Effects of a High Salt Intake and Potassium Supplementation on QT Interval Dispersion in Normotensive Healthy Subjects

Mingjun He, Jianjun Mu, Fuqiang Liu, Keyu Ren, Yang Wang, Tongshuai Guo and Dan Wang

Abstract

Objective To evaluate the effects of dietary sodium intake on QT interval dispersion (QTd) in normotensive healthy subjects and assess the protective effects of dietary potassium.

Methods All subjects were sequentially maintained on a protocol with a three-day baseline investigation, seven-day low-salt period (3 g/day (d), NaCl), seven-day salt loading period (18 g/d, NaCl) and a seven-day salt loading with potassium supplementation period (4.5 g/d, KCl). On the last day of each period, 24-hour urine samples were collected, the blood pressure values were measured and an electrocardiogram was recorded. The QT interval, QTd and T peak-T end interval (Tp-Te) were subsequently measured and calculated.

Patients Sixty-four normotensive subjects, men and women, ranging from 28 to 60 years of age, were enrolled.

Results There were no great fluctuations in heart rate after salt loading, whereas the systolic blood pressure (SBP, mmHg) and diastolic blood pressure (DBP, mmHg) increased and the corrected QT interval (QTc), corrected QT interval dispersion (QTdc) and Tp-Te values were significantly prolonged compared to that observed in the low-salt period (SBP, 118.6±13.5 vs. 111.7±11.3, p<0.01; DBP, 76.9±8.6 vs. 71.7±7.7, p<0.01; QTdc, 60.3±19.4 vs. 55.6±19.4, p<0.05; Tp-Te, 83.0±10.1 vs. 79.8±8.5, p<0.01). Surprisingly, all of these changes were reversed by potassium supplementation (SBP, 114.5±12.3 vs.118.6±13.5, p<0.01; DBP, 72.2±7.9 vs.76.9±8.6, p<0.01; QTd, 42.6±15.1 vs. 47.4±19.0, p<0.05; QTdc, 52.2±18.0 vs. 60.3±19.4, p<0.05; Tp-Te, 79.1±8.5 vs. 83.0±10.1, p<0.01).

Conclusion Salt loading prolongs the QT interval, QTd and Tp-Te, while dietary potassium supplementation reverses these alterations. These findings suggest that potassium supplementation may improve variation in the healing time and prevent arrhythmia.

Key words: QT dispersion, T peak-T end interval, salt, potassium

Introduction

Several epidemiological and interventional studies have demonstrated a clear relationship between salt intake and direct target organ damage that is counteracted by potassium supplementation (1-3). The supplementation of potassium plays a role in protecting the cardiovascular system from damage caused by excess sodium salt (4). Recently, attention has been directed towards the degree of dispersion of the QT interval and QT interval dispersion (QTd) on surface electrocardiography (ECG). In an earlier report, Tzemos et al. (5) administered a high-salt diet (200 mmol/d) for five days (d) in 16 normotensive young adults and found a significant increase in the QTd values. In another report, Franzoni et al. (6) found that the corrected QTd (QTdc) values in patients with anorexia nervosa significantly decrease after oral potassium treatment. The QTd is the difference between...
normotensive rural patients, 28 to 60 years of age, living in Mei County, Shaanxi Province, were enrolled in this study. The subjects included both men and women, excluding those with severe cardiovascular disease, liver, kidney or other acute or chronic diseases and pregnant women according to a detailed history-taking, physical examination and laboratory tests, if necessary. In addition, subjects with frequent drinking habits and those not willing to sign an informed consent form or were unable to complete the experiment were also excluded. In total, 64 patients (29 men, 35 women), with a mean age of 47.8 years, were enrolled. The Institutional Ethics Committee of the Medical School of Xi’an Jiaotong University approved the study protocol, and each subject provided their written informed consent.

