Effects of Dietary Sodium Reduction on Blood Pressure in Subjects With Resistant Hypertension: Results From a Randomized Trial

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Abstract—Observational studies indicate a significant relation between dietary sodium and level of blood pressure. However, the role of salt sensitivity in the development of resistant hypertension is unknown. The present study examined the effects of dietary salt restriction on office and 24-hour ambulatory blood pressure in subjects with resistant hypertension. Twelve subjects with resistant hypertension entered into a randomized crossover evaluation of low (50 mmol/24 hours×7 days) and high sodium diets (250 mmol/24 hours×7 days) separated by a 2-week washout period. Brain natriuretic peptide; plasma renin activity; 24-hour urinary aldosterone, sodium, and potassium; 24-hour ambulatory blood pressure monitoring; aortic pulse wave velocity; and augmentation index were compared between dietary treatment periods. At baseline, subjects were on an average of 3.4±0.5 antihypertensive medications with a mean office BP of 145.8±10.8/83.9±11.2 mm Hg. Mean urinary sodium excretion was 46.1±26.8 versus 252.2±64.6 mmol/24 hours during low- versus high-salt intake. Low- compared to high-salt diet decreased office systolic and diastolic blood pressure by 22.7 and 9.1 mm Hg, respectively. Plasma renin activity increased whereas brain natriuretic peptide and creatinine clearance decreased during low-salt intake, indicative of intravascular volume reduction. These results indicate that excessive dietary sodium ingestion contributes importantly to resistance to antihypertensive treatment. Strategies to substantially reduce dietary salt intake should be part of the overall treatment of resistant hypertension. (Hypertension. 2009;54:475-481.)

Key Words: blood pressure ■ hypertension ■ resistant hypertension ■ sodium ■ diet

Observational studies and clinical trials performed in general populations indicate that a higher salt intake is associated with higher blood pressure (BP). For example, in the INTERSALT multi-national evaluation, which included both normotensive and hypertensive subjects, differences in dietary sodium ingestion of 100 mmol per day were associated with differences in systolic BP of approximately 2.2 mm Hg after adjustment for age, sex, potassium excretion, body mass index, and alcohol intake.1 When limited to hypertensive subjects, the positive relation between salt ingestion and level of BP appears to be stronger. Meta-analyses of low-salt intervention trials indicate decreases in systolic BP of 3.7 to 7.0 mm Hg and diastolic BP of 0.9 to 2.5 mm Hg in hypertensive patients.2-5

Resistant hypertension, defined as BP that remains above goal in spite of use of 3 antihypertensive medications is a common clinical problem.6 Clinical trials suggest that 20% to 30% of hypertensive subjects may be resistant to multi-drug antihypertensive regimens.7,8 Although the effects of reducing dietary sodium intake on office BP levels have been evaluated in general hypertensive patients, studies examining the role of dietary salt in patients with resistant hypertension have not been done. The aim of the present study was to determine the effects of dietary sodium restriction on office and 24-hour ambulatory BP in patients with resistant hypertension. Potential mechanisms of salt-related effects on BP (ie, volume retention and changes in vascular stiffness) were also explored.

Methods

Subjects

Consecutive subjects referred to the University of Alabama at Birmingham (UAB) Hypertension Clinic for resistant hypertension were recruited. The protocol was approved by UAB’s Institutional Review Board for Human Use and all subjects provided written informed consent before study participation. Resistant hypertension was defined as uncontrolled hypertension (systolic BP >140 or diastolic BP >90 mm Hg) determined at ≥2 clinic visits despite the use of ≥3 antihypertensive medications at pharmacologically effec-
tive doses. All subjects had been on a stable antihypertensive regimen, including a thiazide-type diuretic, for at least 4 weeks before enrollment. No medications were discontinued before evaluation. At the time of the initial screening, all patients were queried about prior dietary recommendations.

