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Low Response of Renin–Angiotensin System to Sodium Intake Intervention in Chinese Hypertensive Patients

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Abstract: The interactions of sodium balance and response of renin–angiotensin–aldosterone system are important for maintaining the hemodynamic stability in physiological conditions. However, the influence of short-term sodium intake intervention in the response of renin–angiotensin system (RAS) on hypertensive patients is still unclear. Thus, we conducted a clinical trial to investigate the effects of short-term sodium intake intervention on the response of RAS in hypertensive patients.

One hundred twenty-five primary Chinese hypertensive patients were divided into high, moderate, and low sodium groups by 24-hour urinary sodium excretion (UNa^+). All the patients received a 10-day dietary sodium intake intervention with standardized sodium (173.91mmol/day) and potassium (61.53mmol/day). Blood pressure, urinary sodium, urinary potassium, plasma sodium, potassium, creatinine, the levels of plasma renin activity, plasma angiotensin II concentrations (AT-II), and plasma aldosterone concentrations were detected before and after the intervention.

Before the intervention, no differences were found in blood pressure and RAS among 3 groups. After standardized dietary sodium intake intervention, both UNa^+ excretion and systolic pressure decreased in high-sodium group, while they increased in moderate and low-sodium groups. Intriguingly, there were no changes in the levels of plasma renin activity, AT-II, and plasma aldosterone concentrations among 3 groups during the intervention.

The present study demonstrated that the influenced sodium excretion and blood pressure by short-term sodium intake intervention were independent of RAS quick response in Chinese hypertensive patients.

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Abbreviations: AT-II = plasma angiotensin II concentration, BMI = body mass index, DBP = diastolic blood pressure, HS = high sodium, LS = low sodium, MBP = mean blood pressure, MS = moderate sodium, PAC = plasma aldosterone concentration, PRA = plasma renin activity, RAS = renin–angiotensin system, SBP = systolic blood pressure, UK^+ = urinary potassium excretion, UNa^+ = urinary sodium excretion.

INTRODUCTION

It is widely accepted that high sodium is a significant risk factor for cardiovascular diseases and is strongly correlated with hypertension.[1,2] Strazzullo et al[3] conducted a meta-analysis and found that the risk of cardiovascular diseases and stroke is directly influenced by high dietary sodium intake (86 mmol increase in sodium). However, the benefits of strictly limited sodium intake diet are still under debate. Recently, O'Donnell et al[4] estimated dietary sodium intake by measuring urinary sodium excretion and demonstrated that both high (>7 g/day sodium) and low (<3 g/day sodium) urinary sodium excretions increased the risk of cardiovascular events based on 2 cohorts (n = 28,880) included in the ONTARGET and TRANSCEND trials. Moreover, a few clinical studies also revealed that the incidence of cardiovascular mortality was greater in populations of lower sodium excretion.[5,6] Thus, the relationship between sodium intake and cardiovascular events will continue to attract discussion.

Although reducing the sodium intake has been associated with controlling blood pressure in hypertensive patients, it is difficult to change the sodium consumption among the Chinese hypertensive patients with high salt dietary lifestyles to strictly limited sodium intake diet.[7–9] Studies have demonstrated that the 24-hour sodium excretion (widely used to estimate the daily sodium consumption) in Chinese population (128.1 ± 52.9 mmol/day to 293.2 ± 91.8 mmol/day) is higher than those in many countries such as American (142.3 ± 48.3 mmol/day to 182.7 ± 62.4 mmol/day).[10,11] Additionally, these findings indicated that the daily dietary sodium intake in Chinese population varies widely. So, it is unclear to evaluate the scientific rationality of a constant recommended sodium intake, such as the suggestion of world health organization in hypertension.

