Hypertension Research (2017) 40, 746–751

www.nature.com/hr

ORIGINAL ARTICLE

Relationships between urinary electrolytes excretion and central hemodynamics, and arterial stiffness in hypertensive patients

Weizhong Han[1], Xiao Han[2], Ningling Sun[3], Yunchao Chen[4], Shiliang Jiang[1] and Min Li[1]

High sodium intake plays an important role in the onset and exacerbation of hypertension. However, the relationships between urinary electrolytes excretion and central hemodynamics and between urinary electrolyte excretion and arterial stiffness are still the subject of debate. This study sought to clarify the associations of salt intake with central aortic pressure and arterial stiffness indicators. A total of 431 untreated hypertensive individuals were recruited into the study. Twenty-four-hour urinary samples were collected to measure the excretion of urinary electrolytes. Central hemodynamics parameters and brachial-ankle pulse wave velocity (baPWV) were measured. We evaluated the independent relationship between urinary sodium or potassium excretion and the abovementioned indices. The mean 24-h urinary sodium of all subjects was 166.6 ± 70.0 mmol/24 h. With increases in urinary sodium excretion, central blood pressure and baPWV values markedly increased. Multiple regression analysis showed that urinary sodium was independently associated with increases in central systolic blood pressure, central diastolic blood pressure, the augmentation index, and baPWV. Significant correlations were identified between high dietary sodium and central hemodynamics and between high dietary sodium and arterial elasticity. Prospective interventional studies in hypertensive patients may be required to determine the effect of salt intake on central hemodynamics.
Hypertension Research (2017) **40,** 746–751; doi:10.1038/hr.2017.29; published online 2 March 2017

Keywords: arterial stiffness; central blood pressure; urinary sodium

INTRODUCTION

Hypertension, with a global prevalence of 40%, is a consistent and independent risk factor for cardiovascular disease.[1] High salt intake plays an important role in the onset and aggravation of hypertension. The International Study of Salt and Blood Pressure (INTERSALT) showed an association between higher levels of sodium intake and higher blood pressure (BP) in both normotensive and hypertensive subjects.[2] Conventionally, BP is measured over the brachial artery, which is a poor surrogate for central aortic pressure. The heart, kidneys and major arteries supplying the brain are exposed to aortic rather than brachial BP. Therefore, there is a strong rationale that cardiovascular events may be more closely related to central rather than brachial BP.[3] Studies published over the last 10 years concerning the relationship between central BP and the surrogate markers of risk as well as hard endpoints strongly support this concept.[4,5] Central BP is invariably lower than corresponding brachial values, and this phenomenon of peripheral pressure amplification arises principally because of an increase in arterial stiffness in the periphery. In addition to increasing BP, high dietary salt may independently damage vascular function.[6] This can lead to hypertrophy of arterial walls and vascular smooth muscle, which impairs endothelial function, affects arterial vessel contractility and increases arterial stiffness. Although a number of studies have suggested that daily sodium intake is closely correlated with brachial BP and the risk of hypertension,[7–9] results concerning whether salt intake modifies central aortic pressure and its components have been inconsistent. In our study, we sought to elucidate the relationship between 24-h urine sodium and potassium excretion and parameters of central hemodynamics in untreated hypertensive individuals.

Measurements of arterial function and structure provide additional prognostic information regarding conventional risk factors. Indeed, aortic pulse wave velocity (PWV), an indicator of large artery stiffness, is a predictor of cardiovascular morbidity and mortality and is independent of traditional risk factors in patients with hypertension and in the general population.[10,11] Brachial-ankle PWV (baPWV), which reflects a combination of elastic and muscular arterial stiffness, has been widely used, and its measurement has become more convenient than other invasive methods.[12] However, few studies have evaluated the relationship between baPWV and daily urinary sodium excretion in untreated hypertensive subjects. The present study was

[1]Department of Cardiology, Shandong Provincial Hospital Affiliated to Shandong University, Shandong, China; [2]Department of Shandong Cancer Hospital Affiliated to Shandong University, Shandong, China; [3]Department of Heart Center, Hypertensive Laboratory, Peking University People's Hospital, Beijing, China and [4]Department of Radiology, Shandong Provincial Hospital Affiliated to Shandong University, Shandong, China
Correspondence: Dr W Han, Department of Cardiology, Shandong Provincial Hospital Affiliated to Shandong University, No. 324 Jingwu Road, Ji'nan, Shandong 250021, China.
E-mail: hanweizhong003@163.com
Received 6 September 2016; revised 18 January 2017; accepted 21 January 2017; published online 2 March 2017

also designed to investigate the relationship between baPWV and daily urinary sodium excretion.

METHODS

Subjects and study design

Participants with hypertension defined by the Chinese guidelines for the management of hypertension 2010 (systolic BP (SBP) $\geqslant$140 or/and diastolic BP (DBP) $\geqslant$90 mm Hg at two or more different visits)[13] with no previous treatment for high BP were eligible for the study. The exclusion criteria were the following: any secondary cause of hypertension, such as primary aldosteronism; hypertension emergencies; serious arrhythmia, such as high-degree atrioventricular block and atrial fibrillation; peripheral arterial disease; heart failure; impaired renal function with plasma creatinine $\geqslant$150 μmol l^{-1}; rheumatic and autoimmune diseases; and malignancies.

