Association Between Blood Pressure Responses to the Cold Pressor Test and Dietary Sodium Intervention in a Chinese Population

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**Background:** Blood pressure (BP) responses to the cold pressor test (CPT) and to dietary sodium intake might be related to the risk of hypertension. We examined the association between BP responses to the CPT and to dietary sodium and potassium interventions.

**Methods:** The CPT and dietary intervention were conducted among 1906 study participants in rural China. The dietary intervention included three 7-day periods of low sodium intake (3 g/d of salt [sodium chloride] [51.3 mmol/d of sodium]), high sodium intake (18 g/d of salt [303.8 mmol/d of sodium]), and high sodium intake plus potassium chloride supplementation (60 mmol/d). A total of 9 BP measurements were obtained during the 3-day baseline observation and the last 3 days of each intervention using a random-zero sphygmomanometer.

**Results:** Blood pressure response to the CPT was significantly associated with BP changes during the sodium and potassium interventions (all \( P < .001 \)). Compared with the lowest quartile of BP response to the CPT (quartile 1), systolic BP changes (95% confidence intervals) for the quartiles 2, 3, and 4 were −2.02 (−2.87 to −1.16) mm Hg, −3.17 (−4.05 to −2.28) mm Hg, and −5.98 (−6.89 to −5.08) mm Hg, respectively, during the low-sodium intervention. Corresponding systolic BP changes during the high-sodium intervention were 0.40 (−0.36 to 1.16) mm Hg, 0.44 (−0.35 to 1.22) mm Hg, and 2.30 (1.50 to 3.10) mm Hg, respectively, and during the high-sodium plus potassium supplementation intervention were −0.26 (−0.99 to 0.46) mm Hg, −0.95 (−1.70 to −0.20) mm Hg, and −1.59 (−2.36 to −0.83) mm Hg, respectively.

**Conclusions:** These results indicate that BP response to the CPT was associated with salt sensitivity and potassium sensitivity. Furthermore, a low-sodium or high-potassium diet might be more effective to lower BP among individuals with high responses to the CPT.

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Hypertension is an important public health challenge in the United States and worldwide because of its high prevalence and the concomitant increase in risk of cardiovascular and kidney disease.\(^1\) High dietary sodium and low potassium intake have been associated with an increased blood pressure (BP) in animal experiments, observational epidemiologic studies, and randomized controlled clinical trials.\(^4\) However, there is substantial scientific evidence suggesting that BP responses to dietary sodium or potassium intake vary considerably among individuals.\(^7\) Previous studies have indicated that salt sensitivity or potassium sensitivity is more common among individuals who are older, overweight, hypertensive, or of African American descent.\(^5\) In addition, dietary potassium intake also affects salt sensitivity.\(^11\) However, other predictors for salt sensitivity or potassium sensitivity of BP have not been well studied.

The cold pressor test (CPT), which measures the response of BP to the stimulus of external cold, has long been a standard test to characterize sympathetic nervous system activity and has been documented to predict the subsequent risk of hypertension in normotensive persons.\(^12\) Previous studies have also suggested that sympathetic nervous system activity might play an important role in determining the salt sensitivity of BP.\(^16\) The association between BP responses to the CPT and salt sensitivity, however, has not

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Group Information: The GenSalt (Genetic Epidemiology Network of Salt Sensitivity) Collaborative Research Group members are listed on page 1746.
been well studied. The only published study that examined this association reported that the mean increase in BP and its recovery time from peak to baseline during the CPT was significantly higher in salt-sensitive children compared with their counterparts who were not salt sensitive among 268 school children. In that study, salt sensitivity was tested using a short-term protocol in which children were salt loaded with an oral saline drink and salt depleted by administering furosemide.

A positive association of BP with dietary sodium intake and an inverse association with dietary potassium intake have been reported in rural Chinese populations. In the INTERSALT study (the International Cooperative Study on Electrolytes and Blood Pressure), mean dietary intake of sodium was much higher and the intake of potassium was lower in the Chinese population compared with other populations in the world. Dietary sodium intake was particularly high and potassium intake was low in Chinese living in north China. We examined the association between BP responses to the CPT and BP responses to dietary sodium and potassium interventions among 1906 Chinese men and women aged 18 to 60 years, who participated in the Genetic Epidemiology Network of Salt Sensitivity (GenSalt) study.