Seated clinic BP was measured manually with a mercury column sphygmomanometer and an appropriate size cuff after 5 minutes of rest according to AHA guidelines. Three readings were made at each visit, and the average of the last 2 were considered for analysis. All subjects underwent a validated noninvasive ambulatory BP monitoring (ABPM) (Suntech). The monitor recorded systolic and diastolic BP every 20 minutes during the daytime (6 AM to 10 PM) and every 30 minutes at night (10 PM to 6 AM). The ambulatory data were included in the analysis if the monitoring period was ≥20 hours and there were no periods of ≥2 hours without measurements. Subjects with a history of atherosclerotic disease (myocardial infarction or stroke in the previous 6 months), congestive heart failure, or diabetes on insulin treatment were excluded from study participation. Patients with an office BP >160/100 mm Hg were excluded from participating because of risk of severely elevated BP during high dietary salt ingestion.

Design
The protocol consisted of a 4-week, randomized, crossover evaluation. Participants were randomized to the low- or high-salt diet for 1 week. Subjects resumed their regular diet during the 2-week washout period before crossing over to the opposite diet for the remaining 1 week of the protocol. All of the low-salt meals and snacks were provided to the subject by the General Clinical Research Center nutritional staff. The low-salt meals were formulated to provide 50 mmol of sodium per day. Two diets with different calorie amounts (2000 or 2500) were provided. The 2000 calorie diet was composed of 31.2% fat, 48.4% carbohydrate, and 20.4% protein and included 3699 mg of potassium, 610 mg of calcium, 319 mg of magnesium, and 1445 mg of phosphorus. The 2500 calorie diet was composed of 30.8% fat, 50.4% carbohydrate, and 18.8% protein and included 4149 mg of potassium, 681 mg of calcium, 374 mg of magnesium, and 1741 mg of phosphorus. Percentages of macronutrients were similar to a typical American diet. The calorie levels were based on the subject’s height, weight, and age and designed to maintain each subject’s baseline body weight. The sodium content was slightly below the 65 mmol a day that is currently recommended for people who are considered salt-sensitive (blacks, middle aged and older individuals, and people with hypertension, diabetes, or chronic kidney disease). During high dietary salt intake, NaCl tablets (6 g/24 hours) were added to the subject’s regular diet with the intention to increase dietary sodium intake to >250 mmol/d. Body weight, office BP, and 24-hour ABPM, biochemical evaluation, pulse wave analysis, and pulse wave velocity (PWV) were determined immediately before randomization and at the end of each 1-week dietary intervention.

Laboratory Assessment
Biochemical evaluation was performed on morning blood specimens obtained from ambulatory patients after sitting for 5 minutes. Assays included: serum potassium, creatinine, brain natriuretic peptide (BNP), plasma aldosterone concentration (PAC), and plasma renin activity (PRA). Twenty-four-hour urine collections were obtained for measurement of aldosterone (Ualdo), sodium, potassium, and creatinine.

BNP, PAC, PRA, and Ualdo levels were measured by radioimmunoassay (Mayo Clinic Laboratories). The reference range for upright PRA is 1.31 to 3.95 ng/mL/h (0.36 to 1.10 ng/L/s), for Ualdo 2 to 16 µg/24 hours (5.5 to 44 nmol/24 hours), and for BNP 0 to 100 pg/mL (0 to 100 ng/L).

Pulse Wave Analysis and Pulse Wave Velocity
Aortic PWV was calculated from measurements of common carotid and femoral artery wave-forms using an automatic application tonometry-based device, ie, the SphygmoCor system (AtCor Medi-cal). ECG gated pulse waveforms were obtained sequentially over the common carotid and femoral arteries. PWV was calculated as the distance between recording sites measured over the surface of the body, divided by the time interval between the feet of the pressure waves.

Central artery waveforms were obtained with the same device and derived from the radial artery waveform and pressure by using a transfer function validated previously during catheterization studies. The point at which the central aortic pressure becomes augmented by wave reflection is recognized by a computer program, and the degree of increase is expressed as the aortic augmentation index (AIx), which is quantified as a percentage of aortic pulse pressure. PWV and AIx are markers of arterial stiffness.