From 2009 to 2014, participants were recruited from the BP outpatient clinic and cardiovascular inpatient department at Peking University People's Hospital in the Beijing area as well as the Shandong Provincial Hospital in the Jinan area. A total of 431 individuals were recruited into the study. The 24-h urinary sodium excretion test was used to determine the actual levels of salt intake. BaPWV was measured using a semi-automated device. Central hemodynamics and parameters were assessed via pulse wave analysis of the radial artery using a commercially available radial artery tonometry device. The study was approved by the Peking University People's Hospital Research Ethics Committee and the Shandong Provincial Hospital Ethics Committee. Written consent was obtained from all participants.

Biochemical measurement

Participants who agreed to participate in the study were provided a 4-L screw-capped plastic bottle and a 500-ml plastic beaker and were instructed to collect a 24-h urine sample, discarding the first voided urine upon waking up in the morning and collecting all voided urine during the subsequent 24 h, including the first void sample of the following morning. Upon completion of collection, trained staff recorded the urine volume in each collection container to determine the total urine volume during the 24-h collection period. A complete 24-h urine collection was defined as urine volume $\geqslant$500 ml as measured by a technician, recorded collection of $\geqslant$20 h and reports of no spilling of urine or missing a void in 24 h.

Blood samples were taken for routine biochemistry measurements, including serum sodium (Na) and potassium (K), serum creatinine (Cr), fasting blood glucose and total cholesterol (TC). These indicators were measured using an automated analyzer (DXC800, Beckman-coulter Inc, CA 92821, USA). The estimated glomerular filtration rate (eGFR) was calculated using the following equation: estimated glomerular filtration rate (ml per minute per 1.73 m^2) = 175 × [creatinine(mg dl^{-1})] $^{-1.234}$ × [age(year)] $^{-0.179}$ × (0.79 if the patient is female).[14]

Physical assessment of the patients included weight, height, and SBP and DBP with mercury sphygmomanometers. Blood pressure was measured three times by trained and certified observers using a standardized mercuric-column sphygmomanometer on the participant in a sitting position after 5 min of rest, and the time interval between successive pairs of BP measurements was 2 min.

Alcohol consumption was assessed during a baseline clinical visit. Participants were inquired for information on whether they regularly consumed alcohol, their average alcohol consumption per day and the number of days per month that they consumed alcohol. One drink was defined as an average of 15 g of ethanol.[15] Our cut-off values were based on the definition by the National Institute on Alcohol Abuse and Alcoholism on daily alcohol consumption; the participants were classified as abstainers (no alcohol consumption history), moderate drinkers (up to 1 drink per day for women and up to 2 drinks per day for men) and heavy drinkers ($>$1 drink per day for women and $>$2 drinks per day for men).[16] Moderate and heavy drinkers were enrolled in our study.

Central hemodynamics analysis

After the participants had rested for 15 min in the supine position, arterial waveforms at the radial (dominant arm) pulses were recorded by applanation tonometry; each measurement was made during an 8-s period using a high-fidelity SPC-301 micromanometer (Millar Instrument, Inc, Houston, TX, USA) that was interfaced with a computer using the SphygmoCor, version 8.2 software (AtCor Medical Pty Ltd, New South Wales, Australia). We discarded recordings when the systolic or diastolic variability of consecutive waveforms exceeded 5% or when the amplitude of the pulse wave signal was less than 80 mV. We calibrated the pulse wave to the BP measurement in the right arm immediately before the SphygmoCor recordings. Central systolic and diastolic BP (cSBP and cDBP), pulse pressure (cPP), augmentation pressure (AP) and augmentation index (AIx) were derived from the pulse waveform analysis. Pulse pressure was calculated as the difference between SBP and DBP. Augmentation pressure is the difference between the second and the first systolic peak pressures, and the AIx is defined as the ratio of AP to aortic pulse pressure. In addition, given that the AIx is influenced by heart rate (HR), an AIx normalized for an heart rate of 75 beats per minute (AIx at 75) was derived. High-quality recordings, defined as those with a within-device quality index $>$90%, were derived from an algorithm that included average pulse height, pulse height variation, diastolic variation and the maximum rate of rise of the peripheral waveform.

BaPWV measurement

Before the experiments, the subjects abstained from alcohol, caffeine and strenuous exercise for more than 1 day. Subjects were studied under supine resting conditions in a quiet, temperature-controlled room. Measurements were performed after at least 15 min of supine rest. The non-invasive automatic arterial atherosclerosis-measuring system VP-1000 (model BP-203RPE-II; Colin, Osaka, Japan) was used to measure baPWV (cm/s). Electrocardiographic electrodes were attached to the bilateral wrist, and cuffs were applied to the four extremities. A microphone was placed at a sternal angle to record phonocardiographic images. PWV was calculated by dividing the distance from the aortic valve to the ankle artery by the sum of the difference between the time the pulse waves were transmitted to the brachium and the time the same wave was transmitted to the ankle. PWV was also divided by the time difference between the second heart sound on the phonocardiogram and the notch of the brachial pulse waves. BaPWV was defined as the mean of the left and right upper extremities.