Baseline surveys and dietary intervention

All subjects underwent three-day (d) baseline surveys (baseline period), including the collection of detailed demographic information and disease history, as well as a physical examination, anthropometric data measurement (height, weight, waist circumference, continuous three-day blood pressure measurement and ECG recording). Thereafter, a series of investigations were conducted, including: (1) a seven-day low-salt diet (low-salt period), with an NaCl intake of 3 g/d (51.3 mmol/d); (2) a seven-day high-salt diet (salt loading period), with a sodium intake of 18 g/d (307.7 mmol/d); (3) a seven-day high-salt potassium supplementation diet (high-salt potassium supplementation period), with a sodium intake of 18 g/d (307.7 mmol/d) and the oral administration of potassium of 4.5 g/d (60 mmol/d).

All meals were prepared in research kitchens and consumed on-site. During the investigation, each subject was given detailed dietary instructions to avoid table salt, cooking salt and high-sodium foods. All staff participating in the research were trained by the research group and passed a rigorous test. An approach of collective catering and diet with unified management was adopted to maintain the dietary intervention, and special nutritionists were ready in the field to develop special recipes and make sure that the processed food itself did not contain any sodium chloride or sodium chloride-containing products. At meal time, the nutritional supervisor was responsible for adding the quantitative salt into the food and ensuring that the subjects ate all the food. The subjects were not allowed to consume any salt-containing foods without permission. During the experiment, the researchers actively educated the subjects and patiently answered their questions.

Blood pressure (BP) measurement

Blood pressure was measured by trained and certified observers according to the procedures recommended by the American Heart Association. Three random-zero BP measurements were obtained at 30-second intervals in the morning during the three-day baseline observation, as well as on the second, fifth, sixth and seventh days of each intervention period using a Hawksley random-zero sphygmomanometer (Hawksley & Sons Ltd., Lancing, UK; zero range: 0-20 mmHg). Each subject rested for a minimum of five minutes in the sitting position prior to the BP measurements. In addition, the participants were advised to avoid drinking alcohol, coffee or tea, smoke or engage in exercise 30 minutes prior to the BP measurements. The first and fifth phases of the Korotkoff sounds were used to determine the systolic blood pressure (SBP) and diastolic blood pressure (DBP), respectively, and the mean blood pressure (MBP) was obtained according to the following formula: MBP=SBP+1/3×DBP.

Serum sodium and potassium determination

Fasting blood samples were obtained from the peripheral veins and centrifuged immediately at 3,000 g for five minutes. The supernatants were stored at -80°C until the assay. The serum concentrations of sodium and potassium in each sample were determined using an electrolyte analyzer (CIBA CORNING model 288).

ECG measurement

All 12-lead ECGs were recorded using a 12-Channel Electrocardiograph (BIOCARE model ECG-1210) with the subject resting in the supine position at a paper speed of 25 mm/s (gain 10 mm mV⁻¹) on the last day of each intervention period.

QT interval dispersion and T peak-T end interval (Tp-Te) measurement

The QT interval was measured manually in a blinded fashion from the onset of the QRS complex to the end of the T wave. Meanwhile, the T peak-T end interval (Tp-Te) was used to determine the T wave peak (T wave peak vertex) and T wave end (defined as the point of return to the isoelectric line). The method used to determine the T-wave endpoint was as follows: if the end of the T wave could not be identified, the lead was not included; if the T-wave morphology was normal and the declining branch was straight, the intersection of the T wave and the baseline was determined; if the T-wave descending branch was relatively flat,
the intersection of the baseline and the tangent line of the
descending branch at the steepest point was determined; if the
start and endpoints of the U wave were obvious, the
lowest point of the junction of the T wave and U wave was
determined as the endpoint of the T wave; if the T-wave had
two peaks with similar amplitude, the endpoint of the sec-
ond peak of the T wave was measured; if the T and U
waves were partially integrated and not easy to judge, the
extended line of the descending branch of the T wave was
determined, and the intersection of the extended line and the
baseline was evaluated. Due to known difficulties in defin-
ing the end of the T wave, all ECGs were analyzed twice by
two observers. The intraobserver variability in the measure-
ments of the QT interval was <3% and the interobserver
variability of the QT dispersion measurements was <5%.
Differences were resolved by consensus. The QTd was de-
efined as the difference between the longest QT interval
(QTmax) and the shortest QT interval (QTmin). In each
subject, a minimum of nine leads in which the QT interval
could be measured were used to determine the degree of QT
dispersion.

