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 [307.8 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.
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 clinical 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 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 participants 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.

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egorical 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 Z 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.

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 daily intake of sodium and potassium were adjusted in the multivariate models.
etary salt intake as measured by 24-hour urinary excretion of sodium. As expected, the mean maximum changes in both systolic and diastolic BP increased with higher AUC of systolic BP responses to the CPT. The pattern of study participants’ characteristics by quartile of AUC of diastolic BP responses to the CPT was similar to that for the systolic BP responses and therefore is not shown.

**Figure 2** displays the age- and sex-adjusted mean systolic BP responses to the low-sodium, high-sodium, and high-sodium plus potassium supplementation interventions by quartile of AUC of systolic BP responses to the CPT (Figure 2A) and diastolic BP responses to dietary interventions by quartiles of AUC of diastolic BP responses to the CPT (Figure 2B). There were dose-response relationships between systolic BP responses to the CPT and systolic BP responses to the low-sodium, high-sodium, and high-sodium plus potassium supplementation interventions (all \( P < .001 \) for linear trend). A similar pattern was observed for diastolic BP, although the association was only statistically significant for BP responses to the low-sodium intervention (\( P < .001 \) for linear trend).

After adjustment for important covariates, there were statistically significant associations between the quartiles of BP response to the CPT and BP response to the dietary interventions (Table 2). Similar results were found when BP response to the CPT was used as a continuous variable. After adjustment for important covariates, 1 standard deviation difference in the AUC of systolic BP responses to the CPT was associated with a \(-2.59-\text{mm Hg} (95\% \text{ confidence interval } [\text{CI}], -2.91 \text{ to } -2.27 \text{ mm Hg}) (P < .001)\) reduction in systolic BP during the low-sodium intervention, a \(0.98-\text{mm Hg} (95\% \text{ CI}, 0.70 \text{ to } 1.27 \text{ mm Hg}) (P < .001)\) increase in systolic BP during the high-sodium intervention, and a \(-0.72-\text{mm Hg} (95\% \text{ CI}, -0.99 \text{ to } -0.44 \text{ mm Hg}) (P < .001)\) reduction in systolic BP during the high-sodium plus potassium supplementation intervention. One standard deviation difference in the AUC of diastolic BP responses to the CPT was associated with \(-1.35-\text{mm Hg} (95\% \text{ CI}, -1.63 \text{ to } -1.07 \text{ mm Hg}) (P < .001)\) reduction in diastolic BP during the low-sodium intervention, a \(0.33-\text{mm Hg} (95\% \text{ CI}, 0.05 \text{ to } 0.61 \text{ mm Hg}) (P < .02)\) increase in diastolic BP during the high-sodium intervention, and a \(-0.40-\text{mm Hg} (95\% \text{ CI}, -0.64 \text{ to } -0.16 \text{ mm Hg}) (P < .001)\) reduction in diastolic BP during the high-sodium plus potassium supplementation intervention.

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 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-

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**Figure 2.** Age- and sex-adjusted mean systolic blood pressure (BP) responses to low-sodium, high-sodium, and high-sodium plus potassium supplementation interventions by quartiles of area under the curve of systolic BP response to the cold pressor test (A) and diastolic BP response to dietary interventions by quartiles of area under the curve of diastolic BP response to the cold pressor test (B).

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Identifying individuals who are more sensitive to dietary sodium and potassium interventions will enable targeted lifestyle modification among individuals who may particularly benefit from a low-sodium and high-potassium diet. In addition, salt sensitivity has also been associated with increased risk of cardiovascular disease and premature death. From a public health perspective, salt-sensitive individuals at high risk for hypertension and cardiovascular disease could be identified before disease development, and effective and appropriate lifestyle modifications could be implemented for primary prevention. Our study indicates that BP responses to the CPT are significantly related to salt sensitivity and potassium sensitivity. The CPT might help to identify individuals who are more salt sensitive or potassium sensitive. Further studies should examine the reproducibility of BP responses to the CPT and dietary sodium and potassium interventions.

Being highly responsive to the CPT has been associated with an increased risk of hypertension in previous studies. 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.