Statistical analysis

The study of Chinese national nutrition and health in 2002 reported that the daily average salt intake in China is 12 g,[17] which is equivalent to urine sodium of 200 mmol per day and is consistent with the INTERMAP study in 1999.[18] However, the amount of salt intake recommended by the China Hypertension Alliance is 6 g, which is equivalent to urine sodium of 100 mmol per day.[13] Based on these diet characteristics, participants were categorized into group A (low, sodium excretion $\leqslant$100 mmol per day), group B (moderate, sodium excretion $>$100 mmol per day and $\leqslant$200 mmol per day) and group C (high, sodium excretion $>$200 mmol per day) according to their 24-h sodium excretion. Data are shown as the mean ± s.d. if normally distributed or otherwise as a percentage. Continuous variables in the patient groups were compared by analysis of variance (ANOVA) for multiple comparisons. Analysis of covariance (ANCOVA) was used for the comparison baPWV among the three groups with adjustments made for potentially confounding factors, such as age, gender, body mass index (BMI), smoking, fasting blood glucose, TC, TG, mean BP and so on. Categorical variables were compared using the χ^2-test. Using cSBP, cDBP, cPP, AP, AIx and baPWV as dependent variables, independent predictors of such variables were determined via a multiple linear regression analysis. The backward method was adopted, which means significant variables at a P-value of $<$0.10 were used in the regression analysis. All statistical analyses were conducted by using SPSS (version 18.0, SPSS Inc, IBM, US). $P<0.05$ was considered statistically significant. All P-values were two-tailed.

RESULTS

A total of 431 untreated patients were recruited to participate in the study. Demographic characteristics are shown in Table 1. Among groups A, B and C, respectively, the average age was 54.5 ± 12.9,

Table 1 Baseline clinical characterizes of three groups

	Group A n = *112*	*Group B* n = *176*	*Group C* n = *143*	F/χ^2	P-*value*
Man/ women (%)	32.7/67.3	46.0/54.0	62.3/37.7[a]	6.097	0.047
Age (years)	54.5 ± 12.9	52.9 ± 12.6	50.9 ± 11.4	1.077	0.342
BMI (kg m^{-2})	24.8 ± 2.9	25.8 ± 3.3	27.7 ± 4.6[a,b]	8.599	0.000
Smoking (%)	19.2	26.1	34.0	1.983	0.371
Alcohol (%)	13.5	26.2[a]	20.8[a,b]	2.066	0.356
Diabetes (%)	23.1	19.8[a]	15.1[a,b]	1.198	0.552
Serum Na (mmol l^{-1})	140.4 ± 2.1	140.7 ± 2.2	140.8 ± 2.2	0.386	0.680
Serum K (mmol l^{-1})	3.9 ± 0.7	3.8 ± 0.4	3.9 ± 0.3	0.562	0.571
Cr (μmol l^{-1})	63.4 ± 15.2	65.7 ± 17.9	68.1 ± 18.2	0.931	0.396
eGFR (ml min^{-1} 1.73 m^{-2})	102.6 ± 28.4	108.2 ± 30.5	105.7 ± 28.6	0.073	0.620
TC (mmol l^{-1})	4.5 ± 0.7	4.6 ± 0.9	4.7 ± 0.9	0.380	0.685
FBG (mmol l^{-1})	5.96 ± 2.74	5.40 ± ± 3.20	5.36 ± 0.71	0.472	0.653
SBP(mmHg)	138.6 ± 16.5	140.2 ± 15.8	142.6 ± 17.2	0.798	0.451
DBP(mmHg)	83.3 ± 12.4	85.3 ± 12.2	90.1 ± 14.0[a,b]	4.112	0.018
Urinary Cr (mg/24 h)	1137.7 ± 49.2	1249.2 ± 61.1[a]	1313.5 ± 70.3[a,b]	5.427	0.007
Urinary K (mmol/24 h)	31.8 ± 12.1	38.3 ± 13.7[a]	50.3 ± 19.9[a,b]	20.79	0.000
Urinary Na (mmol/24 h)	76.9 ± 20.2	146.6 ± 28.3[a]	258.6 ± 46.5[a,b]	436.4	0.000
Urinary Na/K	2.7 ± 1.3	4.4 ± 2.4[a]	6.1 ± 3.4[a,b]	23.31	0.000

Abbreviations: BMI, body mass index; Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; SBP, systolic blood pressure; TC, total cholesterol.
[a]comparison with group A ($P<0.05$).
[b]comparison with group B ($P<0.05$).

52.9 ± 12.6 and 50.9 ± 11.4 years; the average sodium excretion was 76.9 ± 20.2, 146.6 ± 28.3 and 258.6 ± 46.5 mmol/24-h with remarkable differences, which was roughly equivalent to 4.7, 9.6 and 15.8 g per day of daily salt intake. The mean 24-h urinary sodium excretion of all subjects was 166.6 ± 70.0 mmol/24-h, corresponding to a salt intake of 10.1 g per day. Comparison of baseline characteristics among the three groups revealed no significant differences in age, smoking, alcohol, diabetes, serum sodium, serum potassium, serum creatinine, TC or fasting blood glucose; however, there were significant differences in BMI, sex, 24-h urinary sodium, potassium and the sodium potassium ratio.

Urinary electrolytes and central hemodynamics

The parameters of central aortic pressures are shown in Table 2. Compared with group A, group C displayed a higher cSBP, cDBP, AIx and AIx corrected for a heart rate of 75 beats per minute (AIxHR75). No significant differences were observed between group A and group B for AIx indicators. No remarkable differences were observed between any of the three groups with respect to cPP and AP grades.

