Determinants of Blood Pressure Response to Low-Salt Intake in a Healthy Adult Population

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Although the beneficial effects of lowering salt intake in hypertensive patients are widely appreciated, the impact of promoting dietary salt restriction for blood pressure (BP) reduction at the population level remains controversial. The authors used 24-hour ambulatory BP monitoring to characterize the determinants of systolic BP (SBP) response to low-salt intake in a large, relatively healthy Amish population. Patients received a high- and low-sodium diet for 6 days each, separated by a 6- to 14-day washout period. Variance component analysis was used to assess the association of several variables with SBP response to low-salt diet. Mean SBP was 0.7±5.8 mm Hg and 1.3±6.1 mm Hg lower on the low-salt compared with the high-salt diet during daytime (P=.008) and nighttime (P<.0001), respectively. SBP response to a low-salt diet was significantly associated with increasing age and pre-intervention SBP, in both daytime and nighttime, while the association with female sex and SBP response to cold pressor test (CPT) was significant only during nighttime. Our results suggest that salt reduction may have greater BP-lowering effects on women, older individuals, individuals with higher SBP, and individuals with higher SBP response to CPT. *J Clin Hypertens (Greenwich).* 2011;13:795–800. ©2011 Wiley Periodicals, Inc.

Hypertension (HTN) affects 32% of all Americans[1] and is responsible for 47% of ischemic heart disease, 54% of stroke, and 13.5% of premature death worldwide.[2] HTN is a complex disease influenced by both genes and environmental risk factors, including physical inactivity, obesity, smoking, alcohol consumption, and diets high in fat and salt.[3]

The term salt sensitivity (SS) has been in use for more than 3 decades[4] and is broadly used to denote a substantial increase in blood pressure (BP) in response to higher-salt intake.[5] Results from epidemiologic studies and clinical trials support a role for SS as an independent risk factor for cardiovascular diseases,[5] and at least one study reported SS to be associated with reduced survival in both hypertensive and normotensive individuals.[6] SS has been associated with older age, African American ancestry, female sex, obesity, HTN, diabetes, renal disease,[5,7] and decreased birth weight.[8] There may also be a genetic predisposition to SS.[7,9] Finally, the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study recently reported an association of SS with the BP response to the cold pressor test (CPT), suggesting a role for sympathetic nervous function in the development of SS.[10]

The current level of sodium intake among Americans is much higher than the recommended level of 2300 mg/d.[11] Although much evidence supports the beneficial effect of lowering sodium intake (down to 1500 mg/d according to the 2010 guidelines[11]) in reducing BP in hypertensive patients,[12] the impact of promoting dietary sodium restriction for BP reduction at the population level remains controversial.[5,13] Extrapolating to the population level is difficult because many of the published studies have focused on high-risk populations, used arbitrarily defined thresholds for SS, had limited sample sizes, and/or were based on one-time measures of BP, which have notoriously high variability. Rarely has BP response to low salt been studied in young, relatively healthy populations of fit individuals, nor have many studies used detailed measures of BP in their assessment of the response. To address some of these gaps, we examined systolic BP (SBP) response to low-salt intake in 465 relatively healthy adults using 24-hour ambulatory BP monitoring (ABPM) and standardized dietary conditions. In this report we describe the distribution and determinants of SBP response to a low-salt diet in this relatively healthy population, using assessments of ABPM during daytime and nighttime, defined on the basis of participants' sleep logs. Among the factors we examined were age, sex, pre-intervention SBP, the SBP response to the CPT, and physical activity (PA) levels. A better understanding of the predictors of SBP

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response to low-salt intake can help to assess its impact on the general population and identify population subgroups who can most benefit from lowering salt intake.

METHODS

Study Population

Study patients were participants of the Heredity and Phenotype Intervention (HAPI) Heart Study. HAPI participants were members of the Old Order Amish community of Lancaster County, PA. Individuals and their family members were invited to participate if they were 20 years or older and relatively healthy. Exclusions for the study included high BP (>180/105 mm Hg), active cancer, liver, kidney (serum creatinine [Cr] >2 mg/dL) disease, or untreated thyroid diseases, and being unable or unwilling to discontinue use of nutritional supplements, vitamins, and medications for the period of the study interventions. More information about patient recruitment, interventions, and measurements are available elsewhere.[14] Institutional review board approvals were obtained from the University of Maryland and all patients provided written informed consent.

