Salt loading on QT dispersion and the protective role of potassium supplement in normotensive adults

Abstract
QT interval dispersion (QTd) has been suggested to reflect the heterogeneity of myocardial repolarization and widely used in hypertension, coronary heart disease, arrhythmia, evaluation of a drug and so on. The aim of this study was to investigate the effects of dietary sodium intake on QTd and Tpeak-Tend interval (Tp-Te) in normotensive healthy adults and the protective effect of dietary potassium. Sixty-four normotensive subjects aged 20~60 were selected and involved in a 3-week test in chronic salt loading and potassium supplementation, including baseline survey (baseline phase) for 3d, low-salt diet (3g/day, NaCl, low-salt phase), high-salt diet (18g/day, salt loading phase) and high-salt with potassium supplementation diet (4.5g/day, KCl, salt and potassium supplement phase) each for 7d. Blood pressure was measured and ECG was recorded at the last day of each phase, QT interval, QTd, corrected QTd (QTcd) and Tp-Te were measured and calculated. QTd, QTcd and Tp-Te at low-salt phase were less than those at baseline phase (QTd, 45.6±7.6ms vs. 52.1±5.4ms; QTcd, 53.4±8.4ms vs. 62.9±10.1ms; Tp-Te, 75.2±8.2ms vs. 85.0±9.6ms, P<0.05); QTd and Tp-Te after salt loading were greater than those at low-salt phase (QTcd, 62.3±7.9ms vs. 53.4±8.4ms; Tp-Te, 84.7±10.0ms vs.75.2±8.2ms, P<0.05); compared with those at salt loading phase, QTd, QTcd and Tp-Te were all reduced by large doses of oral potassium supplementation(QTd, 42.6±8.3ms vs. 53.4±9.1ms; QTcd, 52.2±6.2ms vs.62.3±7.9ms; Tp-Te, 75.1±8.5ms vs. 84.7±10.0ms, P<0.05). Salt loading increases blood pressure and prolongs QTd, QTcd and Tp-Te, while potassium supplementation reduces the influences of high salt on QTd, QTcd and Tp-Te, suggesting that high potassium intake may decrease the heterogeneity of cardiac repolarization and prevent arrhythmia by shortening repolarization time.

Keywords: QT, interval dispersion, Tpeak-Tend interval, salt, potassium

Introduction
High salt intake not only raises blood pressure, but also has multi-effectiveness independently of blood pressure, which directly induce target organ damage. As a sodium antagonist, potassium can antagonize increase in blood pressure, and potassium supplementation can protect against the cardiovascular system injuries caused by excessive sodium intake. QT interval dispersion (QTd), which is defined as the difference between the maximum and minimum QT intervals, is an indicator reflecting the degrees of heterogeneity and electrical instability of ventricular repolarization. It is of great value in predicting malignant arrhythmias and sudden cardiac death. It has also been widely applied in researches, as well as evaluations of drug efficacy, on heart diseases including hypertension, coronary heart disease, arrhythmia, etc. Tpeak-Tend interval (T-T) is an interval from the peak to the end of T wave, which closely represents transmural dispersion of repolarization. It is also an important predictor of ventricular arrhythmia events. Wolke et al., reported the changes in T-T and other indices of electrical dispersion in patients with hypertensive left ventricular hypertrophy. Tzemo et al., found that QTd had been significantly increased in 16 healthy young normotensives after dietary high salt intervention (200mmol/d) for 5d, while Franzoni et al., found that QTd had been significantly reduced in patients with anorexia nervosa after oral administration of potassium. This study aimed to observe the influences of dietary high salt intake on QTd, T-T, and changes after simultaneous potassium supplementation in normotensive healthy adults.

Materials and methods
Participants
Normotensive subjects aged 20~60 were enrolled from the Chinese Han population in the rural area of Mei County, Shaanxi Province, to participate in the tests. Cases, such as patients with severe cardiovascular disease, liver and kidney diseases and other acute or chronic diseases, pregnant women, frequent drinkers, those who were unwilling to sign the informed consent form and those who could not adhere to complete the test, were excluded. A total of 64 cases were selected, including 29 males and 35 females, aged 47.8±6.0. All participants signed the informed consent form. The study was approved by the ethics committee of our hospital.