Considering cSBP, cDBP, cPP, AP and AIx as the dependent variables, multivariate linear regression analysis indicated that 24-h urinary sodium was independently correlated with cSBP, cDBP, AIx and AIx (HR75) when controlling for age, sex, BMI, smoking, alcohol intake, mean office BP, TC, heart rate and fasting blood glucose. See Table 3. By contrast, no such relationship has been detected for 24-h urinary potassium or the sodium potassium ratio.

Urinary electrolytes and brachial-ankle pulse wave velocity

The average baPWV of group A was 1495.9 ± 329.5 cm s^{-1}, and the average baPWV was 1602.5 ± 310.1 cm s^{-1} and 1620.2 ± 295.4 cm s^{-1} for group B and group C, respectively, both of which were significantly higher than group A as shown in Figure 1.

The associations between urinary electrolytes and baPWV are shown in Table 4. Multivariate regression revealed that urinary sodium was positively associated with baPWV after controlling for age, sex, BMI, smoking, alcohol intake, mean office BP, TC and fasting blood glucose. However, such a relationship was not found between baPWV and urinary potassium or between baPWV and the sodium potassium ratio.

DISSCUSION

Central (aortic and carotid) pressures are pathophysiologically more relevant than peripheral pressures for the pathogenesis of cardiovascular disease.[19] Central hemodynamics can now be reliably assessed non-invasively with a number of relatively inexpensive devices.[20] The present study was designed to demonstrate that dietary salt intake was independently correlated with central hemodynamics parameters such as cSBP, cDBP and AIx in hypertensive patients. In addition, our study helped to identify that urinary sodium was closely related to arterial stiffness as measured by baPWV.

Dietary salt (sodium chloride) plays an important role in regulating BP, and our current high salt intake is largely responsible for the rise in hypertension with age. There is compelling evidence from randomized controlled trials that sodium reduction lowers BP.[21,22] However, the relationship between central BP indices and daily sodium intake has not been well established. In the present study, not only the cSBP and cDBP but also the cPP were independently associated with 24-h urinary sodium excretion when controlling for age, sex, BMI, mean BP, and other variables. A randomized, controlled study published recently had examined the effects of sodium and potassium supplementation on central BP.[23] Sodium supplementation resulted in a significantly higher cSBP of 8.5 mm Hg, cDBP of 3.6 mm Hg and cPP of 4.8 mm Hg compared with placebo, while potassium supplementation resulted in a significantly lower cPP of 2.9 mm Hg. Another research intervention of 12 months with salt substitution found significant reductions in peripheral and central SBP levels as well as central pulse pressure.[24] These results confirm our conclusion that salt may affect the central hemodynamics remarkably.

By contrast, a high-potassium diet has been shown to blunt the hypertensive effect of high sodium intake[25] and inhibit neointimal

Table 2 Comparison of central hemodynamics parameters of three groups

	Group A n = *112*	*Group B* n = *176*	*Group C* n = *143*	F/χ^2	*P*-value
cSBP	114.2 ± 15.4	121.8 ± 12.6[a]	124.9 ± 14.2[a]	8.872	0.000
cDBP	75.6 ± 11.8	80.9 ± 10.5[a]	83.9 ± 9.7[a]	8.292	0.000
cPP	38.7 ± 7.9	40.7 ± 9.6	41.8 ± 11.6	0.851	0.429
AP	9.3 ± 5.8	10.2 ± 6.0	11.3 ± 7.4	0.472	0.624
AIx	20.7 ± 13.0	23.5 ± 11.8	27.2 ± 15.1[a]	2.102	0.030
AIx(HR75)	18.9 ± 10.8	22.6 ± 10.8	26.0 ± 10.5[a]	2.219	0.029

Abbreviations: Aix, augmentation index; AIx (HR75), augmentation index corrected for heart rate 75 beat per minute; AP, augmented pressure; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cSBP, central systolic blood pressure.
[a]comparison with group A ($P<0.05$).

Table 3 Multivariate regression analysis between urinary electrolytes and central aortic pressure parameters

Dependents	*Independents*	*B*	*SE*	β	t	*P*-value
cSBP	Urinary K	−0.010	0.055	−0.011	−0.178	0.859
	Urinary Na	0.039	0.013	0.195	3.016	0.003
	Na/K ratio	0.748	0.330	0.043	0.864	0.362
cDBP	Urinary K	0.066	0.088	0.097	1.711	0.088
	Urinary Na	0.027	0.009	0.173	2.944	0.004
	Na/K ratio	0.185	0.236	0.045	0.783	0.435
cPP	Urinary K	−0.015	0.071	−0.014	−0.210	0.834
	Urinary Na	0.020	0.009	0.146	2.359	0.019
	Na/K ratio	0.522	0.215	0.144	1.424	0.156
AP	Urinary K	−0.023	0.022	−0.060	−1.044	0.298
	Urinary Na	0.005	0.005	0.056	0.918	0.360
	Na/K ratio	0.208	0.137	0.089	1.517	0.131
AIx	Urinary K	0.051	0.044	0.064	1.141	0.255
	Urinary Na	0.023	0.011	0.125	2.165	0.031
	Na/K ratio	0.255	0.266	0.054	0.960	0.338
AIx(HR75)	Urinary K	0.056	0.038	0.084	1.497	0.141
	Urinary Na	0.018	0.009	0.118	1.997	0.047
	Na/K ratio	0.178	0.227	0.045	0.786	0.433