Study Procedures and Variables

Pre-intervention phenotypes were obtained during an initial clinic visit at the Amish Research Clinic in Strasburg, PA. All medications, vitamins, and supplements were discontinued for at least 1 week prior to the initial clinic visit. Pre-intervention BP was measured in triplicate using a standard sphygmomanometer in the sitting position after 5 minutes rest, and the average of the 3 measures was used for analysis.

PA was assessed during the dietary intervention by Actical activity monitors (versions 8.2 and 8.3; Mini Mitter Co Inc, Bend, OR) worn by the patient for 7 consecutive days. These devices incorporate an accelerometer, sensitive to 0.01 times gravity in multiple directions, electronic circuitry, and a memory. Acceleration of the device is integrated and expressed in units of activity counts within each 15-second recording interval. The daily mean of these counts was used for this analysis.

Dietary Salt Intervention. The dietary salt intervention study began following the initial clinic visit. Study patients consumed a standardized high-sodium (Na) diet (280 meq/d=6440 mg/d) for 6 days, and then after a 6- to 14-day washout period, consumed a standardized low-Na diet (40 meq/d=920 mg/d) for 6 days. The potassium (K) level was held constant at 140 meq/d during both diets. All meals were prepared in a specially outfitted kitchen by an Amish cook according to instructions carefully designed by the study nutritionist (NHB), and delivered to the patients' home by an Amish caterer. To test for dietary compliance, Na, K, and Cr levels were measured from the first morning urine sample obtained at the last day of each dietary intervention, and the Na/Cr and K/Cr ratios were calculated from this single spot urine specimen. The HAPI Heart Study includes 868 patients in total, of whom 533 completed both arms of the dietary intervention.

Measurement of 24-Hour ABPM. Twenty four–hour BP and heart rate (HR) measurements were recorded at 30-minute intervals by an ambulatory BP monitor worn by study patients on the last day of each diet intervention. Based on logs maintained by the study participants asking about the times they went to bed and woke up, we divided the 24-hour period into daytime (after rising in the morning) and nighttime (after bed time) and estimated the mean of the SBP recorded within each period. In daytime and nighttime separately, we defined the SBP response to low-salt diet as the difference in mean SBP between the low and high standardized salt diets. We excluded from analysis patients with <5 measurements in any one period (n=68), leaving 465 patients with complete data.

Cold Pressor Test. The CPT was performed in a temperature-controlled room at the Amish Research Clinic. BP was first measured every 5 minutes for at least 20 minutes or until a stable baseline BP was obtained, and then the patients were asked to immerse their right hand and wrist in ice water (0–2°C) for 2.5 minutes. BP was measured 9 times during and after the CPT at 1, 2, 3, 4, 5, 7.5, 10, 15, and 20 minutes. The calculations of SBP response to CPT were previously detailed.[15] Briefly, the SBP response to CPT was calculated as the incremental area under the curve (iAUC), defined as the difference between the area under the response curve and the area below baseline (defined as the average of the last 2 measures before the CPT). We further subdivided the iAUC into a component representing the reactivity phase (BP response during the first 2 minutes of the CPT) and a recovery phase (BP response during minutes 3–5 of the CPT).[15]

Statistical Analysis

We evaluated compliance to the high- and low-salt diets by comparing mean estimated levels of 24-hour urinary Na and K excretion between groups via paired *t* test. The Statistical Analysis System programming language (SAS 9.1, Cary, NC) was used for descriptive analysis. Association analysis was carried out using the variance component method implemented in SOLAR.[16] We analyzed measurements of SBP response to low salt obtained from daytime and nighttime separately to allow for the possibility that associations might be stronger during nighttime when patients were supine and during which there might be less variation in BP.

RESULTS

Basic characteristics of the 465 study participants for whom SBP response to low-salt diet was computed are

presented in Table I. The sample included 245 men and 220 women, whose mean (±SD) ages were 42.2±12.9 years and 45.5±13.7 years, respectively. After adjusting for age, men had significantly higher levels of PA counts and lower body mass index compared with women ($P<.0001$). There was no significant difference between men and women in the level of pre-intervention SBP. While 18.5% of men were smokers (mostly light pipe-smoking), none of the women reported tobacco use.