### Table 2. Multivariate Regression Analyses of BP Responses to Dietary Interventions According to Quartile of BP Responses to the Cold Pressor Test

<table>
<thead>
<tr>
<th>Quartiles of AUC of BP Responses to Cold Pressor Test</th>
<th>Effect (95% CI), mm Hg</th>
<th>P Value for Trend</th>
<th>Effect (95% CI), mm Hg</th>
<th>P Value for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-sodium intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1 (lowest)</td>
<td>1 [Reference]</td>
<td></td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>-2.02 (-2.87 to -1.16)</td>
<td>&lt;.001</td>
<td>-0.68 (-1.39 to 0.04)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-3.17 (-4.05 to -2.28)</td>
<td></td>
<td>-1.67 (-2.41 to -0.93)</td>
<td></td>
</tr>
<tr>
<td>4 (highest)</td>
<td>-5.98 (-8.89 to -3.08)</td>
<td></td>
<td>-3.41 (-4.19 to -2.63)</td>
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<tr>
<td>High-sodium intervention</td>
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<td></td>
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</tr>
<tr>
<td>1 (lowest)</td>
<td>1 [Reference]</td>
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<td>1 [Reference]</td>
<td></td>
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<tr>
<td>2</td>
<td>0.40 (-0.36 to 1.16)</td>
<td>&lt;.001</td>
<td>0.34 (-0.37 to 1.06)</td>
<td>0.4</td>
</tr>
<tr>
<td>3</td>
<td>0.44 (-0.35 to 1.22)</td>
<td></td>
<td>0.70 (-0.04 to 1.44)</td>
<td></td>
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<tr>
<td>4 (highest)</td>
<td>2.30 (1.50 to 3.10)</td>
<td></td>
<td>0.89 (0.11 to 1.67)</td>
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<tr>
<td>High-sodium plus potassium supplementation intervention</td>
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<tr>
<td>1 (lowest)</td>
<td>1 [Reference]</td>
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<td>1 [Reference]</td>
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</tr>
<tr>
<td>2</td>
<td>-0.26 (-0.99 to 0.46)</td>
<td>&lt;.001</td>
<td>-0.33 (-0.95 to 0.28)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>-0.95 (-1.70 to -0.20)</td>
<td></td>
<td>-0.46 (-1.09 to 0.18)</td>
<td></td>
</tr>
<tr>
<td>4 (highest)</td>
<td>-1.59 (-2.36 to -0.83)</td>
<td></td>
<td>-0.88 (-1.55 to -0.21)</td>
<td></td>
</tr>
</tbody>
</table>

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

The 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).

**Figure 3.** Age- and sex-adjusted prevalence of high salt sensitivity or high-potassium sensitivity defined as a systolic blood pressure change in the top 30th percentile during the dietary sodium and potassium interventions among all study participants according to quartiles of area under the curve of blood pressure responses to the cold pressor test.

- Low-Sodium Intervention
- High-Sodium Intervention
- High-Sodium Plus Potassium Supplementation Intervention

- High Salt or Potassium Sensitivity, %
  - Area under the curve
    - ≤558.9
    - 558.9-607.0
    - 607.1-667.3
    - ≥667.4

- P<.001 for trend
tem activity and BP has been suggested. Blood pressure response to the CPT predicts the subsequent risk of hypertension.14,15 Indeed, previous studies have indicated that systolic but not diastolic BP response to the CPT is associated with salt sensitivity and potassium sensitivity estimated by this method is a reproducible phenomenon.34,35

In conclusion, our study indicates that BP response to the CPT is a stronger predictor of salt sensitivity or potassium sensitivity than diastolic BP response. Systolic BP is affected directly by arteriolar vasoconstriction due to sympathetic activation induced by the CPT. Indeed, previous studies have indicated that systolic but not diastolic BP response to the CPT predicts the subsequent risk of hypertension.14,15

Our findings are noteworthy because they are based on a large, well-controlled dietary intervention study. Compliance to dietary intervention and to the CPT was excellent. In addition, careful measures of study and outcome variables allowed for precise estimation of the association. To our knowledge, this study is the first to report a strong relationship between the CPT and salt sensitivity and potassium sensitivity in adults. Our study also has limitations. Although exposure to a 1-week low-sodium and 1-week high-sodium intervention has become the standard method for testing salt sensitivity in clinical research, the relationship between the effects of this relatively short intervention and an individuals’ long-term response to dietary sodium intake is unknown. Several clinical studies, however, have indicated that salt sensitivity estimated by this method is a reproducible phenomenon.34,35

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

<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>
</tr>
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<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value for Trend</td>
</tr>
<tr>
<td>Low-sodium intervention</td>
<td></td>
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<tr>
<td>1 (lowest)</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>2.23 (1.56-3.19)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3</td>
<td>3.17 (2.22-4.52)</td>
<td></td>
</tr>
<tr>
<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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<td></td>
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<tr>
<td>1 (lowest)</td>
<td>1 [Reference]</td>
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<tr>
<td>2</td>
<td>1.27 (0.92-1.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>3</td>
<td>1.57 (1.14-2.16)</td>
<td></td>
</tr>
<tr>
<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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<tr>
<td>1 (lowest)</td>
<td>1 [Reference]</td>
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<tr>
<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>
<tr>
<td>4 (highest)</td>
<td>1.56 (1.14-2.13)</td>
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</tbody>
</table>

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

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