Abbreviations: AIx, augmentation index; AIx (HR75), augmentation index corrected for heart rate 75 beat per minute; AP, augmented pressure; cDBP, central diastolic blood pressure; cPP, central pulse pressure; cSBP, central systolic blood pressure; K, potassium; Na, sodium.

proliferation in animal studies,[26] which tends to be associated with lower BP and better arterial function. Nevertheless, recently published studies have cast some doubt on the conclusions drawn above. Polonia and his colleagues found, in a study of 638 hypertensive patients followed for 7 years, that an independent relationship was not observed between 24-h urinary potassium and central BP or between 24-h urinary potassium and central AIx.[27] In a randomized placebo-controlled study, although 24-h BP was significantly reduced by 3.9/1.6 mm Hg after potassium supplementation, pulse wave velocity and AIx were not significantly affected.[23] In another randomized crossover research, there were no significant differences in carotid-femoral PWV and central AIx after a high-potassium, high-sodium meal compared with a low-potassium, high-sodium meal.[28] Note that subjects enrolled in this study shared a similar dietary pattern, characterized as low-potassium and high-sodium, as those in the present study. Therefore, none of the interactions between urinary potassium and arterial stiffness parameters were evident.

The ratio of sodium to potassium has been identified as a more useful predictor of cardiovascular disease than sodium or potassium intake alone.[29,30] Several studies reported that the sodium potassium ratio was associated with central hemodynamics, such as central pulse pressure and AIx.[31,32] A study by Redelinghuys *et al.*[31] demonstrated the above relationship in a black African population. Another study by Park *et al.*[32] documented that both estimated 24-h urine sodium excretion and the sodium potassium ratio were correlated with increases in central pulse pressure, augmented aortic pressure and AIx. However, these relationships were not found in the present study. There are several reasons that account for this phenomenon. First, there were some striking differences in the characteristics of enrolled subjects, for example, age, baseline BP and most importantly 24-h urinary sodium levels. In the present study, the average 24-h urinary sodium excretion was 166.6 ± 70.0 mmol/24 h, which was significantly higher than the mean of 105.4 ± 72.9 mmol/24 h observed in Redelinghuys' study. Second, with regard to the second study, our data suggested that estimating sodium excretion from the sodium creatinine ratio in spot urine was less reliable than directly measuring 24-h urinary sodium, which may result in a deviation from true values.[33] Finally, increasing dietary potassium intake may favorably lower BP, especially in hypertensive individuals, nevertheless excessive salt intake may negate the protective effects.[27] The very-high level of salt intake that we observed could also be an explanation why, in contrast to the two other studies, we did not find any correlation of central hemodynamics with the ratio of sodium potassium in urinary excretion.

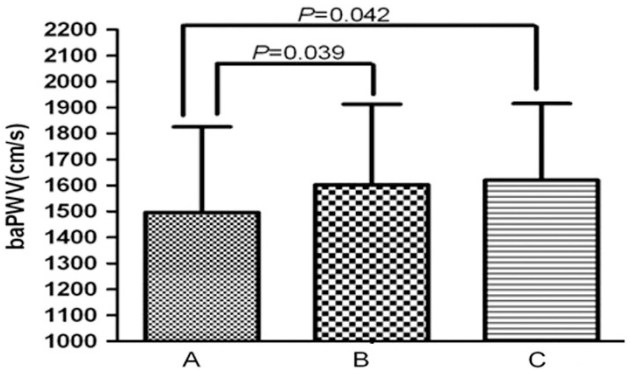

Figure 1 Comparison of brachial-ankle pulse wave velocity (baPWV) in three groups.

Our earlier study described the independent relationship between sodium excretion and baPWV. The study of 341 untreated hypertensive patients showed that baPWV was significantly increased with high urinary sodium excretion compared to low urinary sodium excretion.[34] To our knowledge, only a few studies have shown a significant association of urinary sodium excretion with central AIx and baPWV in hypertensive patients. It is not surprising that similar findings have been reported in the present study. BaPWV measurement has become more convenient than other invasive methods. It can be widely used in large populations and has become available in clinical settings in East Asian countries.[35] This method would provide a simpler examination method for estimating early arterial distensibility associated with dietary salt intake.

There are several possible mechanisms for the results observed in our study. First, increased sodium reabsorption in proximal tubules may affect BP and arterial wall damage.[36] Cwynar *et al.*[37] revealed that in the hypertensive population with high sodium intake, patients with fractional lithium excretion below the median value showed significantly higher cSBP, cDBP, AP, PWV and AIx; such relationships were

Table 4 Association between urinary electrolytes and baPWV

	B	*SE*	β	t	*P*-value
Urinary K	−0.537	1.194	−0.030	−0.480	0.632
Urinary Na	0.447	0.126	0.110	2.112	0.036
Na/K ratio	0.312	0.129	0.124	21.213	0.092
Age	10.844	1.597	0.434	6.866	0.000
Mean BP	3.287	1.635	0.131	2.010	0.046

Abbreviations: K, potassium; mean BP, mean office blood pressure; Na, sodium.