Both sodium retention and improper activation of the renin–angiotensin system (RAS) are important mechanisms of hypertension.[12,13] The response of RAS to sodium intake intervention plays a pivotal role in maintaining serum sodium.[14] Under normal physiological conditions, sodium intake intervention influences the response of RAS. High sodium intake resulted in the

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decreased levels of plasma renin activity (PRA), plasma angiotensin II concentrations (AT-II), and plasma aldosterone concentrations (PAC), while opposite change occurred after low sodium intake.[15,16] Conversely, disorder of RAS response contributes to the adverse outcomes. The response of the RAS to volume stimuli in aged people is reduced whereas the reactivity of sodium elimination is preserved. This might be the key mechanism for salt-sensitive hypertension. Thus, the response of RAS is a central determinant of hypertension and sodium balance. Although a series of factors that may affect the response of RAS include race, gene, age, prostanoids, and cyclooxygenase,[17,18] whether this short-term sodium intake intervention could influence the RAS response in Chinese hypertensive patients has not been systematically explored.

In the present study, we explored the effects of short-term dietary sodium intake intervention on the change of blood pressure in hypertensive patients that sodium intake varied widely, and further investigated the relationship between dietary sodium intake and the response of RAS.

METHODS

Study Participants

From June 2012 to October 2014, all the patients who were newly diagnosed with hypertension and underwent treatment in Sun Yat-sen memorial hospital of Sun Yat-sen University were enrolled in this study. Exclusion criteria included body mass index (BMI) lower than 18.5 kg/m^2, primary aldosteronsim, kidney disease, hepatopathy, acute inflammatory, pregnancy, and diabetes. Furthermore, administration of antihypertensive drugs including diuretics and RAS inhibitor had been stopped less than 2 weeks before this study. To avoid risks of untreated hypertension, long-acting calcium channel blocker or $\alpha - 1$ adrenergic receptor blocker were used if necessary. The antihypertensive scheme was kept alike throughout the process of study. All the patients were divided into different groups according to their primary urinary sodium excretions and provided a steady dietary sodium intake intervention (173.91 mmol/day, about 4 g/day sodium or 10 g/day salt, according to epidemiological surveys of China).[10,19]

Ethics Statement

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the Ethics Committee of Sun Yat-sen Memorial Hospital of Sun Yat-sen University. Informed consent was obtained from each participant.

Basic Clinical Characteristics and Dietary Sodium Intervention

The scheme of this study is shown in Figure 1. According to the scheme,[20,21] the 24-hour urinary basal values were collected from the patients following their normal dietary routines. The urinary sodium/potassium excretion was tested and labeled as primary 24-hour urinary sodium excretion. Then, the participants were grouped into 3 groups according to their primary 24-hour urinary sodium excretion (UNa^+)[4]: high sodium group (HS, over 304.35 mmol/day), moderate sodium group (MS, from 86.96 mmol/day to 304.35 mmol/day), and low sodium group (LS, less than 86.96 mmol/day). They all received a 10-day monitored dietary sodium intervention period (173.91 mmol/day, according to epidemiological surveys of China).[10,19] To avoid the influence of potassium, sufficient potassium (61.53 mmol/day) was supplied. All dietaries were prepared by the department of diet and nutrition with unified planned dietary components and quantities. Body weight and height were measured 3 times before dietary sodium intervention and the average values were collected. Blood pressures were measured 3 times every morning throughout the study and the average values of blood pressures were calculated.

Sample Collection and Detection

Blood samples were collected at the end of both normal dietary period and dietary sodium intervention period. Patients were allowed to have 2 to 4 hours of deambulation and in supine position, and then the levels of PRA, AT-II, and PAC were measured by radioimmunoassay kits (Beckman Coulter Inc, Brea, CA). After 10 days of the 24 hours urinary samples were collected, the average values of UNa^+ and UK^+ were obtained. Urinary sodium, urinary potassium, plasma sodium, and plasma potassium were collected using automatic analyzer (HITACHI, model 7600-010, Tokyo, Japan).