STUDY POPULATION

The GenSalt study was conducted in rural areas in north China from October 2003 to July 2005. A community-based BP screening was conducted among persons aged 18 to 60 years in the study villages to identify potential probands and their families for the study. Those with a mean systolic BP between 130 and 160 mm Hg and/or a mean diastolic BP between 85 and 100 mm Hg and no use of antihypertensive medications and their siblings and offspring were recruited for the dietary intervention study. The detailed eligibility criteria for the probands and their siblings and/or offspring are presented elsewhere. In general, individuals who had stage 2 hypertension, secondary hypertension, use of antihypertensive medications, history of cardiovascular disease or diabetes, or heavy alcohol use or were pregnant or currently on a low-sodium diet were excluded from the dietary intervention. Among the 1906 eligible individuals, 1858 (97.5%) completed the entire dietary sodium and potassium interventions. Of them, a total of 1813 participants also completed the CPT and were included in the current analysis.

institutional review boards at all participating institutes approved the GenSalt study. Written informed consent forms for the baseline observation and for the intervention program were obtained from each participant.

DATA COLLECTION

A standard questionnaire was administered by a trained staff member at the baseline examination to collect information on demographic characteristics, personal and family medical history, and lifestyle risk factors (including cigarette smoking, alcohol drinking, and physical activity).

Three BP measurements were obtained at each clinical visit by trained and certified observers according to a common protocol adapted from procedures recommended by the American Heart Association. Blood pressure was measured with the participant in a sitting position after 5 minutes of rest. In addition, participants were advised to avoid alcohol, cigarette smoking, coffee and/or tea, and exercise for at least 30 minutes before their BP measurement. A random-zero sphygmomanometer was used, and 1 of 4 cuff sizes (pediatric, regular adult, large, or thigh) was chosen on the basis of the circumference of the participant's arm. Blood pressure was measured each morning of the 3-day baseline observation and on days 2, 5, 6, and 7 of each intervention period by the same BP technician using the same sphygmomanometer to avoid interobservation variation.

All BP observers participated in a special training session on the use of a standardized protocol for measurement of BP. To be certified as a GenSalt BP observer, satisfactory performance on a written test of how to prepare study participants for BP measurement, select the correct cuff size, and use standard techniques for BP measurement—during a standardized videotape examination and concordant measurements of BP with an instructor—were required. All BP observers were blinded to the dietary intervention and the CPT results.

COLD PRESSOR TEST

The CPT was conducted during the baseline examination (Figure 1). After the participant had remained sitting for 20 minutes, 3 BP measurements were obtained using a standard mercury sphygmomanometer before the ice water immersion. Then, the participant immersed his or her left hand in the ice water bath (3°C to 5°C) to just above the wrist for 1 minute. Blood pressure measurements at 0, 60, 120, and 240 seconds were obtained using a standard mercury sphygmomanometer after the left hand had been removed from the ice water bath. The CPT was well tolerated in all subjects, and no adverse effect was reported.

DIETARY INTERVENTION

The study participants received a low-sodium diet (3 g/d of salt [sodium chloride] 51.3 mmol/d of sodium]) for 7 days. Then, they received a high-sodium diet (18 g/d of salt [307.8 mmol/d of sodium]) for 7 days. During the first 2 intervention phases, potassium intake remained unchanged. In the final week, the participants maintained a high-sodium diet and took a 60-mmol/d potassium chloride supplement (Figure 1). There was no washout period between the 3 intervention phases in order to observe BP changes from the low-sodium to the high-sodium intervention and from the high-sodium to the high-sodium plus potassium supplementation intervention. All foods were cooked without salt, and prepackaged salt was added to...
the individual study participant’s meal, as specified in the protocol, when it was served by the study staff. Although dietary salt intake was the same for all study participants, dietary total energy intake was varied into 5 levels according to their baseline energy intake. To ensure study participants’ compliance to the intervention program, they were required to have their breakfast, lunch, and dinner at the study kitchen under supervision of the study staff during the entire study period. Food consumption of study participants was carefully recorded at each meal by study staff members. The study participants were instructed to avoid consuming any foods that were not provided by the study. In addition, 3 timed urinary specimens were collected at baseline and in each phase of intervention to monitor participants’ compliance to dietary sodium and potassium intake. The results from 24-hour urinary excretion of sodium and potassium were 241.8 (68.2) mmol and 36.8 (10.0) mmol, respectively, during the high-sodium plus potassium supplementation intervention. Diets and potassium were 244.5 (40.4) mmol and 36.2 (8.1) mmol, respectively, during the high-sodium intervention, and 251.9 (36.9) mmol and 77.3 (12.6) mmol, respectively, during the high-sodium plus potassium supplementation intervention. The results from 24-hour urinary excretion of sodium and potassium were 241.8 (68.2) mmol and 36.8 (10.0) mmol, respectively, during the high-sodium plus potassium supplementation intervention. The mean (SD) 24-hour urinary excretions of sodium and potassium were 241.8 (68.2) mmol and 36.8 (10.0) mmol, respectively, at baseline, 46.7 (15.7) mmol and 31.0 (8.0) mmol, respectively, during the low-sodium intervention, 244.5 (40.4) mmol and 36.2 (8.1) mmol, respectively, during the high-sodium intervention, and 251.9 (36.9) mmol and 77.3 (12.6) mmol, respectively, during the high-sodium plus potassium supplementation intervention.