not observed in the entire group or in patients with fractional lithium excretion above the median value. Second, excess dietary sodium intake is known to impair endothelial function assessed by using flow-mediated dilatation,[38] increase endothelin-1 expression,[39] alter biological molecules such as intercellular adhesion molecule-1,[40] improve the endogenous activity of specific matrix metalloproteinases.[41] Eventually, all of these factors contribute significantly toward decreases in the elasticity of arterial walls. Furthermore, oxidative stress,[42] decreased bioavailability of endothelial-derived vasodilators (for example, nitric oxide),[43] and low-grade inflammation[44] have also been recognized to promote arterial stiffness. Third, high sodium intake may be associated with upregulation of renin–angiotensin–aldosterone activity.[43,45,46] The resulting increase in vascular inflammation and arterial wall remodeling in both peripheral and central arteries may collectively exert a deleterious effect on central hemodynamics. Finally, the release of endogenous digitalis-like factors and salt sensitivity lead to a defect in the renal response to increases in sodium and water intake in hypertensive subjects by vascular Na-K ATPase inhibition, vasoconstriction and increased BP,[47] which suggests a synergistic effect in the alterations of arterial stiffness and compliance.

Several studies have demonstrated that the central hemodynamics in women are more elevated than that in men.[48,49] Nonetheless, our research found that group C showed more elevated central hemodynamics than group A despite having fewer women as subjects. There are several explanations for this finding. First, the focus of our study was the relationship between urinary electrolytes excretion and central hemodynamics. Our results showed that a high-sodium diet was associated with central hemodynamics and arterial elasticity, which implied that excessive salt intake seems to have a greater impact on central BP than gender. On the other hand, it is well known that AIx and other indications of central hemodynamics are affected by various factors, including age, TC, heart rate, and fasting blood glucose, which are not determined solely by gender. All of these will have combined effects on the central hemodynamics in groups A and C.

Limitations of this study include the use of a relatively hypertensive study population, which might have limited our potential to identify the correlations between sodium intake and the vascular variables; in addition, it may have limited the ability to apply our findings to the general population. Furthermore, although this study is based on the best and most-reliable method of measuring salt consumption, the fact that it is based on a single-day measurement limits its value as an indicator of the general habits of salt intake over a long period. Thus, prospective studies should be carried out in hypertensive patients to evaluate the longitudinal and long-term effects of different levels of salt intake on central hemodynamics. Again, the association between the estimated 24-h sodium intake and the indices of central hemodynamics are modest in this study. However, there are numerous factors (aging, vascular stiffness, heart rate, renin–angiotensin system, sex and peripheral vascular resistance) that could have influenced the degree of central dynamics and arterial distensibility. A previous study by Polonia *et al.*[27] showed a modest, partial correlation coefficient between urinary sodium excretion and the indices of central hemodynamics that was similar to the results from this study.

CONCLUSION

In conclusion, in a Chinese hypertensive population, we found that high salt intake was associated independently and positively with central BP values and baPWV. Excessive salt intake is important in the development of arterial stiffness and dysfunction in mildly hypertensive individuals. Prospective interventional studies in patients with hypertension are required to determine the effect of varying levels of salt intake on central hemodynamics.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was supported by the Youth Fund of the Shandong Academy of Medical Sciences (NO 2015-41).

1 Zou G, Zhang Z, Walley J, Gong W, Yu Y, Hu R, Yin J, Yu M, Wei X. Use of medications and lifestyles of hypertensive patients with high risk of cardiovascular disease in rural China. *PLoS ONE* 2015; **10**: e0124484.
2 Intersalt Cooperative Research Group. Intersalt: an international study of electrolyte excretion and blood pressure. Results for 24 h urinary sodium and potassium excretion. *BMJ* 1988; **297**: 319–328.
3 McEniery CM, Cockcroft JR, Roman MJ, Franklin SS, Wilkinson IB. Central blood pressure: current evidence and clinical importance. *Eur Heart J* 2014; **35**: 1719–1725.
4 Pini R, Cavallini MC, Palmieri V, Marchionni N, Di Bari M, Devereux RB, Masotti G, Roman MJ. Central but not brachial blood pressure predicts cardiovascular events in an unselected geriatric population: the ICARe Dicomano Study. *J Am Coll Cardiol* 2008; **51**: 2432–2439.
5 Jankowski P, Kawecka-Jaszcz K, Czarnecka D, Brzozowska-Kiszka M, Styczkiewicz K, Loster M, Kloch-Badelek M, Wilinski J, Curylo AM, Dudek D. Pulsatile but not steady component of blood pressure predicts cardiovascular events in coronary patients. *Hypertension* 2008; **51**: 848–855.
6 Avolio AP, Clyde CM, Beard TC, Cooke HM, Ho KK, O'Rourke MF. Improved arterial distensibility in normotensive subjects on a low salt diet. *Arteriosclerosis* 1986; **6**: 166–169.
7 Chien KL, Hsu HC, Chen PC, Su TC, Chang WT, Chen MF, Lee YT. Urinary sodium and potassium excretion and risk of hypertension in Chinese: report from a community-based cohort study in Taiwan. *J Hypertens* 2008; **26**: 1750–1756.
8 Cook NR, Cutler JA, Obarzanek E, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ* 2007; **334**: 885–888.
9 Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, Lin PH, Karanja N. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; **336**: 1117–1124.
10 Willum-Hansen T, Staessen JA, Torp-Pedersen C, Rasmussen S, Thijs L, Ibsen H, Jeppesen J. Prognostic value of aortic pulse wave velocity as index of arterial stiffness in the general population. *Circulation* 2006; **113**: 664–670.
11 Dzeko M, Peters CD, Kjaergaard KD, Jensen JD, Jespersen B. Aortic pulse wave velocity results depend on which carotid artery is used for the measurements. *J Hypertens* 2013; **31**: 117–122.
12 Sugawara J, Tanaka H. Brachial-Ankle pulse wave velocity: myths, misconceptions, and realities. *Pulse* 2015; **3**: 106–113.
13 Liu LS. Writing Group of 2010 Chinese Guidelines for the Management of Hypertension. 2010 Chinese guidelines for the management of hypertension. *Zhonghua Xin Xue Guan Bing Za Zhi* 2011; **39**: 579–615.
14 Kong X, Ma Y, Chen J, Luo Q, Yu X, Li Y, Xu J, Huang S, Wang L, Huang W, Wang M, Xu G, Zhang L, Zuo L, Wang H. Chinese eGFR Investigation Collaboration Evaluation of the Chronic Kidney Disease Epidemiology Collaboration equation for estimating glomerular filtration rate in the Chinese population. *Nephrol Dial Transplant* 2013; **28**: 641–651.
15 Conen D, Tedrow UB, Cook NR, Moorthy MV, Buring JE, Albert CM. Alcohol consumption and risk of incident atrial fibrillation in women. *JAMA* 2008; **300**: 2489–2496.
16 National Institute of Alcohol Abuse and Alcoholism. *The Physicians' Guide to Helping Patients With Alcohol Problems*. U.S. Department of Health and Human Services, National Institutes of Health: Washington, DC, USA. 1995.