Urine specimen collection and urinary sodium and
potassium determination

Three urine samples were collected on the fifth, sixth and
seventh days of each period [1: 24-hour (h) urine, 2: noc-
turia].

Urine specimen collection

Instructions for collecting the 24-hour and nocturnal urine
samples were distributed to the participants, with emphasis
on the urine collection method and specific processes. A
special urine collecting bucket was given to each subject
that was rinsed clean with water before and after use. A
small amount of boric acid was added to the 24-hour urine
samples as a preservative. Each subject was allotted a 1,000-
ml plastic cup to gather urine when out of the house. No
less than 22 hours was required to gather urine within 24
hours, with a urine output of no less than 500 mL, while no
less than six hours was required for the eight-hour nocturia
time, with a volume of no less than 150 mL. If this require-
ment was not met, it was necessary to repeat the urine col-
lection according to the specific situation. The start and end
times of urine collection were recorded, using the cylinder
to measure the volume. A urine sample of 5 mL was drawn
into each respective urine storage tube, which was kept in

Table 1. General Characteristics of Subjects (x ± s)

<table>
<thead>
<tr>
<th>Items</th>
<th>M</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>Age (y)</td>
<td>49.6±6.1</td>
<td>46.2±5.9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.3±2.4</td>
<td>24.3±3.2</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117.9±13.9</td>
<td>119.1±13.0</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>75.3±10.3</td>
<td>77.2±9.2</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>89.7±12.2</td>
<td>90.9±11.1</td>
</tr>
</tbody>
</table>

Note: 1 mmHg = 0.133 kPa

Table 2. Blood Pressure Changes of Subjects in Each Per-
period (mmHg, x ± s)

<table>
<thead>
<tr>
<th>Periods</th>
<th>SBP</th>
<th>DBP</th>
<th>MAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>117.3±13.8</td>
<td>75.7±9.6</td>
<td>89.0±11.4</td>
</tr>
<tr>
<td>Low salt</td>
<td>111.7±11.3#</td>
<td>71.7±7.7#</td>
<td>86.4±8.3#</td>
</tr>
<tr>
<td>Salt loading</td>
<td>118.6±13.5#</td>
<td>76.9±8.6#</td>
<td>90.8±9.6#</td>
</tr>
<tr>
<td>High salt with potassium supplementation</td>
<td>114.5±12.3#</td>
<td>72.2±7.9#</td>
<td>87.3±9.3#</td>
</tr>
</tbody>
</table>

Note: Compared with the previous period, #p<0.01

All data were statistically analyzed using the SPSS13.0
software package and are presented as the mean ± standard
development (x ± s). A variance analysis of the randomized
block design was used to compare the blood pressure mea-
surements obtained in each period, and the paired t-test was
used to compare the self pre-and post-intervention values for
each period. Multiple linear regression models were adopted
in order to perform a multifactor relativity analysis. A p
value of <0.05 was considered to be statistically significant.

Results

Profiles of the subjects

All 64 patients completed the 21-day intervention trial.
The baseline age, gender, body mass index, systolic blood
pressure, diastolic blood pressure and mean arterial pressure
values of the subjects are shown in Table 1.

Blood pressure changes in each intervention period

The blood pressure values of all subjects fluctuated in
each intervention period, with a decrease in blood pressure
observed after the low-salt period (p<0.01) and in the high-
salt potassium supplementation period (p<0.01) and an in-
crease in blood pressure noted after the salt loading period
(p<0.01) (Table 2, Fig. 1).
Serum levels of potassium and sodium in each period

In the low-salt period, the serum sodium levels decreased in comparison with that observed at baseline period and then rose significantly in the high-salt period, maintaining this trend in the high-salt potassium supplementation period. Meanwhile, the serum potassium levels exhibited no differences between the baseline period and the low-salt period, although they decreased slightly in the high-salt period and then increased obviously in the high-salt potassium supplementation period (Table 3).