Statistical Analysis

Means and standard deviations values were used for statistical description and the data were compared by analysis of variance and Bonferroni among 3 groups such as ages, BMI, blood pressure, plasma sodium, plasma potassium, UNa^+, UK^+, UNa^+/UK^+. The sex difference was compared by χ^2 test. Median and ranges were used to describe the levels of PRA, AT-II, and PAC, and those data were compared by Kruskal–Wallis test and similar normal state method to explore the differences among 3 groups. Paired *t* test (Mann–Whitney *U*) was used to find the differences before and after the

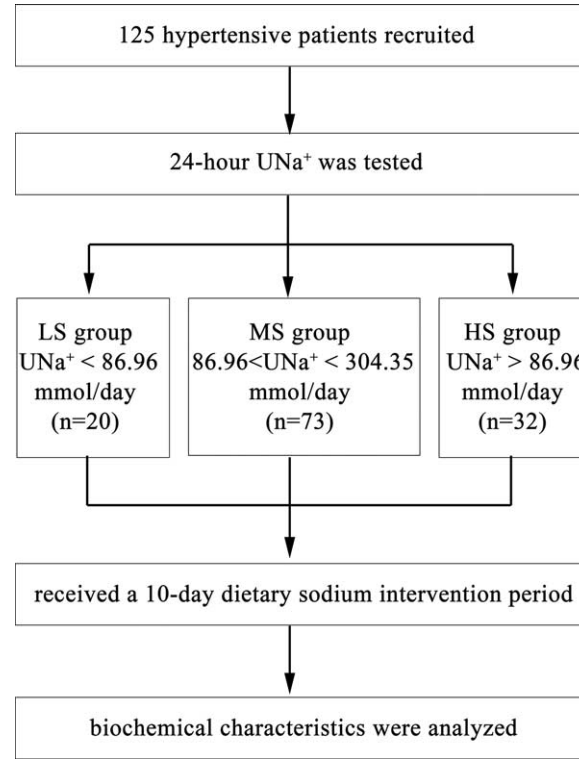

FIGURE 1. The protocol of sodium intake intervention in Chinese hypertensive patients. HS = high sodium; LS = low sodium; MS = moderate sodium; UNa^+ = urinary sodium excretion.

TABLE 1. Baseline Anthropometric and Biochemical Characteristics of Different Groups Before Dietary Sodium Intervention

	LS Group (n = 20)	MS Group (n = 73)	HS Group (n = 32)	P value
Age (yr)	39.31 ± 11.03	41.49 ± 8.68	37.38 ± 9.01	0.75
Sex (female:male)	14:6	44:29	16:16	0.20
BMI (kg/m^2)	23.68 ± 3.45	25.37 ± 3.50	24.38 ± 3.32	0.13
SBP (mm Hg)	154.31 ± 26.41	158.84 ± 21.77	157.42 ± 19.49	0. 14
DBP (mm Hg)	96.11 ± 8.59	97.41 ± 12.85	98.88 ± 11.65	0.17
MBP (mm Hg)	117.59 ± 14.99	119.67 ± 14.70	116.54 ± 16.15	0.65
Plasma sodium (mmol/L)	140.72 ± 2.20	140.12 ± 2.22	140.02 ± 3.07	0.70
Plasma potassium (mmol/L)	3.56 ± 0.42	3.67 ± 0.43	3.69 ± 0.41	0.25
UNa^+ (mmol/day)	52.34 ± 14.88	176.98 ± 62.39	441.74 ± 116.80	<0.001
UK^+ (mmol/day)	24.76 ± 12.19	62.24 ± 13.97	89.48 ± 34.24	<0.001
Ratio of UNa^+/UK^+	2.55 ± 1.32	3.23 ± 1.78	5.09 ± 1.37	<0.001
PRA (ng/mL/h)	1.43 (0.02–4.80)	0.76 (0.02–4.30)	1.34 (0.24–6.71)	0.89
AT-II (ng/L)	32.41 (5.00–92.30)	41.80 (14.10–148.40)	38.30 (10.2–337.5)	0.78
PAC (ng/L)	87.95 (5.00–320.20)	106.45 (21.50–275.00)	132.80 (58.6–289.1)	0.68

AT-II = plasma angiotensin II concentration, BMI = body mass index, DBP = diastolic blood pressure, HS = high sodium, LS = low sodium, MS = moderate sodium, PAC = plasma aldosterone concentration, PRA = plasma renin activity, SBP = systolic blood pressure. *P* values represent the results of the repeated one-way measures of analysis of variance (ANOVA). *P* values represent the results of the repeated one-way measures of ANOVA.

intervention. Less than adjusted significance levels as 0.05 were considered statistically significant. All analyses were done with SPSS version 17.0 (SPSS Inc, Chicago, IL).