17 Li LM, Rao KQ, Kong LZ, Yao CH, Xiang HD, Zhai FY, Ma GS, Yang XG. Technical Working Group of China National Nutrition and Health Survey. A description on the Chinese national nutrition and health survey in 2002. *Zhonghua Liu Xing Bing Xue Za Zhi* 2005; **26**: 478–484.
18 Zhao L, Stamler J, Yan LL, Zhou B, Wu Y, Liu K, Daviglus ML, Dennis BH, Elliott P, Ueshima H, Yang J, Zhu L, Guo D. INTERMAP Research Group Blood pressure differences between northern and southern Chinese: role of dietary factors: the International Study on Macronutrients and Blood Pressure. *Hypertension* 2004; **43**: 1332–1337.
19 Mitchell GF, Hwang SJ, Vasan RS, Larson MG, Pencina MJ, Hamburg NM, Vita JA, Levy D, Benjamin EJ. Arterial stiffness and cardiovascular events: the Framingham Heart Study. *Circulation* 2010; **121**: 505–511.
20 Nichols WW, Denardo SJ, Wilkinson IB, McEniery CM, Cockcroft J, O'Rourke MF. Effects of arterial stiffness, pulse wave velocity, and wave reflections on the central aortic pressure waveform. *J Clin Hypertens* 2008; **10**: 295–303.
21 He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet* 2011; **378**: 380–382.
22 Whelton PK, Appel LJ, Sacco RL, Anderson CA, Antman EM, Campbell N, Dunbar SB, Frohlich ED, Hall JE, Jessup M, Labarthe DR, MacGregor GA, Sacks FM, Stamler J, Vafiadis DK, Van Horn LV. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation* 2012; **126**: 2880–2889.
23 Gijsbers L, Dower JI, Mensink M, Siebelink E, Bakker SJ, Geleijnse JM. Effects of sodium and potassium supplementation on blood pressure and arterial stiffness: a fully controlled dietary intervention study. *J Hum Hypertens* 2015; **29**: 592–598.
24 Hu J, Jiang X, Li N, Yu X, Perkovic V, Chen B, Zhao L, Neal B, Wu Y. Effects of salt substitute on pulse wave analysis among individuals at high cardiovascular risk in rural China: a randomized controlled trial. *Hypertens Res* 2009; **32**: 282–288.
25 Tobian L. Dietary sodium chloride and potassium have effects on the pathophysiology of hypertension in humans and animals. *Am J Clin Nutr* 1997; **65**: 606S–611S.
26 Ma G, Srivastava NT, Anderson PG, Grady AW, Skelton TN, Lyle K, Luo J, Lin H, Waterer HC Jr, Hays JC Jr, Young DB. Elevated potassium intake inhibits neointimal proliferation in the swine coronary artery. *Am J Hypertens* 2001; **14**: 879–886.
27 Polonia JJ, Magalhaes MT, Senra D, Barbosa L, Silva JA, Ribeiro SM. Association of 24-h urinary salt excretion with central haemodynamics and assessment of food categories contributing to salt consumption in Portuguese patients with hypertension. *Blood Press Monit* 2013; **18**: 303–310.
28 Blanch N, Clifton PM, Petersen KS, Keogh JB. Effect of sodium and potassium supplementation on vascular and endothelial function: a randomized controlled trial. *Am J Clin Nutr* 2015; **101**: 939–946.
29 Haring B, Wang W, Lee ET, Jhamnani S, Howard BV, Devereux RB. Effect of dietary sodium and potassium intake on left ventricular diastolic function and mass in adults ≤40 years (from the Strong Heart Study). *Am J Cardiol* 2015; **115**: 1244–1248.
30 Cook NR, Obarzanek E, Cutler JA, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK. Trials of Hypertension Prevention Collaborative Research Group Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Arch Intern Med* 2009; **169**: 32–40.
31 Redelinghuys M, Norton GR, Scott L, Maseko MJ, Brooksbank R, Majane OH, Sareli P, Woodiwiss AJ. Relationship between urinary salt excretion and pulse pressure and central aortic hemodynamics independent of steady state pressure in the general population. *Hypertension* 2010; **56**: 584–590.
