt sensitivity and resistance of blood pressure.28 We arbitrarily defined salt sensitivity as greater than a 10 mm Hg decrease in blood pressure, comparing the value obtained immediately after saline infusion with the value obtained the morning after the low NaCl diet and three oral 40-mg doses of furosemide. Those who showed a less than 5 mm Hg change in blood pressure (or an increase) were designated as salt resistant. By those definitions, we found that 32% of the normal black subjects were salt sensitive compared with 30% of the normal white subjects (p>0.05). Conversely, 73% of hypertensive black subjects were salt sensitive compared with 55% of white subjects (p<0.05).28 Salt-sensitive subjects in both normotensive and hypertensive groups were significantly older (p<0.05) than salt-resistant subjects.28

We have sought to determine the effects of gender on the responses to salt loading and salt depletion. Despite the large numbers of subjects in our investigations, we have been unable to identify consistent blood pressure, PRA, ALD, NE, or electrolyte excretory differences between men and women after these provocative maneuvers.

We conducted an analysis to uncover genetic markers that may predict salt sensitivity and resistance of blood pressure.29 We examined commonly used markers to establish the zygosity of twins. Haptoglobin phenotypes are included in such determinations. We found that individuals with the HP 1-1 phenotype were significantly more likely (p<0.05) to be salt-sensitive than other phenotypes, and those with HP 2-2 were more likely to be salt-resistant (Table 3). Heterozygotes with the HP 2-1 phenotype were more likely to be intermediate in sensitivity.

**Dietary Salt Loading Protocol**

Table 4 displays a synopsis of the dietary salt-loading studies in normotensive white and black men.28 The findings indicate that blood pressure first showed an increase at a dietary intake of 800 mmol/24 hr. Thereafter, blacks had a steeper increase in blood pressure than whites. The potassium excretion in response to salt loading increased with increasing levels of salt intake; however, the potassium excretion of white subjects was greater than that of blacks (p<0.05). Repetition of the protocol when potassium supplementation equal to net urinary potassium deficits were given daily to prevent potassium depletion during salt loading significantly attenuated resultant increases in blood pressure (Table 4). The age range of the subjects was such that the effects of age could be tested.

**Dietary Salt Reduction Protocol**

The dietary salt reduction protocols in families with twin children revealed that population mean blood pressure significantly decreased by 2 mm Hg in the adults.21-26 However, there was no concomitant parallel non–salt-reduced control group for the adult subjects. The children that underwent salt reduction showed no decrease in blood pressure compared with those that were salt replenished with slow-release salt capsules.26

**Sodium Chloride–Sodium Bicarbonate Protocol**

The blood pressure results from the double-blind, crossover NaCl and NaHCO3 loading study are shown in Figure 3.21 NaCl did not influence blood pressure in these normal and very mildly hypertensive individuals. Conversely, the administration of NaHCO3 resulted in a slight but significant (p<0.05)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>1-1</th>
<th>2-1</th>
<th>2-2</th>
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<tr>
<td>Change in mean arterial pressure with volume expansion—contraction</td>
<td>34</td>
<td>90</td>
<td>78</td>
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<tr>
<td>BP change (mm Hg)</td>
<td>10.8±2.6</td>
<td>8.6±1.3</td>
<td>5.2±1.2</td>
</tr>
</tbody>
</table>

**Families of monozygotic twins (baseline blood pressure)**

**Adults**

<table>
<thead>
<tr>
<th>Variables</th>
<th>167</th>
<th>200</th>
<th>66</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>122±1</td>
<td>123±1</td>
<td>116±2*</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>75±1</td>
<td>77±1</td>
<td>69±2†</td>
</tr>
</tbody>
</table>

**Children**

<table>
<thead>
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<th>Variables</th>
<th>129</th>
<th>144</th>
<th>32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>109±1</td>
<td>107±1</td>
<td>101±2‡</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>66±1</td>
<td>67±1</td>
<td>60±2‡</td>
</tr>
</tbody>
</table>

Values are mean±SEM. BP, blood pressure.

