Association between dietary sodium intake and blood pressure variability in Chinese patients with hypertension

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Abstract
Background: The association between dietary sodium intake and blood pressure variability (BPV) in hypertensive patients remains unclear. The objective of this study was to demonstrate whether dietary sodium intake is a predictor of elevated BPV in Chinese patients with hypertension.

Methods: A total of 235 patients with essential hypertension were enrolled in the Department of Cardiology, Chinese People’s Liberation Army (PLA) General Hospital in 2018 to 2019, all of whom underwent 24-h ambulatory blood pressure monitoring. BPV was calculated as the standard deviation (SD), coefficient of variation (CV), variation independent of mean (VIM) of blood pressure measurements, respectively, and divided into diurnal systolic BPV (SBPV), diurnal diastolic BPV (DBPV), nocturnal SBPV, and nocturnal DBPV. 24-h urine samples were collected to measure 24-h urine sodium excretion, which represents dietary sodium intake. The relationship between dietary sodium intake and BPV was analyzed by using Spearman correlations and multiple linear regression analysis.

Results: Nocturnal SBPV-SD, CV, VIM, and nocturnal DBPV-SD in the high urine sodium excretion group were significantly higher than those in the medium and low urine sodium excretion groups, whereas diurnal SBPV-SD, CV, VIM, diurnal DBPV-SD, CV, VIM, and nocturnal DBPV-CV, VIM were not. Using the Spearman correlation analysis, we found a linear correlation between 24-h urine sodium excretion and nocturnal SBPV-SD, CV, VIM (SD, r = 0.22, P = 0.001; CV, r = 0.17, P = 0.009; VIM, r = 0.16, P = 0.020), nocturnal DBPV-SD (r = 0.21, P = 0.001), respectively. After further adjusting for confounding factors by multiple linear regression, the positive correlations remained between 24-h urine sodium excretion and nocturnal SBPV-SD, CV, VIM (SD, \( \beta = 0.224, P < 0.001; \) CV, \( \beta = 0.211, P = 0.001; \) VIM, \( \beta = 0.213, P = 0.001; \) ), nocturnal DBPV (SD, \( \beta = 0.213, P = 0.001; \) ), respectively.

Conclusions: Dietary sodium intake is associated with nocturnal SBPV in Chinese patients with hypertension.

Keywords: Hypertension; Sodium intake; Blood pressure variability

Introduction
Hypertension is one of the most important risk factors of morbidity and mortality in cardiovascular diseases.¹ A higher blood pressure (BP) is strongly related to a higher risk of cardiovascular events.₂ Blood pressure variability (BPV), as a measure of BP fluctuation, is also associated with increased cardiovascular risk, independent of BP level.³⁻⁵ Recent findings have illustrated that the effect of different classes of anti-hypertensive drugs on the risk of stroke is different due to intra-individual BPV.⁶ However, in contrast to BP, few studies have investigated the predictors of BPV. Additionally, high dietary sodium intake is not only an independent risk factor for cardiovascular events,⁷⁻⁸ but also significantly increases the BP level in patients with hypertension.⁷ However, the relationship between sodium intake and BPV is still controversial,¹⁰⁻¹³ and the association between sodium intake and BPV in Chinese patients with hypertension remains unclear. Therefore, we conducted a cross-sectional study on a hospital-based hypertensive population to investigate the association between dietary sodium intake and BPV.

Methods

Ethical approval
This study was approved by the Ethics Committee of Chinese People's Liberation Army (PLA) General Hospital.
Informed consent was obtained from all participants enrolled in this study.

