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Effects of a low salt diet on isolated systolic hypertension

A community-based population study

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Abstract

Evidence has shown that long-term sodium reduction can not only reduce blood pressure, but also provide cardiovascular benefits. To date, there is little evidence related to the effects of salt reduction on isolated systolic hypertension (ISH).

A total of 126 hypertensive patients were divided into an ISH group (n = 51) and a non-ISH (NISH) group (n = 75). The members of each group were then randomly assigned to low sodium salt (LSSalt) or normal salt (NSalt) diets for 6 months. Their blood pressure was measured every 2 months. Serum plasma renin-angiotensin activity, blood biochemical assays and urinary measurements were determined at the baseline and at the end of the 6 months.

At the end of the study, the mean systolic blood pressure (SBP) of the ISH LSSalt group had significantly decreased by 10.18 mm Hg (95% confidence interval (CI): 3.13 to 17.2, $P = .006$) compared with that of the ISH NSalt group, while the mean SBP only decreased by 5.10 mm Hg (95% CI: −2.02 to 12.2, $P = .158$) in the NISH LSSalt group compared with that of the NISH NSalt group. The mean diastolic blood pressure (DBP) had no significant differences in the ISH and NISH groups. No obvious renin angiotensin system activation was found after LSSalt intervention. Regarding the urinary excretion of electrolytes and blood biochemical assays, the LSSalt treatment had the same effects on the ISH group as on the NISH group.

The present study showed that the SBP of ISH patients was significantly decreased with the LSSalt intervention, while neither the SBP of the NISH patients nor the DBP of either group were similarly decreased, which indicated that ISH patients were more sensitive to salt restriction.

Abbreviations: 95%CI = 95%confidence interval, ACEI = angiotensin-converting enzyme inhibitor, ANP = atrial natriuretic peptide, ARB = angiotensin receptor blockers, BP = blood pressure, CCB = calcium channel blockers, DBP = diastolic blood pressure, Er = erythrocyte, HDL = high density lipoprotein, ISH = isolated systolic hypertension, LSSalt = low sodium salt, NISH = nonisolated systolic hypertension, NSalt = normal salt, PRA = plasma renin activity, SBP = systolic blood pressure.

Keywords: cardiovascular disease, isolated systolic hypertension, low sodium salt, salt restriction, systolic blood pressure

1. Introduction

Hypertension is a major risk factor for cardiovascular events, such as stroke, myocardial infarction, heart failure, and renal disease.[1–3] Strong evidence has shown linear relationships between cardiovascular risk and both systolic and diastolic blood pressures (BPs).[4] systolic BP (SBP) is one of the main risk factors affecting cardiovascular events in elderly people.[5] Unlike diastolic BP (DBP), SBP increases gradually with age,[6] and in aging societies, isolated SBP increase is the most common form of hypertension [7,8] However, few clinical trials on isolated systolic hypertension (ISH) have been conducted.

Numerous clinical studies have clearly demonstrated a positive relationship between salt intake and BP elevation, and substantial evidence has shown that daily salt restriction may be a useful lifestyle modification for hypertensive patients.[9,10] Moreover, several large clinical trials have supported the hypothesis that long-term sodium reduction, previously manifested to lower BP, may also provide cardiovascular benefits.[11] As arterial stiffness is one of the most important inducing factors in the development and maintenance of ISH, stiffer arteries are more sensitive to BP changes induced by liquid volume variation.[12,13] Salt restriction could reduce volume load, thereby lowering BP and providing cardiovascular benefits to ISH patients. However, until now, the effect of salt reduction on ISH has been still unclear.

Although moderate salt restriction has proved beneficial in cardiovascular disease, it is difficult to perform studies in large population because long-term established salt intake habits are hard to change. In the treatment of Mild Hypertension Study, the mean salt intake was decreased by 2 to 3 g/day during the first year but regressed to less than 1 g/day after 4 years.[14] In order to

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change this situation, we used a novel low sodium salt (LSSalt) in the present study. This LSSalt is composed of 65% sodium chloride, 30% potassium chloride, 5% calcium salts (4% calcium citrate tetrahydrate and 1% calcium carbonate), and 12 mg/kg folic acid.[15] Compared to normal salt (NSalt), this substitute can significantly decrease sodium intake (a decrease of approximately 40% compared with normal salt) with no obvious difference in the salty flavor. In the present study, we enrolled 126 hypertensive participants who were divided into an ISH group and a non-ISH (NISH) group to investigate the effects of salt restriction on ISH individuals.

2. Methods

2.1. Subjects

This study was a single blind, randomized, controlled trial, conducted in 10 communities in the rural Hedong District, Tianjin, China. Informed consent was obtained from all participants, and the research protocol was approved by the Ethical Committee of Pingjin Hospital in accordance with the principles of the Declaration of Helsinki.

