Salt Sensitivity, Pulse Pressure, and Death in Normal and Hypertensive Humans

Myron H. Weinberger, Naomi S. Fineberg, S. Edwin Fineberg, Morris Weinberger

Abstract—Although factors such as age, blood pressure, and its responsiveness to changes in sodium balance and extracellular fluid volume status (salt sensitivity) are associated with an increased risk of end-organ disease and cardiovascular events in hypertensive subjects, no such relationship with mortality has been demonstrated for salt sensitivity in normotensive subjects. We conducted long-term follow-up of 430 normal and 278 hypertensive subjects in whom assessment of salt sensitivity of blood pressure was performed as long as 27 years ago. We ascertained the status of 596 subjects (85% of the total population), 123 (21%) of whom had died. The following initial measurements were significantly ($P<0.002$) associated with subjects who had died compared with subjects known to be alive: age at study, pulse pressure, systolic, diastolic, and mean arterial pressures, hypertension, salt sensitivity, baseline renin levels, and body mass index (but not body weight). A stepwise logistic regression found the following independent predictors of death (odds ratio, 95% CI): age at initial study (1.08, 1.06 to 1.10), baseline blood pressure (1.03, 1.01 to 1.04), sodium sensitivity (1.73, 1.02 to 2.94), and male gender (1.91, 1.15 to 3.17). When survival curves were examined, normotensive salt-sensitive subjects aged $\geq$25 years when initially studied were found to have a cumulative mortality similar to that of hypertensive subjects, whereas salt-resistant normotensive subjects had increased survival ($P<0.001$). These observations provide unique evidence of a relationship between salt sensitivity and mortality that is independent of elevated blood pressure. (Hypertension. 2001;37[part 2]:429-432.)

Key Words: sodium $\bullet$ pulse $\bullet$ mortality $\bullet$ blood pressure $\bullet$ hypertension, essential

Individuals with elevated blood pressure are at increased risk for cardiovascular (CV) events and death. Tedious and massive outcome studies have been mounted to demonstrate the benefit of various interventions in high-risk populations, but these studies have relied largely on surrogate measures to infer preventive or therapeutic benefits. In addition to systolic, diastolic, and mean arterial pressures, such surrogates have included pulse pressure, nocturnal blood pressure patterns, and responses of blood pressure to the manipulation of sodium and extracellular fluid balance by different techniques. These techniques have permitted identification of salt sensitivity and salt resistance or insensitivity among normotensive as well as hypertensive subjects.1–4

Despite differences in the techniques and criteria used for the definition of salt sensitivity and resistance by different investigators, congruence and reproducibility of the responses have been demonstrated in the majority of carefully performed studies.5 A variety of demographic, physiological, and genetic characteristics differentiate these groups.5 Recent observations suggest that differences also exist in the end-organ effects.6,7 For example, salt sensitivity has been linked to an increased risk for the development of left ventricular hypertrophy, proteinuria, and a blunted nocturnal decline in blood pressure ("non-dipping").6–8 In addition, among Japanese hypertensive subjects, CV events were found to be twice as common among salt-sensitive hypertensives compared with their salt-resistant cohort.6

More than 25 years ago, we conducted studies in 430 normal and 278 hypertensive subjects that enabled us to define salt sensitivity and resistance and to identify the phenomenon for the first time in normotensive subjects.4 These studies also demonstrated the congruence of blood pressure responses to a rapid sodium and volume manipulation maneuver with dietary sodium alterations.5 Our present study enabled us to locate or obtain information on the vital status of 85% of the original cohort. We sought to test the hypothesis that salt sensitivity in normotensive as well as in hypertensive subjects is associated with an increased risk of CV events and reduced survival. We now report the factors that we found to be associated with death in 123 subjects.

Methods

The study cohort consisted of 708 subjects aged 18 to 80 (34±15 [mean±SD]) years when initially studied; it included 313 women (44.2%), 178 African Americans (25%), 278 hypertensive subjects (39.3%), and 338 subjects who were subsequently deemed to be salt sensitive (50%) (see below).4 The assessment of the blood pressure...
response to salt at the initial study required the withdrawal of antihypertensive drug therapy for at least 2 weeks in hypertensive subjects and excluded women receiving oral contraceptives or hormone replacement therapy. On the day after admission to the Clinical Research Center, sodium loading and volume expansion were achieved by the intravenous administration of 2 L normal (0.9%) saline between 8:00 AM and noon. The average of the last 2 of 3 blood pressure measurements made after 2 hours of ambulation before the saline infusion was taken as the baseline “presaline” mean arterial blood pressure (MABP). MABP was derived from the arterial blood pressure (MABP). MABP was derived from the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort (n=708)</th>
<th>Alive (n=473)</th>
<th>Dead (n=123)</th>
<th>Unknown (n=112)</th>
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</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>34±15</td>
<td>31±13</td>
<td>48±14*</td>
<td>29±10*</td>
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<tr>
<td>Follow-up, y</td>
<td>26±6</td>
<td>23±4</td>
<td>15.6±6† NA</td>
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<td>Female, %</td>
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<td>45.0</td>
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<td>A-A, %</td>
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<td>HBP, %</td>
<td>39.3</td>
<td>33.8</td>
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<td>73.4*</td>
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Values are mean±SD or as indicated. A-A indicates African Americans; HBP, hypertensive subjects; S, salt-sensitive subjects; and NA, not applicable.