Statistical Analysis
Values are expressed as mean±SD unless stated otherwise. Analyses were done using mixed modeling for repeated measures via PROC MIXED in SAS. An unstructured covariance structure was used to model the correlation between time 1 and time 2 readings. To test for time order effects, both the treatment and treatment order were included in the model. If the treatment order was not found to be significant, treatment order was dropped from the model. If the treatment order was found significant, an individual 95% confidence interval on the change in the means was obtained. Changes in 24-hour ABPM were considered primary end points. Probability values <0.05 were considered significant. Test for normality of the distribution of the readings were performed separately for each treatment group. For variables found to be not normally distributed (PRA and PWV), PROC MIXED was not used.

Time order was assumed to not be significant, and the sign test was used to test the mean differences. Exact binomial confidence interval for the median is reported for these variables, if found significant, instead of the usual 95% confidence interval for the mean. The study had the power to detect a clinic treatment effect of 13.1/6.7 mm Hg with a power of 90% at the level of 5%, assuming that the SD of the difference for 24-hour systolic BP was 12.7 mm Hg and for 24-hour diastolic BP was 6.5 mm Hg. After the above analysis, a Bonferroni-Holm step-down correction was performed to check the robustness of the results.

Results
Thirteen subjects were recruited and enrolled with 12 completing, including 8 females and 6 blacks. One subject was withdrawn because of his BP being too high to receive the high-salt diet. Mean age was 55.5±9.4 years. Baseline characteristics are presented in Table 1. Overall, subjects were on an average of 3.4±0.5 medications, which included a thiazide diuretic (hydrochlorothiazide 25 mg daily) and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker for all subjects. The mean office BP at baseline was 145.8±10.8/83.9±11.2 mm Hg. All medications, including hydrochlorothiazide, were continued throughout the study protocol. All subjects reported having been previously advised by one or more of their physicians to reduce their dietary salt intake and all reported having done so. None had received expert dietary consultation.

Mean urinary sodium excretion during the low-salt diet was 46.1±26.8 compared to 252.2±64.6 mmol/24 hours during high-salt diet, confirming accomplishment of intended differences in dietary sodium intake. PRA increased significantly after low-salt ingestion, whereas BNP decreased significantly (Table 2). Body weight and creatinine clearance decreased significantly with low- compared to high-salt diet.

Systolic and diastolic BP were distributed normally for each treatment. When treatment group and treatment se-
The above results were not adjusted for multiple testing and hence would likely inflate the probability of committing a type I error. To check the robustness of these results, we performed a Bonferroni-Holm step-down correction adjusting for the fact that 20 variables were tested (Table 2). After the correction, body weight, serum potassium, PRA, UAldo, UK, creatinine clearance, and diastolic office BP were no longer significant. However, office systolic BP and all ABPM measurements remained significant.

Discussion

This is the first study to assess the effects of low dietary salt ingestion in subjects with resistant hypertension. Dietary salt...
restriction substantially reduced both office and 24-hour ambulatory BP. The degree of BP reduction induced by dietary salt restriction in this group of subjects with resistant hypertension is considerably larger than reductions observed in normotensive populations or in cohorts of general hypertensive subjects. These results demonstrate that excessive dietary salt ingestion contributes importantly to elevated BP levels in patients with resistant hypertension.

Observational studies of large unselected cohorts indicate a positive correlation between dietary salt intake and BP. In the INTERSALT Cooperative Research study, urinary sodium was related to the slope of BP increases with age, but not to median BP or prevalence of hypertension.1 In this study, increases in 100 mmol per day of dietary sodium were associated with increases in systolic BP of 2.2 mm Hg. Similarly, intervention studies indicate that reductions in dietary salt intake by 50 mmol per day reduce mean systolic BP in normotensive subjects by approximately 1.7 to 2.9 mm Hg.15,16