RESULTS

Characteristics of Study Population

One hundred twenty-five adults aged from 27 to 52 were enrolled in the study and the average of UNa^+ was 219.76 ± 143.34 mmol/day. The UNa^+ of 48% patients was lower than 173.91mmol/day, 16% was lower than 86.96 mmol/day, and 25.6% UNa^+ was more than 304.35 mmol/day.

Baseline Characteristics Among the 3 Groups Before Dietary Sodium Intervention Period

As shown in Table 1, compared with MS and LS, the UK^+ significantly increased in HS ($P < 0.05$ vs. MS and $P < 0.01$ vs. LS) and the UK^+ in MS was also moderately higher than that in LS ($P < 0.01$ vs. LS). Furthermore, the ratio of UNa^+/UK^+ in the HS was significantly higher than those of MS and LS ($P < 0.05$ vs. MS and $P < 0.01$ vs. LS), and the ratio of UNa^+/UK^+ in MS was moderately increased when compared with the LS. Although urinary sodium excretions were different, blood pressure and the levels of PRA, AT-II and PAC had little differences among 3 groups. There were no significant differences about age and BMI among 3 groups.

Baseline Characteristics Among 3 Groups After Dietary Sodium Intervention Period

After 10-day dietary sodium intervention, changes of characteristics are shown in Table 2. The difference of UNa^+, , UK^+, and UNa^+/UK^+ in the 3 groups was unanimously after the dietary sodium intervention. The systolic blood pressure (SBP) and mean blood pressure (MBP) in HS was reduced,

TABLE 2. Baseline Anthropometric and Biochemical Characteristics of Different Groups After Dietary Sodium Intervention

	LS Group (n = 20)	MS Group (n = 73)	HS Group (n = 32)	P value
SBP (mm Hg)	160.21 ± 20.70	166.11 ± 22.76	145.36 ± 12.91	0.01
DBP (mm Hg)	106.67 ± 11.46	103.50 ± 15.41	97.53 ± 13.09	0.28
MBP (mm Hg)	125.40 ± 12.84	124.52 ± 16.04	107.35 ± 18.49	0.02
Plasma sodium (mmol/L)	140.03 ± 1.95	140.20 ± 1.67	140.32 ± 7.62	0.19
Plasma potassium (mmol/L)	3.63 ± 0.41	3.68 ± 0.49	3.52 ± 0.24	0.39
UNa^+ (mmol/day)	186.07 ± 105.03	251.65 ± 171.93	266.80 ± 170.91	0.08
UK^+ (mmol/day)	47.19 ± 19.52	67.29 ± 37.36	79.99 ± 49.15	0.13
Ratio of UNa^+/UK^+	3.81 ± 1.46	4.08 ± 1.48	3.65 ± 1.43	0.79
PRA (ng/mL/h)	1.50 (0.80–2.08)	1.03 (0.77–5.00)	1.20 (0.58–6.00)	0.46
AT-II (ng/L)	35.41 (13.00–81.30)	39.30 (14.06–119.00)	35.30 (5.00–139.70)	0.56
PAC (ng/L)	112.30 (8.00–269.50)	101.85 (41.00–484.00)	126.40 (64.50–363.30)	0.21

AT-II = plasma angiotensin II concentration, DBP = diastolic blood pressure, HS = high sodium, LS = low sodium, MBP = mean blood pressure, MS = moderate sodium, PAC = plasma aldosterone concentration, PRA = plasma renin activity, SBP = systolic blood pressure. *P* values represent the results of the repeated one-way measures of ANOVA.

