Sodium and Volume Sensitivity of Blood Pressure
Age and Pressure Change Over Time

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Salt sensitivity has been implicated in the age-related increase in blood pressure. We studied the reproducibility of a rapid method for assessing sodium sensitivity and resistance of blood pressure as well as the effect of age on this phenomenon. Blood pressure after volume expansion with 2 l intravenous saline (0.9%) over 4 hours was compared with that after 1 day of 10 mmol sodium chloride intake and 3 and 40 mg oral doses of furosemide. Normal and hypertensive subjects (n=28) were studied twice within a year. Cross-sectional observations of the effect of age were made from studies in 230 hypertensive and 430 normotensive subjects. Longitudinal observations of blood pressure change over time were made 10 or more years after categorization of sodium responsivity in 31 subjects. The blood pressure response was reproducible in 28 subjects studied twice (r=0.56, p<0.002). Four subjects changed salt-responsiveness status and six were indeterminate on restudy. Sodium sensitivity of blood pressure increased significantly with increasing age in the entire population (n=660, r= —0.35, p<0.001). The relation was more striking in hypertensive subjects (n=230, r= —0.31, p<0.001) in whom a progressive increase in salt sensitivity with decades was seen than in the normotensive group (n=430, r= —0.19, p<0.01) in whom salt sensitivity was not observed until the sixth decade. Salt-sensitive subjects had a significantly greater increase in systolic (p<0.001) and diastolic (p<0.01) pressure over time than those who were salt-resistant. Salt sensitivity is a reproducible phenomenon that is related to the age-associated increase in blood pressure characteristic of industrialized societies. In addition, salt sensitivity can be shown to be a predictor of subsequent, age-related blood pressure increase. (*Hypertension* 1991;18:67-71)

Epidemiological and interventional observations suggest a relation between dietary sodium chloride intake and blood pressure.1 Despite these compelling observations, controversy exists regarding the role of salt in hypertension. A variety of studies have demonstrated heterogeneity of blood pressure responses to sodium and extracellular fluid volume manipulation.2-12 This variability of responsiveness has led to the concepts of sodium sensitivity and resistance of blood pressure and has been demonstrated among normotensive as well as hypertensive subjects.7 Well-differentiated approaches have been used for this characterization, some using dietary alterations and others examining the blood pressure responses to sodium and volume expansion and contraction. The reproducibility of the latter maneuver has not been established.

Although it has long been recognized that blood pressure increases with advancing age, it has only recently been found that this is not a universal phenomenon. In fact, the age-related increase in blood pressure appears to be a feature of industrialized or acculturated societies and is not observed in primitive cultures.1 More recently it has been appreciated that this may be associated with excessive dietary sodium intake since a linear relation between measures of sodium intake and blood pressure has been observed in an elderly population13 and this age-related blood pressure increase is not observed in cultures with low dietary salt consumption.1,14

To evaluate the relation of salt sensitivity to age and to the change in blood pressure over time we used a sodium and volume expansion and contraction protocol in making both cross-sectional and longitudinal observations. Our studies also permitted an assessment of the reproducibility of this approach to the characterization of salt sensitivity and resistance of blood pressure in normotensive and hypertensive humans.
Methods

The protocol used for these studies was approved by the Indiana University Medical Center Committee for Protection of Human Subjects, and all participants provided consent after explanation of the procedures involved. The studies were conducted at the Clinical Research Center. Subjects receiving antihypertensive medication had the agents discontinued for at least 2 weeks before study. Individuals receiving estrogens, nonsteroidal anti-inflammatory agents, or drugs known to influence salt and water or hemodynamic function were excluded as were those with diastolic blood pressure of 115 mm Hg or greater, those with a history of myocardial infarction or stroke in the preceding 6 months, congestive heart failure, serum creatinine of 2.0 mg/dl or greater, or other significant medical illness. The design of the protocol has been described previously.15,16 In brief, a rapid increase in extracellular fluid volume and sodium balance was accomplished by intravenous infusion of 2 l normal (0.9%) sodium chloride at a rate of 500 ml/hr between 8:00 AM and noon after a day of acclimatization to the Clinical Research Center. On the following day, sodium and volume depletion were induced by administration of a 10 mmol/day sodium intake and furosemide, 40 mg by mouth at 10:00 AM, 2:00 PM, and 6:00 PM. Blood sampling and blood pressure measurements were made at 6:00 AM (after overnight recumbency) and 8:00 AM (after 2 hours of ambulation) on each of the 3 study days and, after the saline infusion, at noon. Blood pressure responsiveness to this dynamic maneuver was characterized by comparison of mean arterial pressure observed after saline infusion with that at 8:00 AM on the morning after sodium and volume depletion.7 A decrease in mean arterial pressure of 10 mm Hg or greater was identified as a sodium-sensitive response, whereas a change in blood pressure of 5 mm Hg or less and including those with a rise in pressure, was designated as a salt-resistant response. Individuals with a decrease in mean arterial pressure of 6–9 mm Hg were considered to be indeterminate for classification purposes (16% of both normal and hypertensive groups).7