Studies of hypertensive populations suggest a stronger relation between dietary salt and severity of hypertension than observed in normotensive subjects. In evaluations of hypertensive cohorts, dietary salt restriction lowers systolic BP by 2 to 10 mm Hg and diastolic BP by 1 to 6 mm Hg.17–33 For example, in the Dietary Approaches to Stop Hypertension (DASH) trial, 412 patients with mild-moderate hypertension (range 120 to 159/80 to 95 mm Hg) were randomized to the DASH diet (which is rich in vegetables, fruits, and low-fat dairy products) or control diet.17 Each group received increasing levels of dietary sodium (50, 100, 150 mmol/24 hours) for 30 consecutive days in a crossover design. As compared with the control diet during high dietary sodium intake, the DASH diet and low dietary sodium intake lowered systolic BP by 11.5 mm Hg in participants with hypertension (12.6 mm Hg for blacks; 9.5 mm Hg for others).

In an evaluation of subjects with severe hypertension, Fotherby et al assessed the BP effects of low dietary salt ingestion in 17 untreated hypertensive subjects with a mean office BP of 176±17/96±11 mm Hg.20 After 5 weeks of low-salt diet (80 to 100 mmol/24 hours), 24-hour systolic and diastolic BP decreased by 5 and 2 mm Hg, respectively. In a study by Gavras et al, a much greater BP reduction was achieved with extreme dietary salt restriction in combination with intense diuretic therapy in subjects with uncontrolled BP on maximal doses of at least 2 agents (a diuretic and a sympatholytic agent).34 In this study, BP decreased on average by 21/7 mm Hg during ingestion of a diet limited to 10 mmol of sodium with concurrent administration of either hydrochlorothiazide 100 mg or furosemide 80 to 200 mg daily. In the current study, we observed a similar degree of BP reduction with less severe sodium restriction (50 mmol/24 hours) and with continuation of hydrochlorothiazide as conventionally dosed.

The current results suggest that patients with resistant hypertension are exquisitely salt sensitive, manifesting a mean reduction in office BP of 22.7/9.1 mm Hg in response to a low-salt diet. The magnitude of BP reduction was confirmed with the demonstration of a 20.7/9.6 mm Hg reduction in daytime BP by ABPM. This degree of BP reduction is much larger than reductions previously observed in unselected hypertensive subjects. It suggests that patients with resistant hypertension are particularly salt sensitive and emphasizes the importance of low dietary salt intake in the clinical management of resistant hypertension. Treatment with renin–angiotensin system blockers could partially explain the enhanced salt-sensitivity of these subjects. Animal studies demonstrate that long-term administration of angiotensin converting enzyme inhibitors heightens the hypertensive response to high dietary salt.35,36

**Figure.** Comparison of 24-hour ambulatory blood pressure values during low- and high-salt diet. Data presented as mean±SE.
In the present study, the increases in PRA and the decreases in BNP, creatinine clearance, and body weight during dietary salt restriction are consistent with reduction in intravascular volume. Overall, these findings provide support for the hypothesis that persistent fluid retention contributes to resistance to antihypertensive treatment.37–39 The current results suggest that this persistent fluid retention is attributable, at least in part, to excess dietary salt. Importantly, from a clinical perspective, the intravascular fluid retention observed during consumption of the high-salt diet occurred in spite of all subjects receiving hydrochlorothiazide 25 mg daily. This suggests that conventional doses of hydrochlorothiazide, the most commonly used diuretic in the United States, may not be sufficient to overcome sodium-induced fluid retention, at least in this very salt sensitive cohort.

In the current study, we also demonstrate a tendency toward reduction in vascular stiffness with low dietary salt intake as indicated by reductions in PWV and AIx. The lack of significance of changes in AIx and PWV may have occurred because of measurement errors or to the small sample size. If the vascular changes are confirmed in subsequent studies, it would suggest that during reduced dietary salt ingestion improvements in vascular stiffness combine with reductions in intravascular volume to lower BP.

In prior studies we have reported a very high prevalence of aldosterone excess, including classical primary aldosteronism, in patients with resistant hypertension.37,40 Accordingly, aldosterone excess, in causing sodium and fluid retention, likely contributed to salt sensitivity in these patients. In addition, subtle chronic kidney disease may also have exacerbated sodium retention, although this effect should have been minimized as patients with overt renal dysfunction (ie, creatinine clearance <60 mL/min) were excluded from enrollment.