Mean levels of urinary Na and K excretion adjusted for Cr level are shown in Table II for the pre-intervention period and during the high- and low-sodium diets. Mean urinary Na/Cr ratios differed little between pre-intervention and the high-salt diet ($P=.37$) consistent with our prior observation that the typical Amish diet is high in salt content. In contrast, mean levels of urinary Na/Cr ratio decreased by almost 6-fold during the low-salt diet ($P<.0001$) vs the high-salt diet, which is very close to what one would expect based on the 280 meq/40 meq Na content of the provided diets, suggesting a near-perfect compliance. Mean urinary K/Cr ratios were very similar among the pre-intervention and the high-salt diets ($P=.17$), but slightly higher during the low-salt diet.

The distribution of SBP response to low-salt diet in both periods was normally distributed with no indication of bimodality. The mean (±standard deviation) reductions in SBP response to low-salt diet from the high- to the low-salt diet were 0.7±5.8 mm Hg ($P=.008$) and 1.3±6.1 mm Hg ($P<.0001$) during daytime and nighttime, respectively, with considerable variability around both means. The correlation in SBP response to low-salt diet measures computed from daytime and nighttime was 0.49. A decrease of at least 4 mm Hg in SBP levels under the low- compared with the high-salt diet was observed in 25.5% and 28.8% of patients during daytime and nighttime, respectively. In contrast, 20.8% and 16.1% of patients experienced an increase of at least 4 mm Hg in SBP during daytime and nighttime, respectively, on the low-sodium diet.

Table III shows the association of baseline characteristics with SBP response to low-salt diet during daytime and nighttime. Older age and higher pre-intervention SBP were both significantly associated with higher SBP response to low-salt diet during daytime and nighttime,

TABLE I. Basic Characteristics for the HAPI Population

Variable	Men (n=245)	Women (n=220)	All (N=465)	*P* Value[a]
Age, y	42.2 ± 12.9	45.5 ± 13.7	43.8 ± 13.4	.006
PISBP, mm Hg	120.9 ± 13.5	120.9 ± 16.7	120.9 ± 15.1	.27
BMI, kg/m^2	25.4 ± 3.1	27.4 ± 5.2	26.4 ± 4.3	<.0001
Activity (counts), ×1000	511.9 ± 235.3	357.3 ± 185.4	436.7 ± 225.9	<.0001

Values are expressed as mean ± standard deviation. Abbreviations: BMI, body mass index; HAPI, Heredity and Phenotype Intervention Heart Study, PISBP, pre-intervention systolic blood pressure. [a]*P* value for sex differences adjusted for age (except for age).

TABLE II. Urinary Na/Cr and K/Cr Excretion Before and During Dietary Intervention

	Pre-intervention	High Salt	Low Salt
Men			
Na/Cr	12.8 (5.5)	11.9 (5.4)	2.1 (1.2)
K/Cr	3.3 (2.4)	3.4 (1.5)	4.3 (1.4)
Women			
Na/Cr	17.1 (12.8)	17.4 (8.1)	3.2 (2.4)
K/Cr	4.2 (3.2)	4.5 (2.5)	5.2 (2.1)

Values are expressed as mean ± standard deviation. Abbreviations: Cr, creatinine, K, potassium; Na, sodium.

TABLE III. Adjusted SBP Response to a Low-Salt Diet During Daytime and Nighttime by Age, Sex, Pre-intervention SBP, SBP Response to CPT, and Physical Activity

	SBP Response to Low-Salt Diet[a]	
	Daytime	Nighttime
Age, y		
<35	0.01 ± 4.60	−0.03 ± 5.29
35–50	−0.85 ± 5.30	−0.93 ± 5.63
>50	−1.05 ± 6.60	−2.86 ± 5.94
P for difference by age	.001	5.10E-06
Sex		
Men	−0.33 ± 5.72	−0.85 ± 5.49
Women	−1.10 ± 5.31	−1.97 ± 5.78
P for difference by sex	.12	.03
Pre-intervention SBP, mm Hg		
<120	−0.21 ± 4.74	−0.97 ± 5.34
≥120–<140	−0.30 ± 5.79	−1.18 ± 5.85
≥140	−4.48 ± 7.96	−4.33 ± 6.66
P for difference by pre-intervention SBP	2.70E-06	8.80E-06
SBP response to CPT[b]		
Low	−0.45 ± 5.52	−0.98 ± 5.86
Medium	−0.42 ± 5.67	−1.17 ± 5.77
High	−1.18 ± 5.79	−2.26 ± 5.53
P for difference by SBP response to CPT	.29	.02
Physical activity		
Low	−0.80 ± 5.93	−1.65 ± 5.77
Medium	−0.68 ± 5.45	−1.52 ± 5.66
High	−0.61 ± 5.22	−0.78 ± 5.40
P for difference by physical activity	.47	.56