Results

Information was obtained for 596 subjects representing 85% of the original cohort, of whom 123 (20.6%) had died. The 112 subjects who could not be located (15% of the population) were significantly younger at the time of the initial study (26.1±1.1 years, versus 23.4±1.5 years, P<0.001) than were those who survived. There were no significant differences in body weight (152.1±7.5 kg versus 151.0±7.6 kg, respectively; P=0.238) but not body weight (75.5±15.2 versus 73.5±17.1 kg, respectively; P=0.238) when they were initially studied. Although the data are not presented, the men were significantly (P<0.001) taller than the women, but there were no differences in height between deceased and surviving subjects. Initial study blood pressures (Table 3) were significantly higher among those who subsequently died compared with those who survived for baseline cause of death were obtained from death certificates and from the next of kin when available. Subjects were classed as alive, dead, or unknown on the basis of the most recent information. CV death was defined as death due to myocardial infarction, ischemic heart disease, rheumatic heart disease, congestive heart failure, cardiogenic shock, cardiac arrhythmia, cardiac arrest, cerebrovascular disease, or stroke.

Subject identification information did not include an entire name. Raw data identifying the subject by name was kept in a locked room with limited access. Statistical analyses were conducted with the use of t tests, the Fisher exact test, forward stepwise logistic regression, and forward stepwise Cox proportional hazards regression. Because the date of death could not be ascertained for all subjects, we performed logistic regression analyses for all decedents and Cox proportional hazards analyses for those for whom the date of death was known. Kaplan-Meier survival curves were constructed and compared with the use of a log rank test. We also examined survival of the population adjusted for age into 3 roughly equal groups (<25 years, 25 to 45 years, and >45 years at initial study). In the case of measures that were not normally distributed, such as plasma renin activity,4 square root transformation was performed to normalize the data for analyses. Data are presented as mean±SD. A value of P<0.05 was considered to be significant. For hazard analyses, we present odds ratios (ORs) and 95% CIs.

### Table 1. Characteristics of Population and Subgroups at Initial Study

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Values are mean±SD or as indicated. A-A indicates African Americans; HBP, hypertensive subjects; S, salt-sensitive subjects; and NA, not applicable.

### Table 2. Body Weight, BMI, and Plasma Renin Activity at Initial Study

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<th>Dead (n=123)</th>
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<tr>
<td>Weight, kg</td>
<td>73.8±17.3</td>
<td>73.5±17.1</td>
<td>75.5±15.2</td>
<td>73.2±19.7</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.7±5.6</td>
<td>25.5±5.6</td>
<td>26.9±5.2*</td>
<td>25.5±5.9</td>
</tr>
<tr>
<td>Renin, ng - mL⁻¹ - 180 min⁻¹</td>
<td>6.8±6.0</td>
<td>7.1±6.2</td>
<td>5.5±5.3† NA</td>
<td>7.0±5.7</td>
</tr>
</tbody>
</table>

Values are mean±SD. BMI indicates body mass index.

P<0.05 and P<0.01.
systolic (136±28 versus 119±15 mm Hg, respectively; P<0.001), diastolic (87±17 versus 76±13, respectively; P<0.001), mean arterial (103±20 versus 90±14, respectively; P<0.001), and pulse (49±15 versus 43±11, respectively; P<0.001) pressures. Renin levels at baseline, shown in Table 2, were significantly lower for those who subsequently died than for those who survived (5.5±5.3 versus 7.1±6.2 ng/mL for 180 minutes, respectively; P=0.011). The subjects who could not be ascertained were not different from the group who survived for any measurements made at the time of the initial study, except for race and age, as shown in Table 1.