**STATISTICAL ANALYSIS**

Blood pressure levels at baseline and during intervention were calculated as the mean of 9 measurements from 3 clinical visits during the 3-day baseline observation or on days 5, 6, and 7 of each intervention period. Responses were defined as follows: BP response to low sodium intake = BP during the low-sodium intervention − BP at baseline; BP response to high sodium intake = BP during the high-sodium intervention − BP during the low-sodium intervention; and BP response to potassium supplementation = BP during the high-sodium plus potassium supplementation intervention − BP during the high-sodium intervention. Blood pressure responses to dietary sodium and potassium interventions were analyzed as both continuous and categorical variables. High salt sensitivity was defined as a BP decrease in the top 30th percentile of all responses during the low-sodium intervention or a BP increase in the top 30th percentile during the high-sodium intervention. High potassium sensitivity was defined as a BP decrease in the top 30th percentile during the high-sodium plus potassium supplementation intervention among all study participants. The area under the curve (AUC) of BP responses to the CPT was calculated. Area under the curve summarizes the magnitude of BP increase and its recovery time from peak to baseline during the CPT and is more informative than BP change at any single time point.

Age- and sex-adjusted mean values of continuous variables and percentages of categorical variables for exposures, covariates, and outcomes were calculated by quartiles of AUC of systolic BP responses to the CPT. The statistical significance of differences in these characteristics across quartiles was examined by means of the 2 test (continuous variables) or the Wald χ² test (categorical variables) in multivariate regression models after adjustment for age and sex. Multivariate linear and logistic regression analyses were used to explore the association between BP responses to the CPT and BP responses to low-sodium, high-sodium, and high-sodium plus potassium supplementation interventions. The AUC of BP responses to the CPT were categorized into quartiles and the quartile with the lowest value was used as the reference group. To test for a linear trend, the medians of AUC in each quartile were treated as a continuous variable in regression models. Age, sex, education, cigarette smoking, alcohol consumption, physical activity, body mass index, baseline BP, and 24-hour urinary excretion of sodium were adjusted in the multivariate models.

**RESULTS**

The characteristics of study participants by quartile of AUC of systolic BP responses to the CPT are presented in Table 1. On average, participants with higher systolic BP responses to the CPT were older, more likely to be male, cigarette smokers, and alcohol drinkers and more physically active. In addition, those with higher systolic BP responses to the CPT were heavier, had higher baseline BP, and higher di-
The age- and sex-adjusted prevalence of high salt sensitivity or high potassium sensitivity for systolic BP was greater among persons with a higher BP response to the CPT (Figure 3). For instance, according to the quartiles of BP response to the CPT (for systolic BP: <558.9, 558.9-607.0, 607.1-667.3, ≥667.4; and for diastolic BP: <346.0, 346.0-382.3, 382.4-419.0, ≥419.1), the prevalence of high salt sensitivity during the low-sodium intervention was 12.8%, 24.7%, 33.0%, and 48.2%, respectively, for systolic BP and 20.9%, 25.3%, 31.6%, and 42.8%, respectively, for diastolic BP. The prevalence of high potassium sensitivity during the low-sodium intervention was 23.1%, 25.7%, 34.1%, and 35.9%, respectively, for systolic BP and 28.6%, 31.0%, 30.4%, and 30.1%, respectively, for diastolic BP. After adjustment for important covariates, odds ratios of high salt or potassium sensitivity significantly increased by quartiles of AUC of BP response to the CPT for systolic BP (Table 3). The association was not as strong for diastolic BP.