Three different studies were conducted. In study A, 28 individuals agreed to participate in this protocol twice within a 12-month period to assess the reproducibility of the blood pressure responses to this maneuver. In study B, we evaluated the influence of age on the blood pressure response to the protocol in 430 normal and 230 hypertensive subjects. Normal subjects had blood pressure of less than 140/90 mm Hg on all measurements in outpatient and inpatient settings, whereas hypertensive subjects had a history of antihypertensive therapy or at least three readings of 140/90 mm Hg or greater as outpatients or inpatients. Study C was conducted to assess changes in blood pressure over a period of 10 or more years in 31 normal and hypertensive subjects after their classification as sodium-sensitive or sodium-resistant with this protocol.

After coding, entry into a computer, and verification, data were analyzed by paired and unpaired t tests, x² comparisons, repeated-measures analysis of variance and covariance, and linear regression analyses. Differences were considered to be significant at a level of p<0.05.

Results

Study A: Reproducibility

The results of blood pressure observations in subjects undergoing the study twice within a 1-year period are shown in Figure 1. A reproducible (r=0.56, p<0.002) response was observed among these 28 subjects. Four subjects changed categories on restudy (one from resistant on initial study to sensitive and three who were initially defined as salt-sensitive had resistant responses on repeat study). Six subjects changed to the indeterminate category on restudy after initial classification as salt-sensitive (three) or salt-resistant (three).

Study B: Relation to Age

Among 660 combined normotensive and hypertensive subjects, a highly significant (r= -0.38, p<0.001)
inverse correlation was observed between the blood pressure response used to categorize sodium responsivity and subject age. When the normotensive and hypertensive groups were considered separately, these relations remained (normal, \( n=430 \), \( r=-0.19 \), \( p<0.01 \); hypertensive, \( n=230 \), \( r=-0.31 \), \( p<0.001 \)). When the blood pressure responses of normal and hypertensive subjects were compared by decades of age (Figure 2), differing patterns of response were observed. Hypertensive subjects had a progressive increase in sodium sensitivity with increasing age, whereas in normotensive subjects, increased sodium sensitivity was only seen among those 60 and older. Significantly increased (\( p<0.01 \)) sodium sensitivity was observed in the hypertensive subjects in the 31–40, 41–50, and 51–60 age decades when compared with normotensives of the same age group that was not observed in the youngest group, where both normal and hypertensive groups were relatively salt-resistant, or in the oldest group where both populations were similarly salt-sensitive. This included both the magnitude of blood pressure change (Figure 2) as well as the relative proportion of salt-sensitive and salt-resistant responses. Among normotensive subjects in the age group younger than 30, 65% were salt-resistant and 35% salt-sensitive or indeterminate; in the 50 and older normotensive population, 77% were salt-sensitive or indeterminate and 23% salt-resistant. A similar shift was seen in the hypertensive subjects. Among the less than 30 group, 50% were salt-resistant and 50% were not, whereas in the 50 and older category, 85% were salt-sensitive or indeterminate and 15% were not. These differences were significant when analyzed by \( \chi^2 \) test (normotensive \( \chi^2=23.6, p<0.001 \); hypertensive \( \chi^2=10.4, p<0.001 \)). No relation between body mass index and sodium responsivity was observed among normotensive or hypertensive subjects.

**Study C: Change in Blood Pressure With Time**

Thirty-one subjects who were classified as sodium-resistant (\( n=15 \)) or sodium-sensitive (\( n=16 \)) on their initial study, including 18 normotensive (12 salt-resistant) and 13 hypertensive (3 salt-resistant), had blood pressure measurements made 10 or more years after that study. The changes in blood pressure between the two observations were divided by the number of years intervening to provide a rate of blood pressure change. Baseline and follow-up data as well as the rate of change of pressure are shown in Table 1. Salt-resistant subjects were significantly (\( p<0.02 \)) younger. They also had significantly lower systolic and diastolic pressures at both initial and follow-up visits than their sodium-sensitive counterparts. The most striking differences between these groups were seen in the changes in systolic and mean
arterial pressure over time. The resistant subjects had a mean decrease in systolic pressure, averaging -0.32±0.15 mm Hg/year, where the sensitive subjects had a mean increase of 1.42±0.39 mm Hg/year (p<0.001). Over the interval between the two observations, the resistant group had an average change in mean arterial pressure of -0.2±1.8 mm Hg, whereas the change in the sensitive group was 10.2±3.6 mm Hg for the same period (p<0.02). The change in diastolic pressure for the resistant subjects was 0.16±0.23 mm Hg/year, whereas that for the sensitive group was 0.66±0.33 mm Hg/year (p=0.23). When an analysis of covariance was conducted correcting for the age difference between the groups, all three measures of blood pressure change remained significantly different (systolic p<0.001, diastolic p<0.01, mean arterial p<0.001). Figure 3 compares the rates of change in blood pressure between normal and hypertensive subjects, where no significant differences were observed, as well as the significant differences seen between sodium-sensitive and sodium-resistant groups in unadjusted systolic and mean arterial pressures.