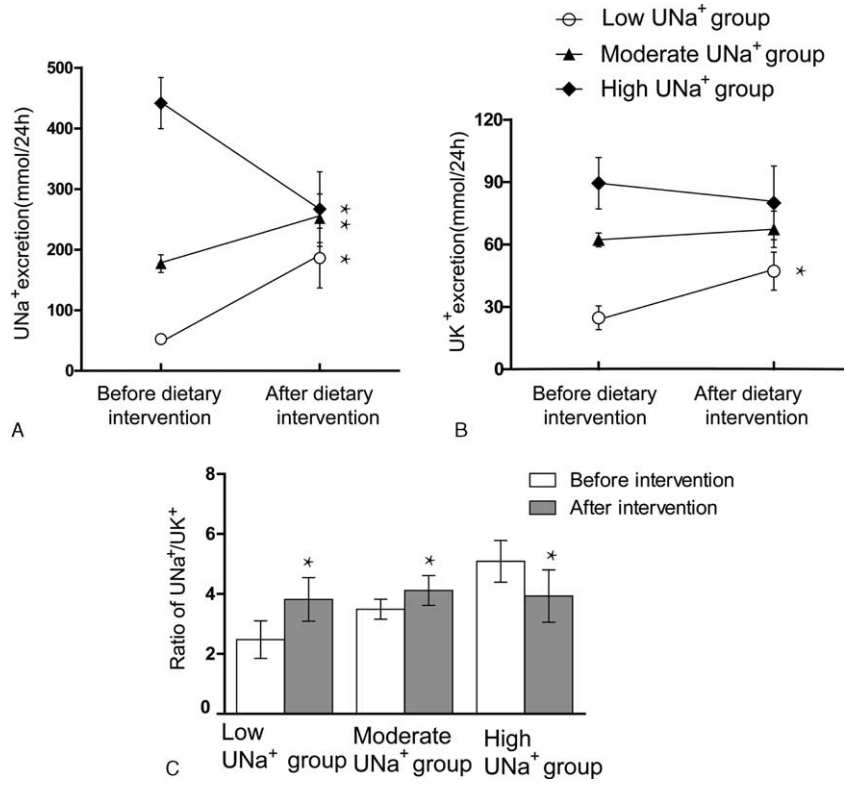

FIGURE 2. (A) Urinary sodium excretions, (B) urinary potassium excretions, and (C) Na^+/UK^+ ratio in different groups before or after sodium intake intervention. UK^+ = urinary potassium excretion; UNa^+ = urinary sodium excretion. $^*P < 0.05$ versus before dietary intervention.

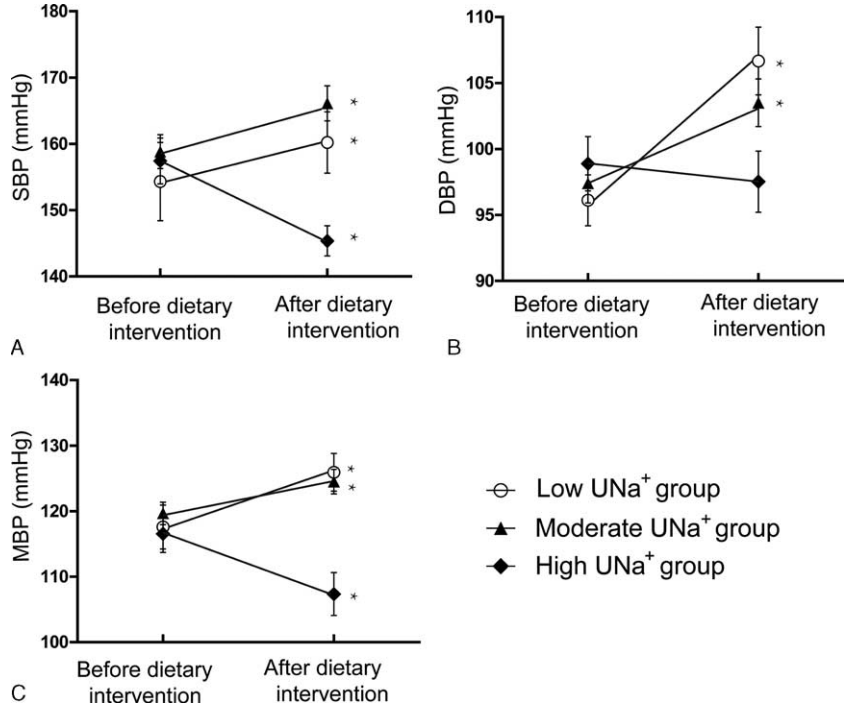

FIGURE 3. (A) Systolic blood pressure, (B) diastolic blood pressure, and (C) mean blood pressure in different groups before or after sodium intake intervention. DBP = diastolic blood pressure; MBP = mean blood pressure; SBP = systolic blood pressure. $^*P < 0.05$ versus before dietary intervention.