Changes in 24-hour urinary sodium and potassium excretion in each intervention period (Fig. 2)

The 24-hour urinary sodium excretion decreased significantly in the low-salt period. In addition, the 24-hour urinary sodium and potassium excretion was significantly higher in the salt loading period than in the low-salt period, and the 24-hour urinary potassium excretion significantly increased in the high-salt potassium supplementation period (p <0.01).

Changes in relevant indicators on ECG in each period

The QTc, QTdc, QTd and Tp-Te values were shorter in the low-salt period than at baseline. In contrast, the QTc, QTdc and Tp-Te values were higher in the salt loading period than in the low-salt period and significantly lower in the high-salt potassium supplementation period than in the salt loading period (Table 4).

Multiple stepwise linear regression analysis

The change in QTdc from before to after the consumption of the low-salt diet was used as the dependent variable, while the changes in age, gender, body mass index, systolic blood pressure, diastolic blood pressure, mean arterial pressure and 24-hour urinary sodium and potassium excretion were used as independent variables. Consequently, the multiple stepwise linear regression analysis showed that the changes in gender and diastolic blood pressure correlated with the change in QTdc, with a corresponding model determination coefficient of R²=0.141 (Table 5). The change in QTdc from before to after the salt loading period was then used as the dependent variable, and the changes in age, gender, body mass index, systolic blood pressure, diastolic blood pressure, mean arterial pressure and 24-hour urinary sodium and potassium excretion were used as independent variables. Consequently, the multiple stepwise linear regression analysis showed that the changes in BMI and 24-hour urinary sodium excretion correlated with the change in QTdc, with a corresponding model determination coefficient of R²=0.147 (Table 6). Finally, an analysis was performed with the change in QTdc from before to after the high-salt potassium supplementation period as the dependent variable.
Table 4. Related Indicator Changes of Subjects in Each Period in ECG (x ± s)

<table>
<thead>
<tr>
<th>Periods</th>
<th>Heart rate (times/min)</th>
<th>QT intervals (ms)</th>
<th>QTc(ms)</th>
<th>QTd(ms)</th>
<th>QTdc(ms)</th>
<th>Tp-Te(ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>67.3±8.5</td>
<td>385.1±19.9</td>
<td>402.4±22.1</td>
<td>52.1±23.4</td>
<td>61.6±23.6</td>
<td>85.0±10.6</td>
</tr>
<tr>
<td>Low salt</td>
<td>72.4±9.6</td>
<td>372.0±21.4</td>
<td>396.0±23.2</td>
<td>45.6±15.6</td>
<td>55.6±19.4</td>
<td>79.8±8.5</td>
</tr>
<tr>
<td>Salt loading</td>
<td>71.2±8.4</td>
<td>370.4±20.2</td>
<td>406.2±22.6</td>
<td>47.4±19.0</td>
<td>60.3±19.4</td>
<td>83.0±10.1</td>
</tr>
<tr>
<td>High salt with potassium supplementation</td>
<td>71.7±9.4</td>
<td>367.7±20.4</td>
<td>394.9±20.0</td>
<td>42.6±15.1</td>
<td>52.2±18.0</td>
<td>79.1±8.5</td>
</tr>
</tbody>
</table>

Note: QTc: corrected QT interval, QTd: QT dispersion, QTdc: corrected QT dispersion, Tp-Te: T peak - end interval, compared with the previous period, *p<0.05, #p<0.01

Table 5. Multiple Linear Regression Analysis of Corrected QT Interval Dispersion

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Partial regression coefficient b</th>
<th>Standard error</th>
<th>Standard partial regression coefficient β</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constants</td>
<td>16.057</td>
<td>9.654</td>
<td>-</td>
<td>1.663</td>
<td>0.101</td>
</tr>
<tr>
<td>Gender</td>
<td>-15.494</td>
<td>6.016</td>
<td>-0.311</td>
<td>-2.576</td>
<td>0.012</td>
</tr>
<tr>
<td>Δ Diastolic blood pressure</td>
<td>-3.450</td>
<td>1.524</td>
<td>-0.273</td>
<td>-2.264</td>
<td>0.027</td>
</tr>
</tbody>
</table>

Note: The regression equation: y= 16.057-15.494 x1-3.45 x2 (x1 is gender, x2 is Δ diastolic pressure).