A total of 138 participants, male and female Han participants, who were 50–80 years of age, and who had mild to moderate hypertension (meeting one of the following criteria: average SBP≥140 mm Hg and/or DBP≥90 mm Hg or being treated with antihypertensive drugs) were recruited in the present study. To minimize the influences of confounding factors on the study, the following inclusion criteria were applied: patients who ate no more than one meal per week outside of their home, did not use potassium-sparing medication, were willing to commit to long-term intake of LSSalt, and had serum potassium levels < 5.5 mmol/L and a net elevation of serum potassium < 1.0 mmol/L at the end of the run-in period. The exclusion criteria included history of a heart attack or stroke within the preceding 6 months, current angina pectoris, congestive heart failure, diabetes mellitus, serious liver and kidney dysfunction, serious mental or physical illness, malignancy, and definite secondary hypertension at end of the run-in period.

All the participants were asked to provide information regarding age, education, marital status, physical activity, history of smoking and alcohol consumption, and family history. Baseline body weights, BP, and levels of blood urea nitrogen, creatinine, and serum potassium were recorded. In addition, 24 hours urine was collected for the determination of sodium, potassium, and calcium excretion. After a 4-week run-in period, the participants were divided into an ISH group (meeting one of the following criteria: SBP≥140 mm Hg and DBP < 90 mm Hg or previously diagnosed with ISH and being treated with antihypertensive drugs) and a NISH group (meeting one of the following criteria: DBP≥90 mm Hg or previously diagnosed with NISH and being treated with antihypertensive drugs). Each group was then randomized to LSSalt or NSalt diets for 6 months. A flowchart is displayed in Figure 1.

2.2. Follow-up and measurements

All the hypertensive participants were followed-up every 2 months. Our primary outcomes were changes in SBP and DBP in the hypertensive patients. And the secondary outcomes were changes in the 24 hours urine excretion of electrolytes and related blood sample analyses.

SBP and DBP were defined by Korotkoff sound phase 1 and phase 5, respectively. The measurement was performed by 2 experienced physicians and was measured twice after a test

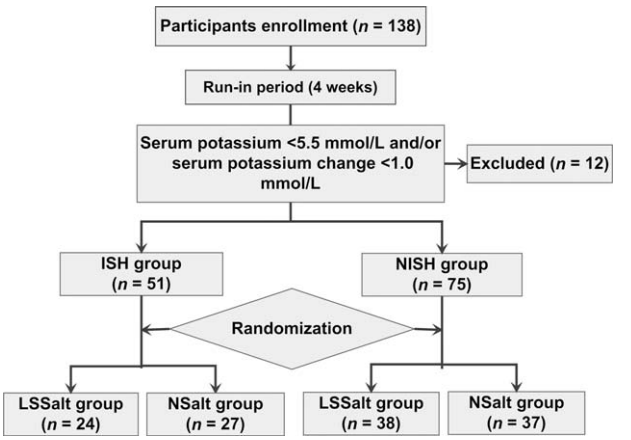

Figure 1. Flowchart of the study. ISH = isolated systolic hypertension, LSSalt = low sodium salt, NISH = nonisolated systolic hypertension, NSalt = normal salt.

measurement. The measurement was considered valid if the difference between the 2 measurements was < 10 mm Hg; otherwise, a third measurement was taken, and the average value was used for analysis. At the end of 6 months, 24 hours urine and blood samples were collected. The urinary and intraerythrocyte Na^+, K^+, and Ca^{2+} levels were determined by atomic absorbance spectrophotometry. The serum assays included total cholesterol, high density lipoprotein, triglyceride, glucose, and insulin. Plasma renin activity, angiotensin II level, and atrial natriuretic peptide (ANP) level were measured by radioimmunoassay as previous described.[15]

2.3. Statistical analysis

The target sample size of 100, with 25 in each subgroup, was estimated to provide 80% power at a two-tailed $P = .05$ to detect a difference of SBP≥8.0 mm Hg between the LSSalt and the NSalt groups in each cohort (ISH and NISH groups). The normal distribution of the data was estimated using the Kolmogorov–Smirnov test. To estimate the overall effects over time of LSS (time × treatment) on BP, two-way analysis of variance repeated measurements was used. Within-group differences were evaluated by paired *t*-test. Considering the influence of seasonal changes on BP,[16] between-group differences in BP and serum and urinary assays were reanalyzed by comparing the net change at the time of randomization and end of the study using unpaired *t*-tests. Net change was calculated as follows: $(V_6 - V_0)_{LSS} - (V_6 - V_0)_{NS}$, where V represents a certain variable and the numbers indicate the months after randomization.[15] Categorical data were compared using χ^2-test and Fisher's exact test when expected cell values were < 5. The relationships between BP and the blood/urinary parameters were evaluated with Pearson's correlation (if the data passed the normality test) or Spearman's rank correlation (if the data failed the normality test). A two-tailed $P < .05$ was considered statistically significant. All analyses were performed using SPSS, version 18.0 (SPSS, Chicago, IL).

3. Results

3.1. Baseline characteristics

As shown in Table 1 and Supplemental Table 1, http://links.lww.com/MD/C188, 126 hypertensive participants were enrolled in

Table 1

Baseline characteristics of all participants.