whereas those in MS and LS increased after dietary sodium intervention. Although diastolic blood pressure (DBP) was also changed, no significant difference was found among the 3 groups. Interestingly, there were no statistical differences in the levels of PRA, AT-II, and PAC among 3 groups after dietary sodium intervention.

Comparisons of Characteristics Before and After a Short-Term Dietary Sodium Intake Intervention

As shown in Figure 2A, after dietary sodium intervention, sodium excretion decreased in HS group and increased in MS and LS groups compared with baseline values before dietary sodium intervention. And UK^+ slightly decreased in HS and MS groups but significantly increased in the LS group ($P < 0.01$, Figure 2B). Meanwhile, the ratio of UNa^+/UK^+ increased in the MS and LS after sodium intervention ($P < 0.01$) compared with the values obtained before intervention (Figure 2C). As shown in Figure 3, dietary sodium intervention decreased SBP and MBP but not DBP in the HS ($P < 0.05$), while it significantly elevated SBP, DBP, and MBP in both MS ($P < 0.01$) and LS ($P < 0.05$). Though blood pressure and sodium intake were changed significantly after dietary sodium intervention, there were no differences in the levels of PRA, AT-II, and PAC with or without sodium intervention (Figure 4).

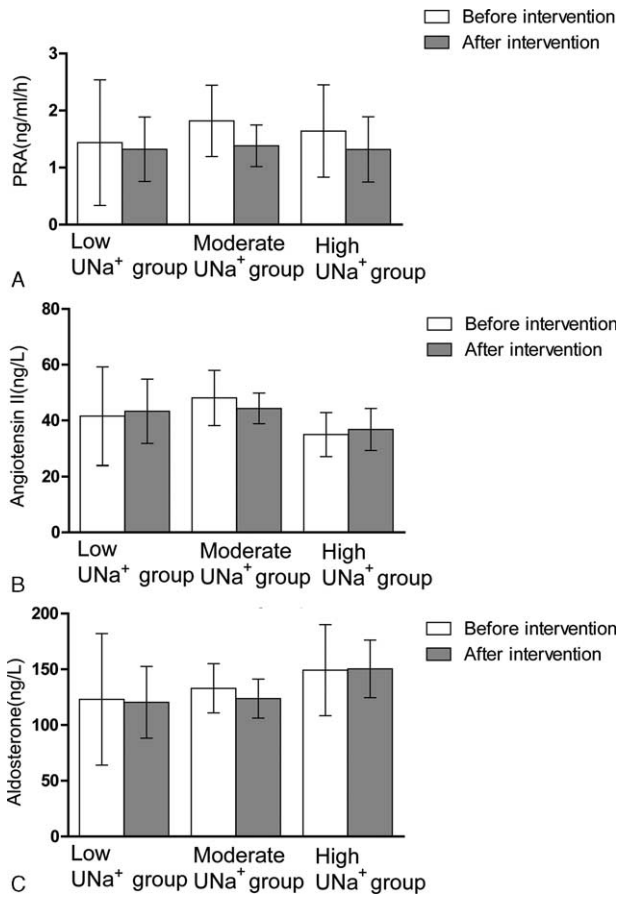

FIGURE 4. Comparison of the levels of (A) plasma renin activity, (B) plasma angiotensin II concentration, and (C) plasma aldosterone concentration in different groups before or after sodium intake intervention. PRA = plasma renin activity.