Subjects

Our study was conducted on 235 hypertensive patients who were admitted to the Department of Cardiology, Chinese People’s Liberation Army (PLA) General Hospital from 2018 to 2019. The diagnostic criterion of hypertension is BP measurement ≥140/90 mmHg or use of anti-hypertensive medication according to the seventh Joint National Committee recommendation.[14] All of the patients enrolled in this study underwent history-taking, physical examination, 24-h ambulatory BP monitoring, 24-h urine electrolyte and albumin detection, and blood biochemical tests. Patients who met any of the following criteria were excluded: (1) age <18 years; (2) secondary hypertension; (3) prior myocardial infarction, heart failure, or valvular heart disease; (4) pulmonary hypertension; (5) diuretic use in the past 4 weeks; (6) estimated glomerular filtration rate (eGFR) <60 mL·min⁻¹·1.73 m⁻²; (7) severe liver dysfunction; or (8) rheumatic immune disease.

24-h ambulatory BP monitoring and BPV evaluation

Ambulatory BP and heart rate (HR) were measured every 30 min during daytime (8 AM to 10 PM) and every 60 min during night-time (10 PM to 8 AM) using fully automatic measuring devices (Oscar 2, SunTech, Morrisville, NC, USA) that were regularly calibrated. BP was measured using an oscillometric method with a cuff wrapped around the patient’s non-dominant arm. Each recording started in the morning. Patients were advised to avoid strenuous exercise and stop any activity when BP was measured. All measurements were recorded automatically, and lost or erroneous readings were <10% in all patients. Each patient’s diurnal and nocturnal average BP were calculated. Nocturnal systolic blood pressure (SBP) or diastolic blood pressure (DBP) decrements of less than 0, compared with diurnal average SBP or DBP, was defined as reverse-dipper BP. BPV was evaluated as the standard deviation (SD), coefficient of variation (CV), and variation independent of mean (VIM) of BP measurements, respectively. CV was calculated as the SD/the mean BP. VIM was defined as the SD divided by the mean to the power of X. Power X was modeled as SD = k × meanX and was derived from fitting curves by non-linear regression analysis. The calculation of power X was implemented in the PROC NLIN procedure of the SAS package (version 9.4; SAS Institute, Cary, NC, USA).[15,16] We separately calculated diurnal systolic BP (SBPV), diurnal diastolic BP (DBPV), nocturnal SBPV, and nocturnal DBPV to observe the effect of sodium intake on different sub-types of BPV.

Dietary sodium intake evaluation

Dietary sodium intake was evaluated by 24-h urine sodium excretion, which reflects more than 90% of the sodium intake from any source and is recognized as the gold standard measure of dietary sodium intake.[17] The 24-h urine collection began after the first urination in the morning and ended with the first urination on the second morning. After mixing, 10 mL of the urine sample was sent for biochemical testing using an auto-analyzer (Cobas s501, Roche, Basel, Switzerland). The 24-h urine sodium excretion was calculated as the sodium concentration (mmol/L) of the sample multiplied by the volume (L) of 24-h urine. All urine samples were collected by trained nurses.

Assessment of other covariates

History-taking and physical examinations were performed by trained physicians and nurses when patients were admitted in the hospital. Body mass index (BMI) was defined as the weight (kg) divided by the square of height (m). Ever-smokers were defined as patients with a history of smoking and ever-drinkers were defined as patients with a history of drinking. Blood samples were collected after an overnight fast and tested for fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), serum creatinine, serum potassium, and serum sodium using an auto-analyzer (Cobas 7000, Roche). We used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation to calculate patients’ eGFR.[18] Diabetes was defined as FBG ≥7.0 mmol/L, 2-h post-glucose load ≥11.1 mmol/L, or self-reported use of hypoglycemic medication.[19] Albuminuria was defined as 24-h albumin excretion ≥0.15 g/day.