	ISH (n = 51)			NISH (n = 75)		
	LSSalt (n = 24)	NSalt (n = 27)	*P* value	LSSalt (n = 38)	NSalt (n = 37)	*P* value
Mean age, years	67.8 ± 5.34	65.9 ± 6.17	.248	67.3 ± 5.62	65.4 ± 6.75	.189
Female sex	14 (58.3%)	16 (59.2%)	.947	21 (55.3%)	21 (56.8%)	.896
Smoking						
Current smoker	5 (20.8%)	6 (22.2%)	.904	8 (21.1%)	9 (24.3%)	.783
Past smoker	2 (8.33%)	3 (11.1%)	1.000	4 (10.5%)	5 (13.5%)	.736
Alcohol use	6 (25.0%)	7 (25.9%)	.940	9 (23.7%)	10 (27.0%)	.739
Exercises	4 (16.7%)	6 (22.2%)	.618	7 (18.4%)	7 (18.9%)	.956
Body mass index, kg/m^2	25.1 ± 3.64	24.7 ± 3.58	.694	25.3 ± 3.93	25.0 ± 3.66	.733
Antihypertensive drugs	13 (54.2%)	15 (55.5%)	.921	20 (52.6%)	20 (54.1%)	.902
Systolic blood pressure, mm Hg	161 ± 11.0	157 ± 10.4	.188	159 ± 12.2	157 ± 13.8	.588
Diastolic blood pressure, mm Hg	80.6 ± 4.94	81.3 ± 4.97	.617	85.0 ± 8.82	83.8 ± 8.21	.544
Serum creatinine, μmol/L	78.2 ± 18.1	76.9 ± 18.7	.802	78.7 ± 19.2	76.8 ± 19.4	.727
Serum K^+, mmol/L	4.50 ± 0.37	4.46 ± 0.39	.710	4.58 ± 0.40	4.51 ± 0.43	.552
Urinary Na^+, mmol/24 h	226 ± 31.0	242 ± 31.9	.076	245 ± 41.2	241 ± 54.7	.772
Urinary K^+, mmol/24 h	23.7 ± 7.38	23.5 ± 7.79	.926	23.3 ± 7.11	25.6 ± 8.15	.291
Urinary Ca^{2+}, mmol/24 h	6.78 ± 3.37	6.71 ± 2.15	.929	7.06 ± 2.36	6.91 ± 2.43	.824

Data are presented as mean ± SD for continuous variables, numbers (%) for categorical variables.
ISH = isolated systolic hypertension, LSSalt = low sodium salt; NSalt = normal salt, NISH = nonisolated systolic hypertension.

the study. No adverse cardiovascular events happened during the follow-up period. No significant differences in baseline characteristics were observed among the different groups (all $P > .05$).

3.2. The BP levels of different groups

As shown in Figure 2 and Supplemental Table 2, http://links.lww.com/MD/C188, in the ISH subjects, there was a continuous decrease of SBP over time with LSSalt treatment ($P = .003$) while no significant differences were found in the NSalt group, and no apparent differences in DBP were found in either the LSSalt or NSalt groups. In the NISH subjects, no marked changes in SBP and DBP were observed in either the LSSalt or NSalt treatment groups, although SBP displayed a decreasing trend in the LSSalt group (all $P > .05$). Compared with mean of the NSalt group, the mean SBP of ISH LSSalt group was significantly decreased by 10.18 mm Hg (95% confidence interval (CI): 3.13 to 17.2, $P = .006$), while it only decreased 5.10 mm Hg (95% CI: −2.02 to 12.2, $P = .158$) in the NISH LSSalt group. No marked differences in the administration of antihypertensive drugs were observed in the ISH and NISH LSSalt and NSalt groups at the end of the study (Supplemental Table 1, http://links.lww.com/MD/C188, all $P > .05$).

3.3. Blood/urinary parameters in ISH participants

As illustrated in Table 2, compared with the NSalt group, the LSSalt group had to average changes in the excretion urinary electrolytes of −55.0 mmol/24 h for Na^+ (95% CI: −86.9 to −23.0, $P = .001$), 8.07 mmol/24 h for K^+ (95% CI: −1.50 to 17.6, $P = .018$), and 2.55 mmol/24 h for Ca^{2+} (95% CI: 0.31 to 4.78, $P = .027$). These changes were accompanied by decreases in intraerythrocyte Na^+ and Ca^{2+} levels. In addition, the plasma ANP level was significantly decreased after LSSalt intervention (−23.2 pg/mL, 95% CI: −32.7 to −13.7, $P < .001$). There were no significant differences in other blood parameters, such as plasma renin activity, plasma angiotensin II, plasma lipid parameters, serum glucose, serum insulin, and the intraerythrocyte K^+ level, between the NSalt and LSSalt groups (all $P > .05$).