32 Park S, Park JB, Lakatta EG. Association of central hemodynamics with estimated 24-h urinary sodium in patients with hypertension. *J Hypertens* 2011; **29**: 1502–1507.
33 Han W, Sun N, Chen Y, Wang H, Xi Y, Ma Z. Validation of the spot urine in evaluating 24-hour sodium excretion in Chinese hypertension patients. *Am J Hypertens* 2015; **28**: 1368–1375.
34 Sun N, Xi Y, Han W, Zhao L, Wang H. Relationship of 24-h urinary sodium excretion with blood pressure, arterial distensibility, and urine albumin in Chinese hypertensive patients. *Eur Heart J Suppl* 2015; **17**: F37–F43.
35 Kim SH, Kim YH, Kim JS, Lim SY, Jung JH, Lim HE, Kim EJ, Cho GY, Baik I, Sung KC, Park J, Lee SK, Shin C. Target-organ damage and incident hypertension: the Korean genome and epidemiology study. *J Hypertens* 2016; **34**: 524–531.
36 Cwynar M, Gasowski J, Gryglewska B, Głuszewska A, Bartoń H, Słowik A, Grodzicki T. The relation between ACE D/I and CYP11B2 C-344T polymorphisms and parameters of arterial stiffness in the context of renal sodium handling. *Blood Press* 2015; **24**: 306–316.
37 Cwynar M, Gąsowski J, Stompór T, Bartoń H, Wizner B, Dubiel M, Głuszewska A, Królczyk J, Franczuk P, Grodzicki T. Blood pressure and arterial stiffness in patients with high sodium intake in relation to sodium handling and left ventricular diastolic dysfunction status. *J Hum Hypertens* 2015; **29**: 583–591.
38 Dickinson KM, Keogh JB, Clifton PM. Effects of a low-salt diet on flow-mediated dilatation in humans. *Am J Clin Nutr* 2009; **89**: 485–490.
39 Gijsbers L, Dower JI, Schalkwijk CG, Kusters YH, Bakker SJ, Hollman PC, Geleijnse JM. Effects of sodium and potassium supplementation on endothelial function: a fully controlled dietary intervention study. *Br J Nutr* 2015; **114**: 1419–1426.
40 Kilic ID, Findikoglu G, Alihanoglu YI, Yildiz BS, Uslu S, Rota S, Evrengul H. Circulating adhesion molecules and arterial stiffness. *Cardiovasc J Afr* 2015; **26**: 21–24.
41 Kalani A, Pushpakumar SB, Vacek JC, Tyagi SC, Tyagi N. Inhibition of MMP-9 attenuates hypertensive cerebrovascular dysfunction in Dahl salt-sensitive rats. *Mol Cell Biochem* 2016; **413**: 25–35.
42 Imaizumi Y, Eguchi K, Murakami T, Arakawa K, Tsuchihashi T, Kario K. High salt intake is independently associated with hypertensive target organ damage. *J Clin Hypertens* 2016; **18**: 315–321.
43 Boegehold MA, Drenjancevic I, Lombard JH. Salt, angiotensin II, superoxide, and endothelial function. *Compr Physiol* 2015; **6**: 215–254.
44 Yilmaz R, Akoglu H, Altun B, Yildirim T, Arici M, Erdem Y. Dietary salt intake is related to inflammation and albuminuria in primary hypertensive patients. *Eur J Clin Nutr* 2012; **66**: 1214–1218.
45 Samuel P, Ali Q, Sabuhi R, Wu Y, Hussain T. High Na intake increases renal angiotensin II levels and reduces expression of the ACE2-AT(2)R-MasR axis in obese Zucker rats. *Am J Physiol Renal Physiol* 2012; **303**: F412–F419.
46 Demura M, Demura Y, Takeda Y, Saijoh K. Dynamic regulation of the angiotensinogen gene by DNA methylation, which is influenced by various stimuli experienced in daily life. *Hypertens Res* 2015; **38**: 519–527.
47 Buckalew VM. Endogenous digitalis-like factors: an overview of the history. *Front Endocrinol* 2015; **6**: 49.
48 Chester R, Sander G, Fernandez C, Chen W, Berenson G, Giles T. Women have significantly greater difference between central and peripheral arterial pressure compared with men: the Bogalusa Heart Study. *J Am Soc Hypertens* 2013; **7**: 379–385.
49 Krzesiński P, Stańczyk A, Gielerak G, Uziębło-Życzkowska B, Kurpaska M, Piotrowicz K, Skrobowski A. Sex determines cardiovascular hemodynamics in hypertension. *J Hum Hypertens* 2015; **29**: 610–617.