Table 6. Multiple Stepwise Linear Regression Analysis of Corrected QT Interval Dispersion

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Partial regression coefficient b</th>
<th>Standard error</th>
<th>Standard partial regression coefficient β</th>
<th>t value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constants</td>
<td>26.911</td>
<td>20.738</td>
<td>-</td>
<td>1.298</td>
<td>0.199</td>
</tr>
<tr>
<td>Body weight index</td>
<td>-0.489</td>
<td>0.233</td>
<td>-0.248</td>
<td>-2.096</td>
<td>0.040</td>
</tr>
<tr>
<td>24h urinary sodium excretion</td>
<td>0.068</td>
<td>0.028</td>
<td>0.293</td>
<td>2.476</td>
<td>0.016</td>
</tr>
</tbody>
</table>

Note: The regression equation: y= 26.911-0.489x1+0.068x2 (x1 is body mass index, x2 is 24h urinary sodium excretion).
and the changes in age, gender, body mass index, systolic blood pressure, diastolic blood pressure, mean arterial pressure and 24-hour urinary sodium and potassium excretion were used as the independent variables. Consequently, the multiple stepwise linear regression analysis showed that the changes in body mass index and diastolic blood pressure correlated with the change in QTdc, with a corresponding model determination coefficient of $R^2=0.141$ (Table 7).

**Table 7. Multiple Stepwise Linear Regression Analysis of Corrected QT Interval Dispersion**

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Partial regression coefficient b</th>
<th>Standard error</th>
<th>Standard partial regression coefficient $\beta$</th>
<th>$t$ value</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constants</td>
<td>-46.697</td>
<td>19.792</td>
<td>-</td>
<td>-2.359</td>
<td>0.022</td>
</tr>
<tr>
<td>Body weight index</td>
<td>1.749</td>
<td>0.809</td>
<td>0.257</td>
<td>2.161</td>
<td>0.035</td>
</tr>
<tr>
<td>$\Delta$ Diastolic blood pressure</td>
<td>4.440</td>
<td>1.831</td>
<td>0.288</td>
<td>2.424</td>
<td>0.018</td>
</tr>
</tbody>
</table>

Note: The regression equation: $\hat{y} = -46.697 + 1.749x_1 + 4.440x_2$ ($x_1$ is body mass index, $x_2$ is $\Delta$ diastolic blood pressure).

Discussion

We herein report for the first time that healthy subjects on a high-salt diet exhibit greater QT interval dispersion and Tp-Te than those on a low-salt diet, with the same trend for the serum sodium concentration. In addition, the significant increase in the serum potassium level induced by oral potassium aspartate supplementation tends to reduce the degree of QT interval dispersion. The present study subjects had three special characteristics. First, all subjects enrolled in this study came from a rural community and had similar lifestyle factors, including diet and physical activity, which reduced the data variation associated with individual lifestyle differences. Second, an approach of collective catering and diet with unified management was adopted to maintain the dietary intervention, which ensured the homogeneity of salt intake. Third, all subjects were cooperative in the different periods, especially regarding urine collection.

The degree of QT interval dispersion reflects regional differences in ventricular repolarization heterogeneity and electrical instability, which are important predictors of malignant arrhythmia and sudden cardiac death. This parameter has been widely used in studies of hypertension, coronary heart disease, arrhythmia and other heart diseases as well as to evaluate drug efficacy (7, 8).

In this study, we found that the amount of salt intake correlated with the QTd, meaning that the QTd values decreased under the low-salt diet in the normotensive subjects and increased under the high-salt diet. Lim et al. (9) reported that the QTd increases after salt loading in patients with hypertension, and Tzemos et al. (5) further observed that the QTd significantly increases after salt loading in normotensive healthy youth; however, why the degree of QT dispersion increases after salt loading remains unknown. After salt loading, an increased level of extracellular sodium ions increases the cytosolic calcium concentration by promoting Na+/Ca2+ exchange, and the cytosolic calcium ions increase myocardial contractions and decrease myocardial relaxation, with subsequently decreased compliance via a mechanical-electrical feedback mechanism, thus inducing an increase in the degree of ventricular repolarization dispersion with prolonged QT dispersion.