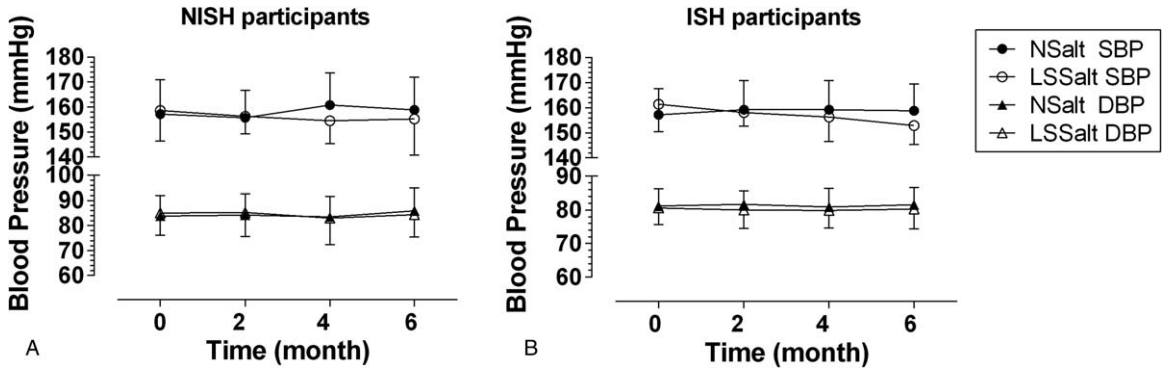

Figure 2. Systolic and diastolic blood pressure changes in ISH and NISH participants after 6 months follow-up. Data are reported as mean ± SD. ISH, isolated systolic hypertension; NISH = nonisolated systolic hypertension; LSSalt = low sodium salt; NSalt = normal salt; SBP = systolic blood pressure; DBP = diastolic blood pressure.

Table 2

24 h urinary excretion of electrolytes and blood biochemical assays at end of run-in period and 6 month after randomization in isolated systolic hypertension group.

	LSSalt (n = 24)			NSalt (n = 27)			
	Run-in	6 months	Difference	Run-in	6 months	Difference	*P* value
Urinary Na^+, mmol/24 h	226 ± 31.0	176 ± 53.1	-50.0 ± 59.3	242 ± 31.9	246 ± 36.5	4.97 ± 54.3	.001
Urinary K^+, mmol/24 h	23.7 ± 7.38	35.2 ± 7.79	11.5 ± 10.5	23.5 ± 7.79	26.9 ± 7.14	3.43 ± 12.7	.018
Urinary Ca^{2+}, mmol/24 h	6.78 ± 3.37	9.29 ± 4.02	2.51 ± 5.26	6.71 ± 2.15	6.67 ± 1.65	-0.04 ± 2.30	.027
Plasma renin activity, ng/mL/h	2.14 ± 0.33	2.79 ± 0.75	0.65 ± 0.79	2.16 ± 0.19	2.61 ± 0.39	0.44 ± 0.47	.269
Plasma angiotensin II, pg/mL	61.4 ± 6.50	67.4 ± 16.4	6.00 ± 16.0	66.8 ± 8.20	70.5 ± 11.4	3.70 ± 10.7	.546
Plasma ANP, pg/mL	71.7 ± 8.99	63.8 ± 12.1	-7.9 ± 12.5	70.0 ± 13.1	85.4 ± 11.4	15.3 ± 20.0	<.001
Plasma total cholesterol, mmol/L	5.71 ± 0.72	5.72 ± 0.88	0.01 ± 1.33	5.63 ± 0.84	5.95 ± 0.87	0.33 ± 1.38	.402
Plasma HDL, mmol/L	2.41 ± 0.26	2.56 ± 0.55	0.14 ± 0.71	2.58 ± 0.34	2.74 ± 0.37	0.16 ± 0.45	.933
Plasma triglyceride, mmol/L	2.02 ± 0.64	2.14 ± 0.69	0.11 ± 0.95	2.06 ± 0.76	2.21 ± 0.68	0.15 ± 1.07	.891
Serum glucose, mmol/L	6.13 ± 1.53	5.81 ± 1.75	-0.32 ± 2.24	5.23 ± 1.00	5.52 ± 1.85	0.29 ± 2.15	.330
Serum insulin, μg/L	22.8 ± 4.65	21.2 ± 4.58	-1.66 ± 5.14	19.3 ± 7.03	21.1 ± 5.42	1.80 ± 8.10	.079
Intraerythrocyte Na^+, mmol/kg·Hb	25.6 ± 5.47	19.1 ± 4.93	-6.43 ± 9.54	24.2 ± 4.82	24.7 ± 5.34	0.56 ± 10.83	.019
Intraerythrocyte K^+, mmol/kg·Hb	107 ± 14.2	102 ± 12.1	-5.31 ± 18.3	106 ± 14.7	102 ± 17.6	-4.42 ± 19.4	.867
Intraerythrocyte Ca^{2+}, mmol/kg·Hb	2.92 ± 0.53	2.32 ± 0.37	-0.60 ± 0.64	2.52 ± 0.33	2.58 ± 0.32	0.06 ± 0.53	<.001

Data are presented as mean ± SD. P values represent the comparison results of the difference values between the two groups.
ANP = atrial natriuretic peptide, HDL = high density lipoprotein, ISH = isolated systolic hypertension, LSSalt = low sodium salt, NSalt = normal salt.