Statistical analysis

Enrolled patients were divided into three groups according to 24-h urine sodium excretion levels: low (<100 mmol/day), medium (>100 and ≤200 mmol/day), and high (>200 mmol/day) sodium groups. Baseline data were expressed as mean ± SD or n (%). Continuous variables were compared using analysis of variance or Jonckheere-Terpstra test, and categorical variables were compared with the Chi square test. We used Spearman correlation coefficients to evaluate the correlation between 24-h urine sodium excretion and ambulatory BP level, BPV, respectively. The adjusted correlation between BPV and 24-h urine sodium excretion was analyzed using multiple linear regression analysis. We used a stepwise method to eliminate potential collinearity between different variables. To minimize the effect of albuminuria on the results of our study, we conducted a sensitivity analysis by excluding participants with albuminuria. Furthermore, to observe whether reverse-dipper BP circadian rhythm would modify the association between sodium intake and BPV, we performed a sub-group analysis by repeating the above statistical analysis in populations with different BP circadian rhythms. All statistical analyses were conducted using SPSS statistical software (version 19.0; IBM Corp., Armonk, NY, USA). A P value <0.05 was considered statistically significant.

Results

Of 235 participants, 91, 103, and 41 were categorized into the low, medium, and high sodium groups, respectively. Baseline characteristics of the study participants are shown in Table 1. Compared with participants in the low and medium sodium groups, those in the high sodium group were younger, had lower serum potassium, had higher proportion of males, ever-drinkers, and albuminuria, had higher BMI, diurnal average DBP, nocturnal average SBP,
In the correlation analysis between 24-h urine sodium excretion and ambulatory BP level, BPV respectively, nocturnal SBPV-SD, CV, VIM, and nocturnal DBPV-SD were positively associated with 24-h urine sodium excretion (nocturnal SBPV-SD, r = 0.22, P = 0.001; nocturnal SBPV-CV, r = 0.17, P = 0.009; nocturnal SBPV-VIM, r = 0.16, P = 0.020; nocturnal DBPV-SD, r = 0.21, P = 0.001) [Table 2 and Figure 2]. Additionally, we also found that 24-h urine sodium excretion was related to diurnal average SBP, diurnal average DBP, nocturnal average SBP, and nocturnal average DBP [Table 2].

Further multiple linear regression analysis showed that, after adjusting for other confounding factors (age, gender, BMI, nocturnal average SBP, nocturnal average DBP, nocturnal average HR, FBG, TG, TC, serum potassium, eGFR, smoking status, drinking status, anti-hypertensive medication use, albuminuria, and reverse-dipper BP), nocturnal SBPV-SD, CV, VIM, and nocturnal DBPV-SD remained independently correlated with 24-h urine sodium excretion (nocturnal SBPV-SD, β = 0.224, P < 0.001; nocturnal SBPV-CV, β = 0.211, P = 0.001; nocturnal SBPV-VIM, β = 0.213, P = 0.001; nocturnal DBPV-SD, β = 0.213, P = 0.001) [Table 3].

In the sensitivity analysis which excluded participants with albuminuria (n = 208), we observed a similar pattern that 24-h urine sodium excretion was independently related to nocturnal SBPV-SD, CV, VIM, and nocturnal DBPV-SD [Table 3]. In the sub-group analysis, the associations between 24-h urine sodium excretion and nocturnal SBPV-SD, CV, VIM, nocturnal DBPV-SD, respectively in reverse-dipper BP participants (n = 93) were still positively linear and more significant [Table 3]. However, in participants without reverse-dipper BP (n = 142), the linear association was observed only between 24-h urine sodium excretion and nocturnal SBPV-SD, CV [Table 3].

### Discussion

This study investigated the relationships between dietary sodium intake and BPV in Chinese hypertensive patients.