Baseline survey and dietary intervention
All participants underwent a baseline survey for 3d (baseline phase), including medical history, lifestyle, risk factor, height, body mass, waist circumference, consecutive 3d blood pressure and electrocardiogram. Then they underwent a 3-week chronic salt
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Instructions for collection of 24 or

It depended on the

-Tpeak

Interval (Tend) were determined. Measurement of Tpeak (QTcd) were calculated according to the Bazzett formula.

-d= maximum QT interval (QTmax) - minimum QT interval (QTmin). The corrected QT interval (QTc) and corrected QT dispersion (QTcd) were calculated according to the Bazzett formula.

Measurement of Tpeak-Tend Interval (Tpeak-Tend): It depended on the determinations of Tpeak and Tend.

i. Tpeak was the vertex of peak of T wave.

ii. Determination of Tend: when the T wave shape was normal with relatively steep descending branch, it was determined at the intersection of T wave and the baseline; when the descending branch of T wave was relatively flat, it was determined at the intersection of the tangent line at the steepest point of the descending branch and the baseline; when both the start and end points of U wave were significant, it was determined at the lowest point of the intersection of T wave and U wave; when the T wave had double peaks with similar amplitudes, the ending of the second peak of T wave was measured; when the T wave and U wave were partially mixed together and difficult to be determined, the descending branch of T wave was extended and the Tend was determined at the intersection of the extended line and the baseline.

Collection of urine specimen and determination of urinary sodium and potassium

Urine specimens were collected 3 times on the 5th, 6th, and 7th day of each phase (124h urine and 2 nighttime urines).

Collection of urine specimens: instructions for collection of 24 or nighttime urine were given to the participants, and the start and end times of urine collection were recorded. The volumes of collected urines were measured with a measuring cylinder. 5ml of urine specimens were drawn and respectively transferred to each urine storage tube, stored at -80°C until test.

Determination of urinary sodium and potassium: concentrations of urinary sodium and potassium were measured with flame photometer (AP1200, Shanghai Precision Instruments Co., Ltd), and the results were multiplied by the total amount of urine, expressed as mmol.

Statistical methods

All the data were expressed as mean±SE. Comparisons between blood pressures of each phase were performed with analysis of variance of randomized block design information, and a paired t test was employed for comparison before and after. Relationship between changes in QTc and multiple factors was analyzed with multiple linear regressions. P<0.05 was considered statistically significant.

Results

General characteristics of participants

All the 64 participants completed the 21-day intervention test. Differences in indicators between male and female were not statistically significant (P>0.05, Table 1).

Table 1 General characteristics of studied subjects

| Parameter | Male(n=29) | Female(n=35) |
|-----------|------------|--------------|
| Age (y)   | 49.6±6.1   | 46.2±5.9     |
| BMI(kg/m²) | 24.3±2.4   | 22.8±1.9     |
| SBP(mmHg) | 125.1±13.9 | 121.8±12.7   |
| DBP(mmHg) | 81.3±7.6   | 79.4±9.2     |
| MAP(mmHg) | 95.3±10.2  | 93.6±11.1    |

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure

Changes in blood pressure in each phase of intervention

All participants showed fluctuations in blood pressure at each phase, as the blood pressure dropped at low-salt phase (SBP, 111.7±10.3mmHg vs. 123.3±12.8mmHg; DBP, 73.7±6.8mmHg vs. 80.7±7.1mmHg; MAP, 86.4±7.5mmHg vs. 94.0±9.1mmHg, P<0.05), increased at salt loading phase, and decreased at high-salt potassium-supplement phase, but the difference was not statistically significant (P>0.05), (Table 2) (Figure 1).