3.4. Blood/urinary parameters in NISH participants

As illustrated in Table 3, compared to the NSalt group, the LSSalt group showed average changes in the excretion of urinary electrolytes, with −75.7 mmol/24 h for Na^+ (95% CI:−108 to−43.9, $P < .001$), 10.3 mmol/24 h for K^+ (95% CI: 4.34 to 16.3, $P = .001$), and 4.15 mmol/24 h for Ca^{2+} (95% CI: 2.25 to 6.04, $P < .001$). These changes were accompanied by an apparent decrease in the intraerythrocyte levels of Na^+ and Ca^{2+}. Furthermore, the ANP level was significantly decreased after LSSalt intervention (−20.9 pg/mL, 95% CI: −28.1 to −13.7, $P < .001$). No significant differences in other blood biochemical assays were observed between the NSalt and LSSalt groups (all $P > .05$).

3.5. Correlation analysis between BP and blood/urinary parameters

Correlation analyses were then carried out to evaluate the association between BP and the blood/urinary parameters. The results showed that the 24 hours urinary Na^+ and intraerythrocyte K^+ levels were positively correlated with SBP and that the 24 hours urinary K^+ level was negatively correlated with SBP in ISH participants, while the 24 hours urinary Na^+ level was positively correlated with DBP in these participants (Figs. 3 and 4). In the NISH participants, no correlations between BP and the blood/urinary parameters were found (Supplemental Figure 1, http://links.lww.com/MD/C188 and Supplemental Figure 2, http://links.lww.com/MD/C188).

4. Discussion

The present study used salts with different sodium chloride contents to observe the effects of low sodium salt intake on the BP of ISH patients. The results showed that in the ISH participants, the SBP of the LSSalt group was significantly decreased compared with that of the NSalt group after 6 months of intervention, while no changes were observed for DBP or in NISH participants.

Table 3

24 h urinary excretion of electrolytes and blood biochemical assays at end of run-in period and 6 month after randomization in nonisolated systolic hypertension group.

	LSSalt (n = 38)			NSalt (n = 37)			
	Run-in	6 months	Difference	Run-in	6 months	Difference	*P* value
Urinary Na^+, mmol/24 h	245 ± 41.2	153 ± 32.1	-91.7 ± 47.3	241 ± 54.7	225 ± 52.3	-16.0 ± 86.0	<.001
Urinary K^+, mmol/24 h	23.3 ± 7.11	35.4 ± 9.63	12.1 ± 11.4	25.6 ± 8.15	27.4 ± 11.3	1.78 ± 14.3	.001
Urinary Ca^{2+}, mmol/24 h	7.06 ± 2.36	11.5 ± 3.89	4.46 ± 5.02	6.91 ± 2.43	7.22 ± 2.05	0.31 ± 2.91	<.001
Plasma renin activity, ng/mL/h	2.04 ± 0.48	3.05 ± 0.75	1.01 ± 0.81	2.09 ± 0.28	2.89 ± 0.33	0.80 ± 0.43	.160
Plasma angiotensin II, pg/mL	60.9 ± 8.32	73.4 ± 14.4	12.6 ± 15.7	65.6 ± 7.46	73.8 ± 15.9	8.19 ± 18.8	.278
Plasma ANP, pg/mL	71.9 ± 9.92	64.3 ± 7.86	-7.57 ± 12.3	76.0 ± 17.3	89.4 ± 8.27	13.3 ± 18.6	<.001
Plasma total cholesterol, mmol/L	5.43 ± 0.95	5.64 ± 0.99	0.21 ± 1.46	5.46 ± 1.19	5.91 ± 1.51	0.45 ± 1.74	.509
Plasma HDL, mmol/L	2.46 ± 0.29	2.74 ± 0.53	0.27 ± 0.56	2.56 ± 0.47	2.90 ± 0.44	0.33 ± 0.55	.663
Plasma triglyceride, mmol/L	2.26 ± 0.84	2.32 ± 0.84	0.06 ± 1.09	2.09 ± 0.87	2.19 ± 0.78	0.11 ± 1.21	.866
Serum glucose, mmol/L	5.52 ± 2.20	6.21 ± 1.71	0.69 ± 2.61	5.13 ± 1.57	5.56 ± 1.72	0.43 ± 2.46	.659
Serum insulin, μg/L	22.2 ± 6.63	21.5 ± 5.89	-0.70 ± 9.06	19.8 ± 5.94	21.1 ± 5.35	1.23 ± 7.35	.316
Intraerythrocyte Na^+, mmol/kg Hb	25.3 ± 5.32	19.4 ± 4.76	-5.96 ± 7.12	23.2 ± 4.31	24.2 ± 5.47	1.03 ± 7.89	.002
Intraerythrocyte K^+, mmol/kg Hb	109 ± 14.2	106 ± 11.7	-3.36 ± 16.8	104 ± 15.2	99.3 ± 19.4	-4.74 ± 22.6	.808
Intraerythrocyte Ca^{2+}, mmol/kg Hb	2.84 ± 0.53	2.28 ± 0.38	-0.56 ± 0.63	2.57 ± 0.31	2.61 ± 18.8	0.04 ± 0.56	<.001

Data are presented as mean ± SD. *P* values represent the comparison results of the difference values between the 2 groups.
ANP = atrial natriuretic peptide, HDL = high density lipoprotein, LSSalt = low sodium salt, NISH = nonisolated systolic hypertension, NSalt = normal salt.