Stimulation of the renin–angiotensin–aldosterone system with low-salt ingestion, as observed in the current study, has raised concerns about potentially accelerating target-organ damage.41 We think this unlikely, at least in the current cohort, as the sizable decrease in BP observed with salt restriction would be expected to substantially reduce cardiovascular risk. Further, we have previously shown that renal deterioration in patients with resistant hypertension, as indicated by the degree of proteinuria, is, in part, volume-dependent.42,43 In addition, Siragy and coworkers have shown that salt restriction in rats activates the kallikrein–kinin system with release of bradykinin, prostaglandin E₂, and cGMP in the kidney, most likely via activation of AT₁ receptors, which should have favorable effects on vascular function.44,45 Taken together, the reduction in intravascular volume that occurs during low dietary salt ingestion should protect against target-organ damage separate from improvements in BP.

Strengths of the present study include its crossover randomized design, use of ABPM, and confirmation of dietary adherence by measurement of 24-hour urinary sodium excretion. Weaknesses include evaluation of a relatively small number of subjects, unblinded administration of the salt diets, and the short duration of the dietary treatment periods. Analysis of data from trials of salt restriction suggest that even greater BP reduction would be achieved with a longer intervention period.4 Although the sample size is small, the crossover design provided sufficient power to assess the primary end points. Bias from unblinded administration of the 2 dietary regimens was minimized by use of ABPM to quantify change in BP.46,47

There was slightly higher urinary potassium excretion during the low- compared to the high-salt diet (difference of 11.4 mmol/d). The difference may have been related to upregulation of the renin–angiotensin–aldosterone system during low-salt intake. Although higher potassium intake may have contributed to the reduction in BP observed during low-salt intake, the effect would be anticipated to be modest as trials of potassium supplementation indicate that on average an additional intake of 75 mmol/24 hours lowers BP by 3.1/2.0 mm Hg.48

An important clinical consideration to be addressed in a separate study is whether or not the current degree of dietary sodium restriction can be accomplished and maintained by patients absent home delivery of specially prepared meals. Taking into consideration that 75% of the daily intake of sodium in Westernized countries is from salt added during commercial processing of foods or during food preparation by restaurants,49 reductions in the sodium content in the food supply would be a critical component to achieve lower levels of sodium intake.

All of the subjects enrolled into the current study reported having been previously advised to lower their dietary salt intake, and all reported having done so. However, the baseline 24-hour sodium excretion in these subjects averaged 195 mmol/24 hours, corresponding to ingestion of 11.6 g of salt per day. Although the current analysis was limited to a small number of subjects, this amount of salt ingestion is similar to that observed in an analysis of 274 patients with resistant hypertension, in whom urinary sodium excretion during ingestion of their normal diet averaged 187 mmol/24 hours or 11 g of salt.37 These findings indicate that in spite of reporting a salt-restricted diet, these patients were continuing to ingest a diet very high in salt content.

In summary, the current study demonstrate that high dietary salt ingestion is an important cause of resistant hypertension. This effect is related to excess intravascular fluid retention that persists in spite of conventional thiazide diuretic use. These data emphasize that the clinical management of patients with resistant hypertension should include intensive dietary salt restriction. The degree of salt restriction needed to overcome resistance to pharmacological therapies needs to be defined, but is unlikely to be accomplished without expert dietary consultation.

Perspectives
Observational studies and clinical trials performed in general populations indicate that a higher salt intake is associated with higher BP. The current study extends those findings in demonstrating that high dietary salt ingestion contributes importantly to the development of resistant hypertension. These data demonstrate that patients with resistant hypertension benefit from intensive dietary salt restriction and provide rational for inclusion of specific recommendations in dietary guidelines regarding salt intake for the treatment of resistant...
hypertension. The current findings also provide additional support of efforts to reduce salt content in foods.

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**Disclosures**

Suzanne Oparil has served as a consultant for The Salt Institute.

**References**

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