Discussion

The age-related increase in blood pressure seen in acculturated societies has been thought to be related to excessive dietary sodium intake. However, sodium sensitivity of blood pressure is not uniform throughout the population. The present observations provide new evidence for a role of sodium sensitivity in the age- and time-related changes in blood pressure among both normotensive and hypertensive subjects. These studies also strengthen the validity and implications of one approach to the assessment of salt sensitivity and resistance of blood pressure in hypertensive as well as normotensive subjects. Sharma and colleagues have recently demonstrated the reproducibility of salt-sensitivity classification based on the change in blood pressure after 7 days of high (220 mmol/day) and 7 days of low (20 mmol/day) sodium intake. They found that the responses of 15 normotensive subjects to dietary sodium manipulation were variable between individuals but highly reproducible for a given subject. The present study demonstrates similar reproducibility for a different approach to the classification of sodium and volume responsibility of blood pressure. However, four subjects changed salt-responsivity classification on restudy, and six were classified as indeterminate on restudy who had been initially classified as sensitive (three) or resistant (three). The majority of subjects studied (18 of 28) were consistent in their responses. Changes in magnitude of response of less than 5 mm Hg could account for the transition from responsive to indeterminate categories in the six subjects showing this change. The explanation for the more marked change in categorization that was observed in four subjects is not clear.

A substantial body of epidemiological evidence suggests that the increase in blood pressure with age may be influenced by sodium intake. To our knowledge, the observations of the present longitudinal study are the first to demonstrate a relation between alterations in blood pressure over time and sodium sensitivity in a prospective fashion. Moreover, our observations indicate that sodium sensitivity of blood pressure, independent of initial blood pressure levels (hypertensive or normotensive), is associated with a greater subsequent rise in blood pressure with time than is sodium resistance. Finally, these differences are also independent of age. The present studies also permit examination of another aspect of the age-related alterations in blood pressure, namely the cross-sectional observations.

Among the normotensive subjects sodium sensitivity, as assessed by the present study, was not consistently observed until age 60, whereas in hypertensive subjects, there was a progressive increase in salt sensitivity of blood pressure throughout the age spectrum studied. We have previously observed a modest age-related increase in blood pressure responsiveness to dietary sodium restriction among normotensive adults (r=0.23, p<0.05). In the youngest age group of the present studies, no differences in sodium responsibility were seen between normal and hypertensive subgroups. This appears to be due to the relative preponderance of salt-resistant subjects at younger ages. Furthermore, this lack of difference in salt responsivity was observed despite significant differences in blood pressure. In the 21-30-year-old age group and the next 2 decades, hyper-
tensive subjects were significantly ($p<0.01$ and $<0.001$) more salt sensitive than the normotensive subjects despite comparable differences in blood pressure between the subgroups as observed in the youngest and oldest decades. Finally, in those over 60 years of age the greatest salt sensitivity was observed, with no significant difference between the responses of normal and hypertensive subgroups, again despite marked differences in blood pressure. These observations thus indicate that sodium responsibility of blood pressure is independent of the blood pressure level itself. The relative absence of salt sensitivity in the younger populations suggests that an age-related component may be necessary for the demonstration of salt sensitivity of blood pressure. It has been suggested that alterations in renal tubular function or genetic factors may be involved in salt sensitivity as well. Perhaps these are sensitizing factors for the sodium- and age-related blood pressure increase.

In summary, the present study demonstrates that the blood pressure response to volume expansion induced by intravenous saline administration compared with rapid sodium and volume depletion secondary to a day of low sodium intake and three doses of furosemide is reproducible and is influenced by age in both normal and hypertensive humans. Moreover the presence of sodium sensitivity, defined by the approach used in these studies, predicts a greater subsequent increase in blood pressure with time than does sodium resistance. These observations have important implications for our understanding of the pathogenesis, treatment, and ultimate prevention of hypertension.

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