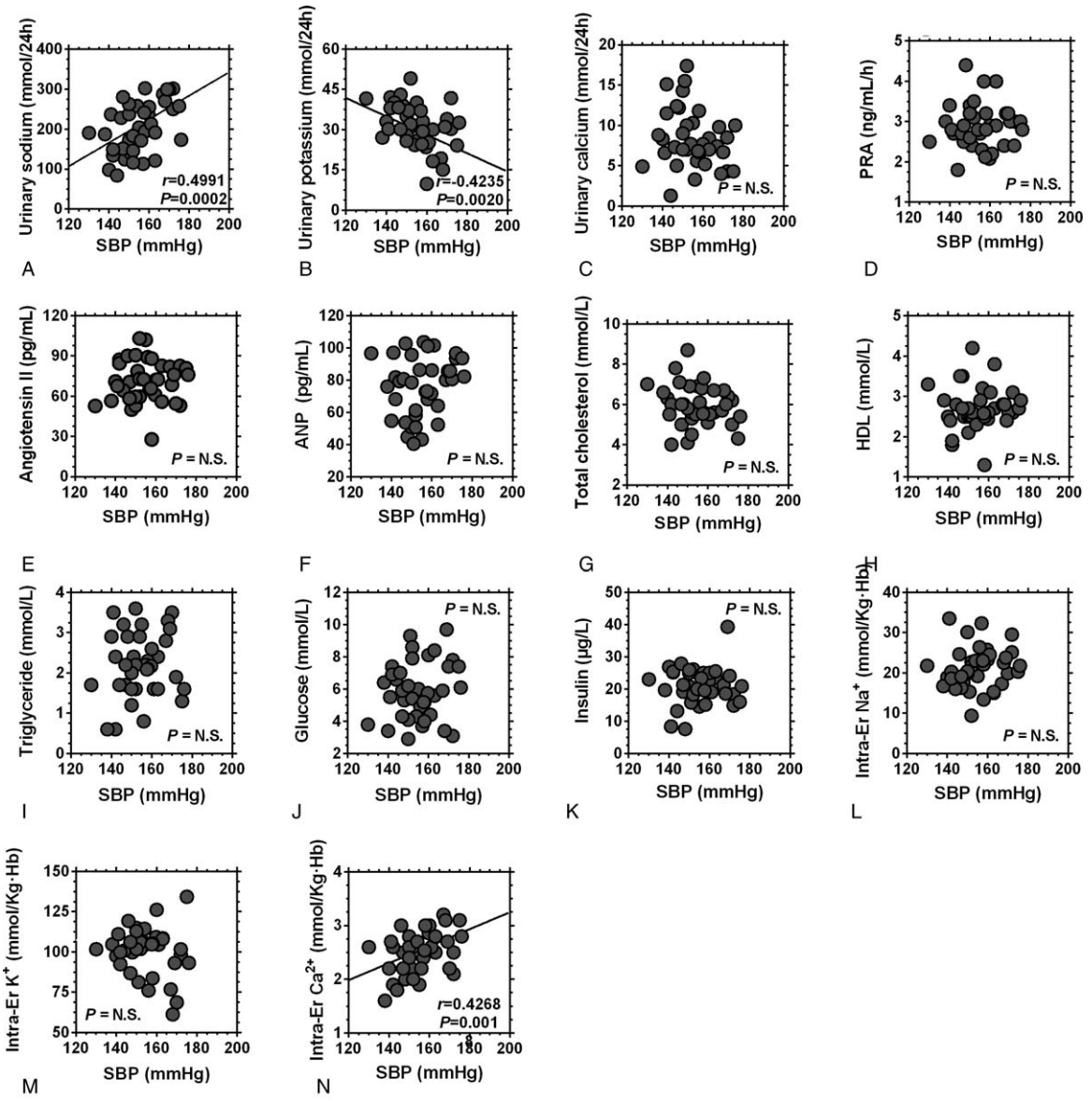

Figure 3. Correlation analysis between the systolic blood pressure and the urinary/blood parameters of ISH participants. Abbreviations= ISH, isolated systolic hypertension; SBP= systolic blood pressure; PRA=plasma renin activity; ANP=atrial natriuretic peptide; HDL=high density lipoprotein, Er=erythrocyte.

Furthermore, the correlation analyses showed that the SBP of ISH participants was positively correlated with the 24 h urinary Na^+ level and negatively correlated with the 24 hours urinary K^+ level, indicating that the ISH patients were more sensitive to the effects of LSSalt.