*p<0.05; †p<0.001; ‡p<0.01 for intragroup differences.
TABLE 4. Blood Pressure of Subjects at Each Level of Sodium Balance

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Blood pressure</th>
<th>Sodium intake (meq/24 hr)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>10</td>
<td>300</td>
</tr>
<tr>
<td>All whites (n=7)</td>
<td>S</td>
<td>111±2</td>
<td>115±2</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>70±2</td>
<td>69±2</td>
</tr>
<tr>
<td>All blacks (n=7)</td>
<td>S</td>
<td>113±2</td>
<td>119±2</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>68±3</td>
<td>71±3</td>
</tr>
<tr>
<td>All subjects (n=14)</td>
<td>S</td>
<td>113±2</td>
<td>117±2</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>69±3</td>
<td>70±2</td>
</tr>
<tr>
<td>Potassium depletion</td>
<td>S</td>
<td>111±2</td>
<td>116±2</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>69±3</td>
<td>71±3</td>
</tr>
<tr>
<td>Potassium repletion</td>
<td>S</td>
<td>114±2</td>
<td>115±3</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>67±5</td>
<td>65±5</td>
</tr>
</tbody>
</table>

Values are mean±SEM. S, systolic; D, diastolic; n, number of subjects.

*Interaction between sodium intake and blood pressure as determined by repeated-measures analysis of variance.

decrease in systolic blood pressure in the hypertensive subjects. No difference in cumulative sodium or potassium excretion was observed when the two regimens were compared. In contrast, a significant difference in urinary calcium excretion was found, even though dietary calcium intake was constant (Figure 4). The administration of NaCl resulted in a greater (p<0.05) urinary calcium excretion (Figure 4) compared with NaHCO3. Moreover, hypertensive subjects excreted more calcium in their urine (p<0.05) compared with normotensive individuals regardless of their sodium regimen. Finally, urinary calcium excretion (Figure 4) was greater in white subjects compared with black subjects (p<0.05). No significant differences between men and women were found regardless of the variable examined. The age range and number of subjects were too small to discern age-related effects.

Discussion

Hypertension and nephrosclerosis are more prevalent in black than white Americans. The association between hypertension and increasing age is well-known. The hereditary nature of essential hypertension in humans is clearly documented. In the present studies, the saline-furosemide protocol revealed consistent abnormalities in all three of those groups of subjects at particular risk for the development of essential hypertension.

Black individuals and older subjects were more sluggish in their natriuretic responses after the saline load compared with white persons and younger subjects. Their sodium excretion was delayed, and they excreted more sodium at night. Furthermore, blacks had a greater response to the natriuretic effect of furosemide, which resulted in their return to a state of sodium balance not different from the white subjects. These data are consistent with relative blunted sodium excretion in blacks compared with whites. Blacks demonstrate a particular responsiveness to the diuretic treatment of hypertension, although in a recent trial, Hawkins et al34 found that the diuretic–metoprolol combination was more effective than high-dose diuretic therapy in blacks regardless of renin status. Blacks have lower renin values than whites. Helmer, and more recently Grim, have speculated that blacks evolved particularly keen mechanisms of sodium retention, which may possibly lead to a disadvantage when NaCl consumption is generous. Such mechanisms would contribute to lower renin values in blacks. Sowers et al35 have identified a relative decrease in renal dopamine production compared with whites, which may be responsible for the greater salt sensitivity in blacks. Furthermore, Aviv et al36,37 have drawn attention to differences between blacks and whites in ion regula-
Sodium sensitivity of blood pressure may be influenced by other ions. Our data show that massive changes in dietary intake of NaCl are necessary to produce changes of blood pressure in normal individuals; we also found that potassium losses may play a role. Potassium loading may lower blood pressure by facilitating natriuresis. When our NaCl-loaded subjects were replenished, they became relatively salt-resistant. Our potassium supplementation studies in families with young children failed to identify a significant effect on blood pressure. The normal blood pressure of all the participants and the nonchloride formulation used may be responsible for these findings. We were unable to show that an increase in dietary calcium confers salt resistance or augments urinary calcium excretion; however, a study was recently published that reported such effects.

In summary, differences in race and age may reveal the mechanism responsible for salt-sensitive hypertension. Racial differences may be the result of altered ion transport at a cellular level. Age-related differences could be more dependent on renal function. The intake and excretion of other electrolytes, including potassium and calcium, perhaps modify the propensity for salt sensitivity.

### References


### FIGURE 4

Bar graph showing final day's calcium excretion (UCaV) in normotensive and hypertensive whites and blacks receiving either sodium chloride (NaCl) or sodium bicarbonate (NaHCO3). UCaV was greater in whites than blacks, hypertensive compared with normotensive subjects, with NaCl compared with NaHCO3. HTN, hypertensive subjects; NTN, normotensive subjects.


**Key Words**: sodium chloride • salt • potassium • calcium • diet • sodium-dependent hypertension • natriuresis • genetics • ethnic differences
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