DISCUSSION

It is well known that the excessive activation of RAS increases the risk of cardiovascular diseases, while there are insufficient evidences to determine if strictly limited sodium intake confers any influence on the risk of cardiovascular disease, stroke, or mortality rates. The response of RAS to different levels of sodium intake is vital, and it is evidently linked to the dietary habits of each individual. Although previous studies demonstrated that changes of RAS in hypertensive patients were different from those of normotensive individuals under conditions where sodium intake levels are above or below the recommended ranges,[21,22] extremely high or low sodium intakes levels were rare in the daily life of the normal population. In the present study, short-term standardized sodium intervention was given to estimate the changes of blood pressure and RAS in Chinese hypertensive patients with different sodium intake backgrounds, and demonstrated that the urinary sodium excretions and blood pressures were changed but they did not attribute to the corresponding changes of PRA, AT-II, and PAC in Chinese hypertensive patients.

The previous study demonstrated that the modest sodium intake reduction (the decrements of sodium intake were between150 and 50 mmol/day sodium) decreased blood pressure, reduced the urine protein, and improved capillary structure and functions in hypertension.[23–25] And increased sodium intake in hypertensive patients might indistinctively elevate blood pressure; however, they reduce the protective effects of antihypertension drugs.[26] In our study, the sodium intake was still higher than the recommendation of world health organization, but a reduced sodium intake from 304.35 mmol/day to 173.91 mmol/day was beneficial in decreasing the SBP but not DBP in high sodium group. Meanwhile, both SBP and DBP were significantly elevated in low and moderate sodium groups even though the increased sodium intake was slight and transitory increased. Moreover, the SBP in the high sodium group was lower than those in low or moderate sodium groups after dietary sodium intervention. These data demonstrated that sodium restriction was more helpful for the hypertensive patients with high dietary sodium habits. Additionally, it warrants the assumption that the vascular responses to dietary sodium intervention were more sensitive in high sodium excretion group of hypertensive patients compared with low sodium excretion patients.[27]

The response of RAS to the changes in sodium intake varies widely because of different races or dietary habits. He et al[22] gave both hypertensive and normotensive white individuals a high sodium intake of 350 mmol/day for 5 days followed by a low sodium intake of 10 to 20 mmol/day for 5 days, and the blood pressure dropped significantly in hypertensive patients after the strictly low sodium intake, and the alteration in the PRA levels was less than that of normotensive patients. These results imply that the activity of RAS in the white hypertensive patients was less responsive to short-term sodium intake intervention. Conversely, Chamarthi et al[27] have shown that low sodium intervention would increase the levels of PRA and PAC in American hypertensive patients; however, these elevated ranges were lower than those of normotensive patients. In this study, we found that both blood pressure and urinary sodium excretion were changed after dietary sodium intervention in the 3 groups, but no significant differences were

found in the levels of PRA, AT-II, and PAC among them. Combined with results of previous studies, we could draw the conclusion that the activity of RAS in Chinese hypertensive patients is low-response to sodium intake levels. Though we could not make the conclusion that it is a characteristic change of Chinese hypertensive patients, we assumed that it might be related to the genetic factor or the customary high salt consumption of Chinese population, and this needs further study and exploration.

The response of RAS to sodium is influenced by multiple factors, such as COX, NO,[28–32] gene polymorphisms,[33] as well as abnormal intake of some dietary components such as 25-hydroxyvitamin D.[34] However, the detailed mechanisms of RAS response to sodium in Chinese hypertensive patients need further study.

Meanwhile, there are several limitations in the present study. First, the number of study participants was relatively small. In addition, the study population was restricted to Chinese hypertensive patients. Thus, our findings will require further replication in a larger population in other races by different short-term sodium intake interventions. Furthermore, since the complicated mechanisms by which low response of RAS to sodium intake intervention in Chinese hypertensive patients has not yet been completely clarified, we will explore the potential mechanisms in animal model in further study.

In conclusion, this study demonstrated that the decreased blood pressure in Chinese hypertensive patients induced by short-term sodium intake intervention was associated with sodium excretion; however this was independent of RAS. Moreover, in this study, it was concluded with evidence that in addition to antihypertensive drugs, sodium administration plays a key role in the management of hypertension. Of importance, our findings raise a new reminder about the significance of short-term diet control in hypertension. At the same time, we provide a new direction and strategies for the management of hypertension in the Chinese population.

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