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**Table 1: Baseline characteristics of study population in different 24-h urine sodium excretion groups.**

| Characteristics | Low sodium (n = 91) | Medium sodium (n = 103) | High sodium (n = 41) | F/J/X² | P |
|-----------------|--------------------|------------------------|----------------------|-------|---|
| Age (years)     | 55.73 ± 16.06      | 54.50 ± 13.19          | 52.34 ± 11.80        | -1.68*| 0.090|
| Male, n (%)     | 38 (41.8)          | 62 (60.2)              | 31 (75.6)            | 14.60*| <0.001|
| BMI (kg/m²)     | 25.27 ± 3.66       | 26.36 ± 3.34           | 27.79 ± 3.78         | 3.34* | 0.001|
| Diurnal average SBP (mmHg) | 132.96 ± 18.56 | 138.70 ± 16.55        | 137.66 ± 19.30       | 1.97* | 0.048|
| Diurnal average DBP (mmHg) | 78.02 ± 13.57 | 82.32 ± 11.58         | 84.27 ± 12.76        | 3.27* | 0.001|
| Diurnal average HR (beats/min) | 72.00 ± 9.38 | 71.14 ± 9.80          | 73.07 ± 8.55         | 0.65†| 0.520|
| Nocturnal average SBP (mmHg) | 129.64 ± 20.80 | 134.42 ± 17.34        | 137.90 ± 22.31       | 2.47* | 0.010|
| Nocturnal average DBP (mmHg) | 74.25 ± 14.49 | 78.27 ± 12.41         | 84.15 ± 15.38        | 3.78* | <0.001|
| Nocturnal average HR (beats/min) | 62.11 ± 7.78 | 62.27 ± 8.78          | 64.68 ± 9.08         | 0.38* | 0.380|
| FBG (mmol/L)    | 5.26 ± 1.09        | 5.51 ± 1.60            | 6.30 ± 3.28          | 1.53* | 0.130|
| TG (mmol/L)     | 1.45 ± 0.71        | 1.88 ± 1.32            | 2.01 ± 1.20          | 3.09* | 0.002|
| TC (mmol/L)     | 4.35 ± 1.18        | 4.10 ± 0.98            | 4.16 ± 1.09          | -0.87*| 0.390|
| Serum potassium (mmol/L) | 3.81 ± 0.32 | 3.78 ± 0.32           | 3.64 ± 0.32          | 4.25†| 0.020|
| Serum sodium (mmol/L) | 142.12 ± 2.09 | 141.70 ± 2.32         | 142.31 ± 2.06        | -0.33*| 0.740|
| eGFR (mL/min·1.73m⁻²) | 92.26 ± 14.98 | 91.78 ± 13.62         | 98.29 ± 11.63        | 3.51†| 0.030|
| Ever-smoker, n (%) | 23 (25.3) | 40 (38.8)              | 17 (41.5)            | 5.17†| 0.080|
| Ever-drinker, n (%) | 23 (25.3) | 35 (34.0)              | 20 (48.8)            | 7.09†| 0.030|
| Anti-hypertensive medication, n (%) | 72 (79.1) | 83 (80.6)              | 30 (73.2)            | 0.98‡| 0.610|
| Diabetes, n (%) | 15 (16.5)          | 24 (23.3)              | 13 (31.7)            | 3.95‡| 0.140|
| Albuminuria, n (%) | 8 (8.8) | 8 (7.8)                | 11 (26.8)            | 11.54‡| 0.003|
| Reverse-dipper BP, n (%) | 34 (37.4) | 38 (36.9)              | 21 (51.2)            | 2.82‡| 0.240|