Numerous clinical studies have demonstrated the benefits of reducing BP in ISH patients.[8,17,18] A recent study demonstrated that after 1 month of low salt intervention, the average SBP of ISH patients was decreased from 166 to 156 mm Hg ($P < .001$), but no significant reduction was found in DBP, which agrees with the results of the present study.[19] However, a reanalysis of NHANES III and IV showed that salt intake was only related to isolated diastolic hypertension, and there was an inverse effect in the BP levels of ISH patients.[20] This disparity in the effects of salt intake on the BP of ISH individuals may be partly attributed to differences in the dietary intake of various components, such as energy, protein, total fat, carbohydrates, potassium, magnesium, and calcium, which may also influence the BP levels.[19,21] The other interpretation is that location and ethnicity may result in different reactivities of BP levels to salt intake.[22,23]

The low sodium content of the LSSalt could be the major contributor to the decrease in BP. The 24 hours urinary Na^+ excretion was a good marker of the daily sodium intake.[15] In the present study, compared with the ISH NSalt group, the sodium intake decreased by 55.0 mmol/24 h in the ISH LSSalt group, and the SBP decreased by 10.18 mm Hg. In the NISH participants, the SBP of the LSSalt group only decreased 5.10 mm Hg compared with that of the NSalt group, when the sodium intake decreased by 75.7 mmol/24 h, which indicated that the ISH patients were more sensitive to salt restriction, as found in a previous study.[19] Additionally, because salt restriction leads to an increase in Na^+ reabsorption, the excretion of other urinary electrolytes could also be influenced.[15] In the present study, the decrease in the urinary excretion of Na^+ was accompanied by apparent increases in the urinary excretion of K^+ and Ca^{2+}, which indicated that there was an increase in the active reabsorption of Na^+.

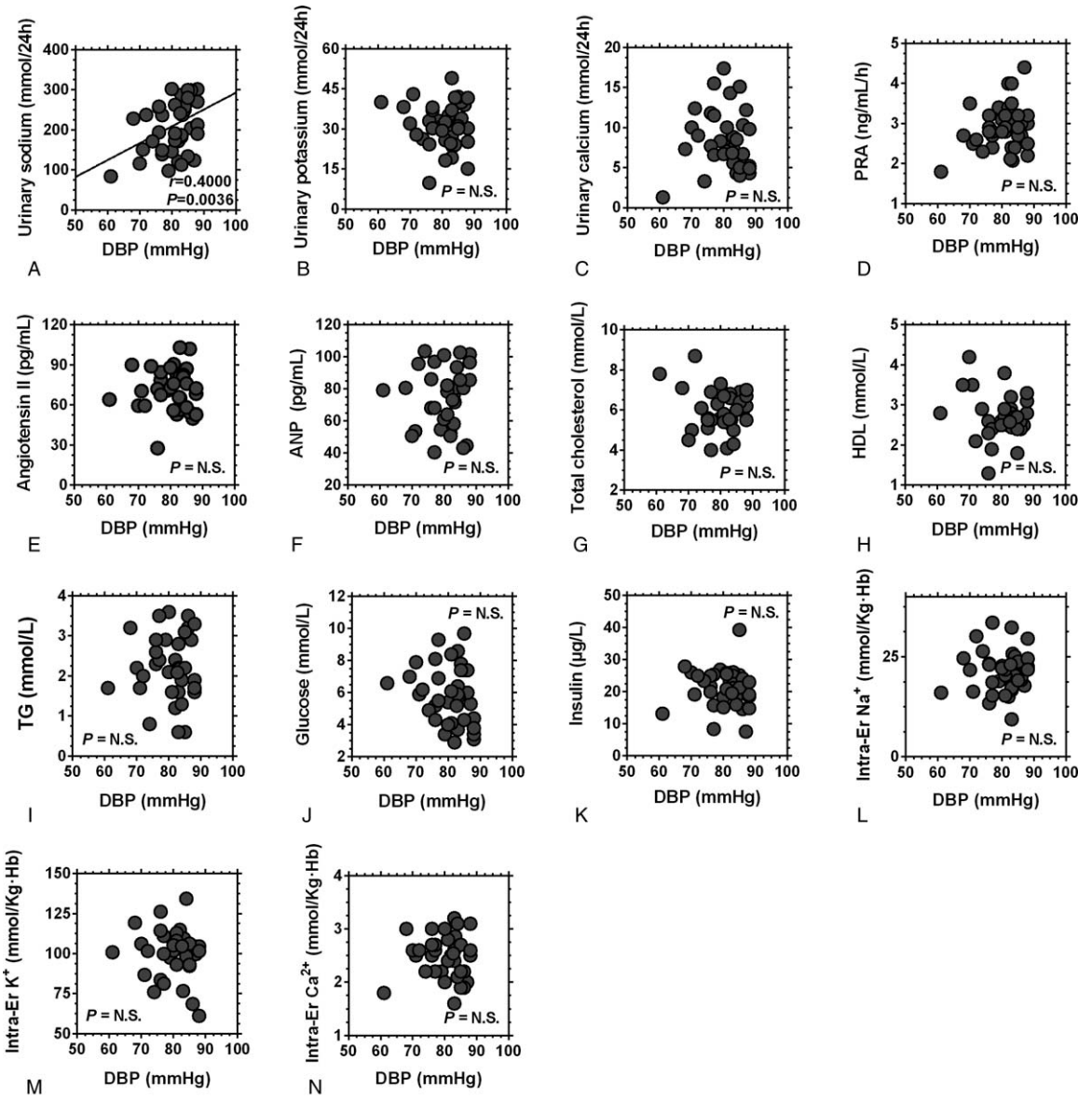

Figure 4. Correlation analysis between the diastolic blood pressure and The urinary/blood parameters of ISH participants. Abbreviations= ISH, isolated systolic hypertension; DBP=diastolic blood pressure; PRA=plasma renin activity; ANP=atrial natriuretic peptide; HDL=high density lipoprotein, Er=erythrocyte.