Forward stepwise logistic regression analysis with death as an outcome yielded 4 variables of significance: baseline MABP (OR 1.03, CI 1.01 to 1.04; P=0.001), age at time of initial study (OR 1.08, CI 1.06 to 1.10; P<0.001), salt sensitivity (OR 1.73, CI 1.02 to 2.94; P=0.002), and male gender (OR 1.91, CI 1.15 to 3.17; P=0.012). Cox proportional hazards regression was used to examine time to death and yielded age at initial study (OR 1.06, CI 1.04 to 1.07; P<0.001) and baseline diastolic pressure (OR 1.03, CI 1.01 to 1.04; P<0.001) as independent predictors. In addition, an interaction term reflecting the relationship between sodium sensitivity and hypertension, as seen in the Kaplan-Meier cumulative survival analysis (Figure), was significant. This term was coded as 1 for subjects who were normotensive and sodium resistant and as −1 for all others. The hazards ratio was 0.56 (CI 0.38 to 0.82, P=0.002), indicating that being normotensive and sodium resistant at the initial study improved survival.

As shown in the Figure, which depicts Kaplan-Meier cumulative survival curves analyzed by log rank test, the survival curves for individuals who were normotensive and salt sensitive at the time of the initial study were not different from those of initially hypertensive subjects. The only group in whom survival was significantly better (P<0.001) was normotensive subjects in whom salt resistance of blood pressure was initially observed. When the age-stratified Kaplan-Meier survival analyses were performed in the 3 age groups and pooled, the log rank test was significant (P<0.006). Within age groups, the effect of salt sensitivity on survival was borderline for the 2 older groups (P=0.065 and P=0.075) and not significant in those aged <25 years at the time of the initial study.

CV causes of death were identified for 60 of the decedents. When those dying of non-CV causes were combined with those known to be alive and compared with the CV group, the following respective differences emerged: age at initial study (50.3±13.9 versus 32.8±14 years, P<0.001), body weight (79.1±15.4 versus 73.4±16.9 kg, P<0.014), body mass index (28.2±5.6 versus 25.4±4.4, P<0.003), salt sensitivity (73.7% versus 47.6%, P<0.001), and hypertensive status (78.3% versus 35.8%, P<0.001). All measures of baseline blood pressure (systolic, diastolic, mean arterial, and pulse pressures) were significantly (P<0.001) higher in the CV death group. Baseline plasma renin activity was lower in the CV group (4.8±4.4 versus 7.0±6.2 ng/mL for 180 minutes, P=0.001).

Discussion

The opportunity to obtain long-term (almost 30-year) follow-up data on a large diverse cohort of initially normotensive and hypertensive individuals has provided insight into factors associated with subsequent mortality. Not surprisingly, long-recognized factors such as age, gender, body mass index, and all measures of blood pressure (systolic, diastolic, mean arterial, and pulse pressures) were associated with a significant increase in the risk of death in our sample. This provides reassurance regarding the representativeness of our study cohort and its similarity with other populations. In addition, for the first time, salt sensitivity of blood pressure was found to be associated with mortality in normotensive as well as hypertensive subjects who were aged >25 years when they were initially studied. This finding is similar to previous observations in a smaller population of Japanese hypertensive subjects.6 However, to our knowledge, this is the first demonstration of the increased risk of salt sensitivity in nonhypertensive individuals. Additional information is needed to understand the mechanisms by which salt sensitivity may contribute to mortality.

Among hypertensive subjects, salt sensitivity of blood pressure has been shown to increase with increasing age and to be more frequent in hypertensive than in normotensive subjects.4 Age and blood pressure were associated with increased risk of mortality in our sample, as has been shown in many other studies. Thus, the link between salt sensitivity and increased risk of death among hypertensive subjects is
not surprising. However, the observation of a decreased survival among initially normotensive individuals aged >25 years who were salt sensitive requires further consideration.

We have previously reported that 26% of our normotensive population was salt sensitive. We have also observed, during a 10-year follow-up of a small mixed group of subjects previously assessed for salt responsiveness of blood pressure, a significantly (P<0.001) greater rise in blood pressure with age and over time among those initially identified as salt sensitive compared with those who were salt resistant. These observations suggest that salt-sensitive normotensive subjects may be at an increased risk for subsequent age-related hypertension. The ongoing analyses of the surviving subjects in our follow-up study may permit us to test the hypothesis that salt-sensitive normotensive subjects are more likely to develop hypertension with aging. This suggestion is supported by epidemiological findings indicating that age-related increases in blood pressure are observed only in societies in which the ambient sodium intake exceeds 50 to 100 mmol/d. If salt sensitivity of blood pressure is found to be associated with the future development of hypertension, it is possible that intervention in susceptible individuals, by reducing salt intake, could prevent or delay the subsequent age-related increase in blood pressure, the development of hypertension, and the increased risk of CV events and death.

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References
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