Citation: Lian Q, Wang X, Jiang W, et al. Salt loading on QT dispersion and the protective role of potassium supplement in normotensive adults. J Nutr Health Food Eng. 2015;2(4):139–143. DOI: 10.15406/jnhfe.2015.02.00063
Changes in ECG-related indicators at each phase

QTd, QTcd, and T<sub>p</sub>-T<sub>e</sub> at low salt phase were less than those at baseline phase (QTd, 45.6±7.6ms vs. 52.1±9.4ms; QTcd, 53.4±8.4ms vs. 62.9±10.1ms; T<sub>p</sub>-T<sub>e</sub>, 75.2±8.2ms vs. 85.0±9.6ms, P<0.05); QTcd and T<sub>p</sub>-T<sub>e</sub> at salt loading phase were greater than those at low-salt phase (QTd, 62.3±7.9ms vs. 53.4±8.4ms; T<sub>p</sub>-T<sub>e</sub>, 84.7±10.0ms vs.75.2±8.2ms, P<0.05); QTd, QTcd, and T<sub>p</sub>-T<sub>e</sub> at high-salt potassium-supplement phase were less than those at salt loading phase (QTd, 42.6±8.3ms vs. 53.4±9.1ms; QTcd, 52.2±6.2ms vs.62.3±7.9ms; T<sub>p</sub>-T<sub>e</sub>, 75.1± 8.5ms vs. 84.7±10.0ms, P<0.05, (Table 3).

Multiple linear regression analysis

With changes in QTcd before and after low-salt diet as the dependent variable, factors including age, gender, BMI, changes in systolic and diastolic blood pressure, changes in mean arterial pressure, and variations in the excretions of 24h urinary sodium and potassium as the independent variables, the multiple linear stepwise regression analysis was performed. Results showed that there was a linear regression relationship between changes in QTcd and gender and changes in diastolic blood pressure, with gender making a bigger difference in QTcd before and after low-salt diet (Table 4). With changes in QTcd before and after salt loading as the dependent variable, factors including age, gender, BMI, changes in systolic and diastolic blood pressure, changes in mean arterial pressure, and variations in the excretions of 24h urinary sodium and potassium as the independent variables, the multiple linear stepwise regression analysis was performed. Results showed that changes in QTcd were related to BMI and changes in excretion of 24h urinary sodium (Table 5). With changes in QTcd before and after high salt with potassium supplement as the dependent variable, factors including age, gender, BMI, changes in systolic and diastolic blood pressure, changes in mean arterial pressure, and variations in the excretions of 24h urinary sodium and potassium as the independent variables, the multiple linear stepwise regression analysis was performed. Results showed that changes in QTcd were related to BMI and changes in diastolic blood pressure (Table 6).

Changes in excretion of 24h urinary sodium and potassium in participants at each phase

At low-salt phase, excretion of 24h urinary sodium in participants was significantly reduced; at salt loading phase, excretions of 24h urinary sodium and potassium were significantly higher than those at low-salt phase; at high-salt with potassium-supplement phase, excretion of 24h urinary potassium was significantly increased (P<0.01, Figure 2).
Table 3 Changes in ECG-related indicators in subjects at each phase

| Stage           | Heart rate (b/min) | QT (ms)  | QTc (ms) | QTd (ms) | QTcd (ms) | Tp–Te (ms) |
|-----------------|--------------------|----------|----------|----------|-----------|------------|
| Baseline        | 65.3±8.1           | 385±19.9 | 402±22.1 | 52.1±9.4 | 62.9±10.1 | 85.0±9.6   |
| Low salt        | 73.4±7.6*          | 362.0±21.4* | 386.0±23.2* | 45.6±7.6* | 53.4±8.4* | 75.2±8.2*   |
| High salt       | 71.2±8.4           | 370.4±20.2 | 406.2±22.6 | 53.4±9.1 | 62.3±7.9* | 84.7±9.9*   |
| High salt and K+| 71.7±9.4           | 367.5±18.4 | 394.9±20.0 | 42.6±8.3* | 52.2±6.2* | 75.1±8.5*   |