This large population-based diet intervention study identified a dose-response relationship between BP responses to the CPT and to dietary sodium and potassium interventions. This relationship was statistically significant and independent of other covariates. To our knowledge, our study is the first investigation to report a relationship between BP responses to the CPT and salt sensitivity and potassium sensitivity. These findings have important clinical and public health implications.

Dietary sodium reduction and potassium supplementation have been recommended as an effective approach for the treatment and prevention of hypertension in popu-
The CPT is known to cause a global sympathetic activation and result in significant arteriolar vasoconstriction, with a subsequent increase in BP. 

Menkes et al. reported a significant association between BP response to the CPT and subsequent risk of hypertension among 910 young white men. Among those in the lowest, middle 2, and upper quartiles of maximum systolic BP response to the CPT, the cumulative incidence of hypertension was 2.4%, 3.0%, and 6.7%, respectively, over 20 to 36 years of follow-up. Kasagi et al. reported that systolic hyperreactors (defined as maximal systolic BP response to the CPT ≥15 mm Hg) had a 37% higher risk of hypertension compared with systolic normal reactors over 28 years of follow-up among 824 normotensive participants. Our study indicated that individuals who were highly responsive to the CPT might be more sensitive to dietary sodium and potassium interventions. Therefore, a diet low in sodium or high in potassium should be recommended to this group for the purpose of prevention and treatment of hypertension.

The CPT is known to cause a global sympathetic activation and result in significant arteriolar vasoconstriction, with a subsequent increase in BP. Several studies have shown that the CPT increases plasma norepinephrine concentration and muscle sympathetic nerve activity. The increase in muscle sympathetic nerve activity correlates highly with increases in both mean arterial BP and peripheral venous norepinephrine concentration. Salt sensitivity has also been related to heightened sympathetic nervous system activity.
Diastolic BP Response
to the Cold Pressor Test

Table 3. Multivariate-Adjusted Odds Ratios of High Salt and Potassium Sensitivity According to Quartiles of BP Responses to the Cold Pressor Testa

<table>
<thead>
<tr>
<th>Quartiles of AUC of BP Responses to the Cold Pressor Test</th>
<th>Systolic BP Response ≥70th Percentile</th>
<th>Diastolic BP Response ≥70th Percentile</th>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value for Trend</td>
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<tr>
<td>Low-sodium intervention</td>
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<tr>
<td>1 (lowest)</td>
<td>1 [Reference]</td>
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<tr>
<td>2</td>
<td>2.23 (1.56-3.19)</td>
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<tr>
<td>3</td>
<td>3.17 (2.22-4.52)</td>
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<td>4 (highest)</td>
<td>5.54 (3.89-7.90)</td>
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<tr>
<td>High-sodium intervention</td>
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<tr>
<td>2</td>
<td>1.27 (0.92-1.74)</td>
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<td>3</td>
<td>1.57 (1.14-2.16)</td>
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<td>4 (highest)</td>
<td>2.26 (1.64-3.10)</td>
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<td>High-sodium plus potassium supplementation intervention</td>
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<td>2</td>
<td>1.07 (0.78-1.45)</td>
<td>.001</td>
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<tr>
<td>3</td>
<td>1.55 (1.14-2.11)</td>
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<tr>
<td>4 (highest)</td>
<td>1.56 (1.14-2.13)</td>
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</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; BP, blood pressure; CI, confidence interval; OR, odds ratio.

aThe cut points of AUC quartiles of BP responses to the cold pressor test were the following: for systolic BP, lower than 558.9 (quartile 1), 558.9 to 607.0 (quartile 2), 607.1 to 667.3 (quartile 3), and 667.4 or greater (quartile 4); and for diastolic BP, lower than 346.0 (quartile 1), 346.0 to 382.3 (quartile 2), 382.4 to 419.0 (quartile 3), and 419.1 or greater (quartile 4).

In conclusion, our study indicates that BP response to the CPT is associated with salt sensitivity and potassium sensitivity. The CPT might aid in identifying individuals who are more sensitive to dietary sodium or potassium interventions. In addition, a low-sodium or high-potassium diet might be more effective to lower BP among individuals who are highly responsive to the CPT. Future studies to confirm our findings will have important clinical and public health implications.

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REFERENCES