The present study also showed that the plasma ANP level was significantly decreased by LSSalt intervention in both the ISH and NISH groups. ANP is secreted by mammals and released into circulation in response to acute or chronic atrial stretch, playing an important role in circulatory homeostasis.[24] It can regulate BP by modulating fluid homeostasis and vascular function,[25,26] which may be a mechanism of BP reduction by low salt intake in hypertensive patients.

The detailed mechanism underlying the lowering of BP due to salt restriction is still unclear, although several possible mechanisms have been elucidated.[27] First, high salt intake could lead to increases in blood volume and peripheral vascular resistance; thus, salt restriction could weaken these effects and reduce BP accordingly.[28] The second proposed mechanism suggests that compared with high salt intake, salt restriction could inhibit the production of reactive oxygen species, reducing the activity of nitric oxide, improving peripheral vascular resistance and lowering BP.[29] Another possible mechanism is that the low level of inflammation induced by inflammatory cells and factors is an important factor inducing increased BP.[30] Salt restriction could inhibit inflammatory cell infiltration and decrease the production of inflammatory factors, thereby lowering BP.[31]

The reason for the enhanced sensitivity of ISH patients to salt restriction needs further study to be elucidated. One possible reason is that ISH is the most dominant form of hypertension with increasing age,[6] among people aged 70 and older, the prevalence is 8%, and it rises to $> 25\%$ among those aged 80 years or older.[8] Previous studies have shown that most ISH patients have a more severe arterial stiffness than is found in patients with other types of hypertension, and that stiffer arteries are more sensitive to BP changes induced by variation in liquid volume.[12,13] Salt restriction could reduce the volume load, leading to lower BP. A second possible reason is that

inflammation is one of the most important causes of arterial stiffness,[32,33] and salt restriction can inhibit inflammatory cell infiltration, decreasing the production of inflammatory factors, improving arterial stiffness and lowering BP. Another possible reason is that most ISH patients may have salt sensitive hypertension, resulting in a stronger effect on BP of salt restriction. This may be supported by the fact that only ISH patients had a positive correlation between 24 hours urinary sodium levels and BP. However, this proposed mechanism still needs further study to be confirmed.

There were several novel findings in the present study. First, although studies have investigated the relationship between low sodium salt intake and BP of ISH patients, the results have been controversial.[19,20] In He's study,[19] the SBP of the ISH group decreased 10 mm Hg after 1 month of low sodium intervention while another study showed that salt intake had an inverse relationship with BP levels in ISH patients.[20] Therefore, we further investigated the relationship of low sodium salt intake and BP in ISH patients and found that the ISH patients experienced larger decreased in SBP after moderate salt restriction. The second finding was that an increasingly lower salt intake does not continue to confer additional benefits, high salt intake ISH population, moderate salt restriction is beneficial. In the present study, the excretion of sodium in the ISH LSSalt group decreased from a relatively high level (226 mmol/L) to a low level (176 mmol/L), and the SBP decreased 10.10 mm Hg without obvious RAS activation. But in He's study,[19] the sodium excretion of the ISH group decreased from a relatively low level (175 mmol/L) to a lower level (87 mmol/L), and the SBP decreased 10 mm Hg, accompanied by significant RAS activation. Another previous study has shown that salt restriction with RAS and sympathetic nerve system activation may offset the benefits of salt restriction on high BP and may even cause adverse effects.[34] The third finding was that the novel low sodium salt used in this study can not only decrease sodium intake with no obvious difference in salty flavor but also replenish potassium which may also lower BP, as the correlation analysis in the present study showed an inverse relationship between 24 hours urinary of excretion of K^+ and SBP in ISH participants.

Several limitations should be acknowledged in our study. First, this community-based ISH salt restriction trial was a single-blinded, single-center study, which may lead to systematic bias in BP measurements. Second, we selected LSSalt as the low salt intervention, and it may be exaggerate the effect of salt restriction because several other components of LSSalt (potassium, calcium, and folic acid) may also lower BP.[35–38] Third, the measurement of BP in the study was office BP, not ambulatory blood pressure monitoring or home monitoring data, which may be different from the patients' usual BP. Fourth, to enrol participants with good compliance, we recruited an relatively old population and a small sample; thus, to extrapolate the results to a more general population, further studies are needed.

5. Conclusions

The present study showed that the SBP of ISH patients, but not that of NISH patients or the DBP of either group, was significantly decreased under LSSalt intervention, which indicated that ISH patients were more sensitive to salt restriction. More benefits in the secondary prevention of hypertension might be obtained in ISH patients from moderate salt restriction.

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