Data were presented as mean ± standard deviation or n (%). * J value was evaluated using Jonckheere-Terpstra test. † Value was evaluated using one-way analysis of variance. ‡ X² value was evaluated using Chi-square test. BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; bpm: Beats per minute; FBG: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; eGFR: Estimate glomerular filtration rate.
In the present study, we found that nocturnal SBPV-SD, CV, VIM, and nocturnal DBPV-SD were positively associated with 24-h urine sodium excretion. This linear association was also observed after excluding patients with albuminuria, particularly in the reverse-dipper BP population. These findings indicate that high dietary sodium intake is a predictor for elevated nocturnal SBPV. High dietary sodium intake has been shown to increase BP\(^7,20\) and the risk of cardiovascular events.\(^7-9\) Interestingly, previous findings suggested that elevated BP did not fully explain the increased risk of cardiovascular events due to high sodium intake.\(^7\) Ambulatory BPV is a hemodynamic factor independent of BP level and maybe another potential target that is affected by sodium intake. In the present study, we found that 24-h urine sodium excretion was a robust predictor for nocturnal SBPV, and this correlation was more significant in patients with reverse-dipper BP. Compared with diurnal BPV, nocturnal BPV changes are less affected by other random factors, including mood change, daily activities, and unpredictable situations. Therefore, nocturnal BPV more accurately reflects the condition of BP fluctuation.\(^23\) Studies have reported a consistent association between 24-h urine sodium excretion and both 24-h BPV and nocturnal BPV in non-diabetic and non-obese hypertensive patients.\(^10\) Another study in a normotensive population showed the same positive linear association between diurnal BPV and 24-h urine sodium excretion.\(^11\) However, a separate study has reported that a low-sodium diet intervention in overweight or obese individuals with only high-normal DBP did not reduce visit-to-visit BPV.\(^12\) Similarly, no significant changes in participants’ ambulatory BPV was observed using a 7-day low-sodium intervention in ten patients with hypertension and diabetes in another study.\(^13\) Several factors might explain these conflicting results. First, sodium intake has different effects in normotensive and hypertensive individuals.\(^17\) Second, given that genetic susceptibility to hypertension differs between populations in China and other countries,\(^12\) so too might the sodium sensitivity of BPV vary in different ethnic populations. Third, sample size can affect results, although our research included a relatively large sample size compared with former studies. In addition,

| Items                        | 24-h urine sodium excretion |
|------------------------------|-----------------------------|
|                              | \(r\) | \(P\) |
| Diurnal average SBP          | 0.18 | 0.006 |
| Diurnal average DBP          | 0.21 | 0.001 |
| Nocturnal average SBP        | 0.20 | 0.002 |
| Nocturnal average DBP        | 0.24 | <0.001 |
| Nocturnal SBPV-SD            | 0.22 | 0.001 |
| Nocturnal SBPV-CV            | 0.17 | 0.009 |
| Nocturnal SBPV-VIM           | 0.16 | 0.020 |
| Nocturnal DBPV-SD            | 0.21 | 0.001 |

BP: Blood pressure; SBPV: Systolic blood pressure variability; DBPV: Diastolic blood pressure variability; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; SD: Standard deviation; CV: Coefficient of Variation; VIM: Variation independent of mean.
the hypertensive patients in the present study were selected based on strict diagnostic criteria and precise 24-h urine sodium excretion data. Our findings represent the character of sodium intake affecting BPV in Chinese hypertensive patients.

The potential mechanisms for the relationship between dietary sodium intake and nocturnal SBPV remain unclear. Previous studies in rats showed that high sodium intake modulated the central gain of sympathetic circuits by acting on the anteroventral third ventricular region to alter the functional regulation of sympathetic nerve activity, which further increased BPV. In addition, hypertensive patients with the reverse-dipper pattern of BP circadian rhythm are more likely to be salt-sensitive. The night/day ratio of sodium excretion has been shown to be higher in reverse-dipper individuals and positively correlated with sodium intake. Thus, the conspicuous correlation between sodium intake and nocturnal BPV in patients with reverse-dipper BP can be explained in part by salt sensitivity and elevated nocturnal sodium excretion.

Strengths and limitations

Our study further explored the relationship between sodium intake and BPV in a Chinese hypertensive population. All hypertensive patients in the current study were selected based on strict physical examination, complete medical history collection, and secondary hypertension screening. The 24-h urine samples were collected under the guidance of trained nurses to ensure the integrity of the specimens. All patients were restricted from leaving the department or having strenuous activity during hospitalization, which further minimized sodium excretion through sweat and BPV changes affected by daily activities. However, some limitations must be considered. Our study was based on a cross-sectional analysis, which does not...
allow us to determine the causal relationship between high sodium intake and elevated nocturnal SBPV. In addition, limited by the sample size, only the SD of nocturnal DBPV increased with 24-h urine sodium excretion groups, whereas no significant difference was found among CV and VIM of nocturnal DBPV in different groups. This situation may change as the sample size increases. Besides, our study population was from a single center. Therefore, further large multi-center prospective intervention studies should be considered.