Values are expressed as mean ± standard deviation. [a]*P* values age adjusted for sex and pre-intervention systolic blood pressure (SBP); *P* values sex-adjusted for age and pre-intervention SBP; *P* values for pre-intervention SBP adjusted for age and sex; *P* values for SBP response to cold pressor test (CPT), and physical activity adjusted for age, sex, and pre-intervention SBP. [b]Low: first quartile; medium: second quartile; high: upper quartile.

while female sex and higher SBP response to CPT were associated with higher SBP response to low-salt diet only during nighttime. Subsequent analyses were carried out to examine the association of SBP response to low-salt diet with the reactivity and recovery phases of the CPT, and the same pattern of association was observed with each phase separately as with the combined CPT response (data not shown). PA levels were not significantly associated with SBP response to low-salt diet measured during either daytime or nighttime.

Because HR changes in response to salt intake,[17] we examined whether any of the observed correlations of SBP response to low salt were altered when adjusted for HR changes. We found that lower SBP response to low salt was correlated with increasing HR during daytime (P=.006) and nighttime (P=.004). However, the correlations of age, sex, pre-intervention SBP, and SBP response to CPT with SBP response to low salt remained after adjustment for HR, the only exception was that the association with sex was attenuated from P=.03 to P=.06 during nighttime.

Hypothesizing that SBP response to a low-salt diet might be correlated with other cardiovascular risk factors, we examined its association with body mass index, brachial artery flow–mediated dilation (measured as percent change in brachial artery diameter at peak hyperemia [diameter postprandial − diameter at baseline]/diameter at baseline), lipid parameters (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), inflammation measures (serum levels of C-reactive protein, interleukin [IL] 6, IL-1b, matrix metalloproteinase [MMP] 1, MMP-9, and white blood cell count), and two measures of kidney function (estimated glomerular filtration rate and microalbumin to Cr ratio). None showed any association with SBP response to low-salt diet independently of age. We additionally considered whether the SBP reduction in response to low salt was more pronounced in the summer than in the winter because of the possibility of increased salt loss due to perspiration and no significant difference in the SBP response was found.

DISCUSSION

This study used a well-controlled standardized dietary intervention design to investigate the characteristics and correlates of SBP response to low-salt intake in 465 healthy drug-naive Amish patients. Our study has several distinguishing features that set it apart from other previously published similar studies. First, our study population was relatively young and healthy, enabling us to evaluate the distribution and predictors of SBP response to low-salt diet in a population without comorbidities and to make inferences about the impact of low-salt diet at the population level. Second, BP in our study was measured using 24-hour ABPM, extracting data during daytime and nighttime based on the participants' sleep log, to provide as representative a measure of this trait as possible in a population setting. Third, the high- and low-salt diets were carefully standardized, and urine collections were obtained to monitor and verify dietary compliance, which was found to be excellent.

A salt-sensitivity study, GenSalt, was recently carried out in China.[18] Both the HAPI Heart Study and GenSalt participated in the Program for Genetic Interaction (PROGENI) network, and the dietary interventions in the GenSalt (51 mmol and 308 mmol of Na/d for 7 days for the low- and high-salt diets, respectively) and HAPI (40 mmol and 280 mmol of Na/d for 6 days for the low- and high-salt diets, respectively) studies were coordinated to be comparable. Similar to our Amish population, the GenSalt population was relatively young (mean age=50.1±16.8 years.). However, in contrast to our study, GenSalt was designed to include families at high risk for developing HTN by restricting the study to families having a proband and at least one sibling with pre-HTN or stage 1 HTN (SBP 130–160 mm Hg and/or diastolic BP 85–100 mm Hg).[18] In fact, average SBP decreases in response to low-salt diet in the GenSalt study were 7 mm Hg and 8 mm Hg in men and women, respectively.[19]