Moreover, a high salt intake impairs the endothelial function and increases ventricular stiffness, while an elevated systolic and diastolic blood pressure increases the load on the heart as well as wall stress. Furthermore, a high level of salt affects the cell membrane, cell adhesion molecules and cytoskeletal components, passes into stretch-activated channels (10-13) and has an impact on the action potential, which is an important factor causing increased QT dispersion. In addition, previous studies have shown an increase in ventricular repolarization heterogeneity to be associated with the reentrant activity, resulting in a variety of ventricular arrhythmias.

Finally, long-term sodium intake leads to cardiac myocyte hypertrophy and increased interstitial collagen formation by mediating various hemodynamic and neurohormonal factors. Cardiac myocyte hypertrophy subsequently induces changes in ion channels and prolongs the duration of action potentials, while interstitial collagen reduces the current action and membrane potential, resulting in an increase in myocardial repolarization heterogeneity in different regions, which may participate in the increase in QTd observed after salt loading.

A prior study found that hypokalemia increases ventricular repolarization heterogeneity, which easily induces arrhythmias (14). In addition, supplementing potassium through the diet lowers the potassium levels to normal in Sprague-Dawley rats, while also shortening the QT interval and reducing the QTd. Furthermore, Choy et al. (15) found that intravenously supplementing potassium shortens the QT interval and QTd, even when the serum potassium concentration is within the normal range in patients with long QT syndrome, and Franzoni et al. (6) suggested that the low potassium levels noted in patients with anorexia nervosa is an important factor leading to an increase in QTd and that oral potassium may increase the serum potassium concentration to some extent, thus improving the cardiac electrical repolarization process. Meanwhile, the present study found that,
among normotensive healthy adults on a high-salt diet, supplementing high-dose potassium not only reduces blood pressure, but also significantly shortens the QTc, QTd and QTdc. One possible mechanism underlying these findings is elevation of the extracellular potassium ion concentration after oral potassium supplementation, which improves cardiac cell excitability and the action potential repolarization velocity (16, 17), increases the net myocardial repolarization current, shortens the action potential duration (18, 19) and narrows the action potential duration (APD) (19) between Purkinje fibers and myocardial fibers, thereby improving myocardial repolarization heterogeneity. Additionally, the fact that the degree of QT dispersion is shortened by oral potassium supplementation indicates that, in addition to antagonizing the pressor effect of sodium, supplementing potassium reduces the impact of a high salt intake on the QTd and QTdc values and lessens cardiac repolarization heterogeneity, which may have a preventive effect on arrhythmia. Hence, in addition to salt restriction, increasing the potassium/sodium ratio, is an important strategy for the primary prevention of hypertension and cardiovascular disease.

There are several limitations associated with this study. First, although the salt sensitivity status is an important factor influencing the QT and QTd values, the subjects were not assessed according to salt sensitivity due to the small size. Second, since all subjects enrolled in this study were Chinese, it is not clear whether our results are applicable to other races. Third, the mechanisms underlying the changes in the QT and QTd values in different periods are not clear. Further studies are therefore required to overcome these limitations.

Conclusion

In this study, the subjects underwent a three-day baseline examination with a seven-day low-salt period, seven-day salt loading period and seven-day high-salt potassium supplementation period. Consequently, the QT and QTd values increased significantly in the salt-sensitive subjects following the consumption of the high-salt diet. Prolonged QT and QTd values are a dangerous signal of malignant arrhythmia and sudden cardiac death. Hence, increasing potassium intake, and thereby improving the dietary potassium/sodium ratio, is thus considered to be an effective means of achieving cardiovascular protection.

The authors state that they have no Conflict of Interest (COI).

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References