In conclusion, our results indicate that dietary sodium intake is a robust predictor for nocturnal SBPV in Chinese hypertensive population, particularly in patients with reverse-dipper BP.

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Conflicts of interest

None.

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Table 3: Multiple linear regression for the association between nocturnal BPV and 24-h urine sodium excretion.

| Parameters | B     | SE    | β     | t     | P     |
|------------|-------|-------|-------|-------|-------|
| 24-h urine sodium excretion, all patients (n = 235) |       |       |       |       |       |
| Nocturnal SBPV-SD | 0.015 | 0.004 | 0.224 | 3.762 | <0.001 |
| Nocturnal SBPV-CV | 9.28 x 10^-5 | 2.77 x 10^-5 | 0.211 | 3.349 | 0.001 |
| Nocturnal SBPV-VIM | 4.83 x 10^-5 | 1.43 x 10^-5 | 0.213 | 3.390 | 0.001 |
| Nocturnal DBPV-SD | 0.010 | 0.003 | 0.215 | 3.459 | 0.001 |
| 24-h urine sodium excretion, excluding patients with albuminuria (n = 208) |       |       |       |       |       |
| Nocturnal SBPV-SD | 0.013 | 0.004 | 0.189 | 2.942 | 0.004 |
| Nocturnal SBPV-CV | 7.12 x 10^-5 | 3.10 x 10^-5 | 0.138 | 2.299 | 0.020 |
| Nocturnal SBPV-VIM | 3.34 x 10^-5 | 1.65 x 10^-5 | 0.140 | 2.032 | 0.040 |
| Nocturnal DBPV-SD | 0.011 | 0.003 | 0.212 | 3.198 | 0.002 |
| 24-h urine sodium excretion, patients with reverse-dipper BP (n = 93) |       |       |       |       |       |
| Nocturnal SBPV-SD | 0.020 | 0.006 | 0.295 | 3.261 | 0.002 |
| Nocturnal SBPV-CV | 1.19 x 10^-4 | 4.01 x 10^-5 | 0.298 | 2.975 | 0.004 |
| Nocturnal SBPV-VIM | 1.29 x 10^-5 | 4.64 x 10^-6 | 0.284 | 2.784 | 0.007 |
| Nocturnal DBPV-SD | 0.021 | 0.005 | 0.411 | 4.243 | <0.001 |
| 24-h urine sodium excretion, patients without reverse-dipper BP (n = 142) |       |       |       |       |       |
| Nocturnal SBPV-SD | 0.011 | 0.005 | 0.172 | 2.143 | 0.030 |
| Nocturnal SBPV-CV | 8.74 x 10^-5 | 3.91 x 10^-5 | 0.183 | 2.236 | 0.030 |

* Adjusted for age, gender, BMI, nocturnal average SBP, nocturnal average DBP, nocturnal average HR, FBG, TG, TC, serum potassium, serum sodium, eGFR, smoking status, drinking status, anti-hypertensive medication use, albuminuria, and reverse-dipper BP.  † Adjusted for age, gender, BMI, nocturnal average SBP, nocturnal average DBP, nocturnal average HR, FBG, TG, TC, serum potassium, serum sodium, eGFR, smoking status, drinking status, anti-hypertensive medication use, and reverse-dipper BP.

β: Coefficient; SE: Standard error; CV: Coefficient of variation; VIM: Variation independent of mean; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HR: Heart rate; FBG: Fasting blood glucose; TG: Triglyceride; TC: Total cholesterol; eGFR: Estimate glomerular filtration rate.
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