The benefit of salt restriction for BP reduction in the general population has been debated for a long time. There is now ample evidence from numerous clinical trials showing that salt reduction is associated with a 1-mm Hg to 5.5-mm Hg reduction in SBP, with smaller reductions (1–2 mm Hg) observed in normotensive individuals and larger reductions (1.5–6 mm Hg) observed in hypertensive individuals.[20] Similar results were also reported recently from a European longitudinal observational study, for which only a 1.7-mm Hg increase in SBP was detected with a 100-mmol increase in sodium excretion in young healthy individuals.[21] The magnitudes of changes reported in normotensive individuals in these studies are in line with what we have observed in our relatively healthy Amish population (ie, 0.7- to 1.3-mm Hg reduction).

The associations of age and pre-intervention SBP with SBP response to low-salt diet observed in the Amish are well established.[19,22–24] These associations are possibly explained by the age-related decline in both kidney function and the activity of membrane sodium/potassium-adenosine triphosphate, as well as reduced production of natriuretic factors such as dopamine.[25,26]

The larger SBP reduction in response to low salt observed in women compared with men in our Amish study has been observed in several previous studies, including the Dietary Approaches to Stop Hypertension (DASH)-Sodium trial and GenSalt.[19,27] This sex effect might be attributable in part to the effect of reproductive hormones on body fluids and sodium regulation[28]; however, that effect was attenuated after considering the change in HR.

Similarly, our observation in the Amish that patients experiencing a larger reduction in SBP in response to low salt also experienced a larger reduction in their SBP response to the CPT is consistent with previous observations reported in Chinese adults[10] and children.[29] The

CPT activates a global sympathetic response mediated by catecholamine release that produces vasoconstriction and increased BP.[30] In general, increased Na intake requires a corresponding increased renal handling and excretion to avoid retention of blood volume and subsequent increase in BP. Possibly, those with a proclivity for sympathetic overactivity are less able to increase renal Na excretion in the face of a higher salt load.[31,32] The larger SBP response to low salt observed during nighttime, as well as the associations of female sex and higher SBP response to CPT only during nighttime, may reflect the relative stability of BP measured during nighttime, as a result of lower sympathetic activity in the supine position vs the upright position.

We looked at the association between SBP response to low salt and habitual levels of PA because exercise is known to improve insulin sensitivity, which may be linked to BP through the sympathetic nervous system.[33] PA was not associated with SBP response to low salt in this population. However, the Amish tend to have relatively high levels of PA relative to non-Amish by virtue of their rural lifestyle and non-adoption of modern technologies in the home, and it is possible that a more sedentary lifestyle than found in the Amish may be associated with a larger SBP response to low-salt diet.

Although the distribution of SBP response to a low-salt diet in this healthy population is relatively similar to the changes in SBP observed with previously published dietary salt restriction trials, it is important to bear in mind that our intervention was of short duration. At present there are limited available data from well-controlled feeding studies that address the effects of long-term low-salt intake on BP or other health parameters in normotensive salt-resistant individuals. As such, it remains difficult to ascertain whether the increase in BP in response to low-salt intake represents a regression toward the mean (ie, random variation in salt-resistant individuals) vs an acute or long-term physiological response to salt restriction (eg, activation of the renin-angiotensin system) or a combination of these scenarios. Interestingly, the previously mentioned recent longitudinal study showed an association between low salt and increased cardiovascular disease outcomes.[21] This observation, as well as other arguments raise the intriguing speculation that there may be possible counter-responses to low-Na intake in susceptible individuals.[34–36] Further experimental and longitudinal outcomes studies related to both cardiovascular and renal response to short- and long-term dietary sodium intake, notably in normotensive individuals, are warranted to explore this possibility.

CONCLUSIONS

In summary, our study confirms the previous observations that BP response to salt intake is a normally distributed trait with no evidence of bimodality[31] and extends the epidemiology of SBP response to low-salt diet to a relatively healthy population in whom the response was measured using rigorous and standardized methods. A sizable proportion of this population experienced an increase in SBP during the low-salt diet. Thus, overall, our data suggest that salt restriction (at least in the short-term) might not have BP-lowering benefits for everyone, but, rather, may be of most benefit to women, older individuals, those who are prehypertensive or hypertensive, and those who have higher SBP response to CPT.

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