Discussion

QTd is often used to evaluate the cardiac electrical activity status and predict the occurrence of ventricular arrhythmias. QTd is significantly increased in patients with ventricular arrhythmias or sudden cardiac death, showing more value in predicting sudden cardiac death.\(^\text{10-13}\) Mediated by hemodynamic factors and neurohormonal factors, hypertension can cause cardiac myocyte hypertrophy and increase interstitial collagen. The former leads to prolonged action potential duration, while the latter can reduce the action potential current and membrane potential, increasing the heterogeneity of myocardial repolarization. Sodium salt is one of the most important environmental factors for hypertension. In this study, QTd was reduced in normotensives after low-salt diet while increased after high-salt diet intervention, suggesting the correlation between salt intake and QTd. Lim et al.\(^\text{14}\) reported that QTd had been increased in hypertensive patients after salt loading, while Tzemos et al.\(^\text{15}\) further observed that QTd had also been increased in normotensive youngs after salt loading. High salt intake impairs vascular endothelial functions and increases the ventricular stiffness. Furthermore, the elevated systolic and diastolic blood pressure can increase the cardiac load, and the ventricular wall stress transmitted to the stretch stress, through the cell membrane, cell adhesion molecules and cytoskeletal, can activate the ion channels\(^\text{15-17}\) and impact the action potential, which may be the reason for the increase in dispersion of ventricular repolarization. Studies have shown that the increased heterogeneity of ventricular repolarization is prone to form re-entry activities, causing a variety of ventricular arrhythmias. Studies have found that the increased heterogeneity of ventricular repolarization during hypokalemia tends to induce arrhythmias.\(^\text{15}\) However, dietary supplement of potassium can turn the low serum potassium levels back to a normal one, simultaneously shortening the QT interval and reducing the QTd. Choy et al.\(^\text{16}\) found that the QT interval and QTd in patients with long QT

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syndrome could be reduced by intravenous supplement of potassium, even if their serum potassium were at normal levels. Franzi On et al. Believed that the low levels of serum potassium in patients with anorexia nervosa was an important factor leading to the increase in QTd, and oral potassium supplement might adequately increase the concentration of serum potassium and improve the process of myocardial electrical repolarization. This study found that, for healthy adults with normal blood pressure, on the basis of high salt, large dose of potassium supplement could not only decrease the blood pressure, but also significantly shorten the QTc, QTd and QTcd. This suggested that, in addition to antagonizing the pressor effects of sodium salt, potassium supplement could also lower the impacts of high salt on QTd and QTcd, reduce heterogeneity of cardiac repolarization, and probably be effective in preventing arrhythmia.

In China, the incidence of hypertension has been increased year by year. Dietary high sodium but low potassium intake is an important factor in the pathogenesis of hypertension among the Chinese population, especially in the rural areas of Northern China. Most of the clinical manifestations are salt-sensitive hypertension, moreover, the high incidence of stroke, coronary heart disease and cardiovascular disease death continues to increase. Therefore, it is of important clinical significance to further explore the pathogenesis of target organ damages induced by high salt, as well as the effects of potassium supplementation. This study observed that large dose of potassium supplementation could shorten QTd, QTdc and Tc-Tp caused by high-salt diet, thereby making it possible to reduce the incidence of cardiovascular events. Therefore, in addition to salt restriction, increasing potassium intake and improving of dietary potassium/sodium ratio is another crucial strategy for primary prevention of hypertension and cardiovascular protection.

Conclusion

This study has shown that high salt intake increases blood pressure and prolongs QTd, QTcd and Tc-Tp, while oral potassium supplementation reduces the influences of high salt on QTd, QTcd and Tc-Tp, suggesting that high potassium intake may decrease the heterogeneity of cardiac repolarization and prevent arrhythmia by shortening repolarization time.

Acknowledgements

This work was supported by grants 81070218 and 30900616 from the National Natural Science Foundation of China.

Conflict of interest

The author declares no conflict of interest.

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