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Research Article

Effect of Changes in Salt Intake on Nocturnal Blood Pressure Dipping and Diurnal Urinary Sodium Excretion in Normotensive Adolescents

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Abstract

Objective: To determine effect of changes in salt intake on nocturnal dipping of blood pressure and diurnal urinary sodium excretion in normotensive adolescents

Methods: Thirty-six normotensive adolescents (age = 15.9 ± 0.9yr) were maintained on high salt intake (supplement of salt by 0.12 g/kg body weight/day in addition to normal diet) for one week followed by one- week washout on a regular diet and then low salt intake (regular meal with low salt and avoid salty food) for another one week. On the last day of each intervention period, 24-h ambulatory blood pressure was measured every 30 minute interval with an automatic device (Spacelab 90207) and urine samples were collected for both daytime and nighttime separately and the urinary concentration of sodium was measured by atomic absorption spectrometer.

Results: At the end of one-week high salt intake, 19 subjects (52.8%) were classified as non-dippers (those who had < 10% decrease in MAP from awake to sleep) and 17 subjects (47.2%) were as dippers (those who had ≥ 10% decrease in MAP from awake to sleep). When switched to low salt intake, 13 out of 19 previously non-dippers were shifted to dippers and therefore, 30 subjects (83.3%) became dippers and only 6 (16.7%) were non-dippers. The mean 24-h urinary sodium excretion was 200.8 ± 56.3 mmol/d during high salt intake and 86.2 ± 22.3 mmol/d during salt restriction. A significant nocturnal increase in urinary sodium excretion rate was observed in non-dippers during high salt and low salt intake ($p < 0.05$). In dippers, a significant nocturnal decrease in urinary sodium excretion rate was observed during low salt intake ($p < 0.05$) but it was not significant during high salt intake. Nighttime urinary sodium excretion rate of non-dippers was significantly higher than that of dippers during high salt intake ($p < 0.05$).

Conclusion: The present study demonstrated that high dietary salt intake would induce attenuated nocturnal dipping of blood pressure with concomitant changes in enhanced nocturnal natriuresis in normotensive adolescents.

Keywords: *Ambulatory Blood Pressure Monitoring; Dipper; Non-Dipper; Salt Intake; Adolescents; Urinary Sodium Excretion Rate*

Abbreviations

ABPM: Ambulatory Blood Pressure Monitoring; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure; $U_{Na}V$: Urinary Sodium Excretion Rate

Introduction

There is a diurnal variation of blood pressure (BP) with 10% to 15% lower values during the night (i.e. nocturnal dip) than during the day. Individuals with a fall of mean arterial pressure (MAP) more than 10% from day to night are "dippers," whereas those without a fall in BP are "non-dippers" [1]. Nocturnal dipping of BP is more than a physiological curiosity because evidences indicated that it is associated with increased risk for cardiovascular events [2-5].

Many studies have been conducted to study the nocturnal dipping of BP in salt-sensitive and salt-resistant hypertensive patients [6-10]. Salt sensitivity can be defined as a 10 % or 8, 5, 3 mmHg increase in MAP with a sodium load. The prevalence of non-dippers was not significantly different between salt-sensitive and salt-resistant hypertensive patients during low salt intake but it was significantly higher in salt-sensitive than in salt-resistant hypertensive patients on a high salt intake [10]. Low salt intake can restore the nocturnal dipping of BP in salt-sensitive hypertensive subjects [7]. Salt sensitivity index (the ratio of the change in 24-h MAP divided by the change in sodium excretion on high and low sodium diets in steady state) was significantly correlated with nighttime MAP during high salt intake but not during the low salt intake [8]. In normotensive subjects, 50% of the salt-sensitive subjects were non-dippers while only 5.4% of the salt-resistant subjects were non-dippers [11]. However, most of normotensive subjects maintain normal nocturnal BP dipping irrespective of salt intake and of individual salt sensitivity [12,13].

Urinary sodium excretion normally declines at night, however sodium retention during day must be compensated for at night to maintain long term sodium balance. A few studies pointed out that dippers and non-dippers have different circadian rhythm of urinary sodium excretion [6,14,15]. Nighttime urinary sodium excretion rate ($U_{Na}V$) was significantly higher in hypertensive non-dippers than in dippers [6,14]. During salt restriction, nighttime sodium excretion was reduced in non-dippers but not in dippers [6]. The capacity to excrete sodium during daytime is a significant determinant of nocturnal dipping of BP [15].

Based on finding of previous studies, it can be noted that night/day ratio of $U_{Na}V$ is associated with nocturnal dipping of BP in hypertensive patients. To confirm this issue in normotensive subjects, low salt and high salt intervention study is required to investigate the association between nocturnal dipping of BP and diurnal urinary sodium excretion in normotensive individuals.

Myanmar people traditionally take salty diet that leads to increased risk of hypertension. The prevalence of hypertension was 31% in males and 29.3% in females in Myanmar [16]. The daily salt intake of Myanmar people was about 11 g/day which is higher than WHO recommendation of salt intake (5 g/day) [17,18]. Ambulatory blood pressure (ABP) non-dipping status is an alarming sign that significant life style changes are urgently required. Identifying disease-state markers at young age is important for preventing the development of serious health problems in their later life. Thus, the purpose of the present study was to determine the effect of salt intake on nocturnal dipping of BP in normotensive Myanmar adolescents. This study also assessed whether the circadian pattern of sodium excretion was indeed accompanied with nocturnal dipping of BP.

Materials and Methods

Subject selection

This experimental study was carried out in Department of Physiology and Common Research Laboratory, University of Medicine 2, Yangon. A total of 36 apparently healthy normotensive male adolescents (between 15 and 19 years of age) were recruited. History taking and physical examination including anthropometric measurement were done. Normotensive healthy adolescents without having acute illness (influenza, diarrhoea, urinary tract infection), history of smoking, diabetes mellitus, hypertension, cardiovascular diseases like valvular heart diseases, and renal diseases (e.g. nephritis, nephrotic syndrome) were included in the study. All subjects and their parents gave written informed consent. The protocol was approved by the Ethical Review Board of University of Medicine 2, Yangon, Myanmar.

After 5-minute rest in a sitting position, office BP was measured and average of two readings was taken as resting BP. Then, 5 ml of venous blood was withdrawn under sterile aseptic condition and serum creatinine was determined (Auto creatinine liquicolor, Human, Germany; Humalyzer 2000, Human, D-65205 Wiesbaden, Germany). Spot urine sample was taken and the concentration of sodium in the urine was measured by electrolyte analyzer (URIT 910, China). Then, baseline sodium intake was determined by Tanaka's method [19].

High salt and low salt regimens

In this study, the participants were instructed to take high salt intake for one week followed by one-week washout on a regular diet and then salt restriction for another one week. During 7-day high salt period, the participants were given salt tablets containing 300 mg NaCl in each tablet according to their body weight; 0.12 g/kg body weight per day for one week in addition to normal diet (ad lib diet). During 7-day period of salt restriction, the subjects were instructed to take regular meal with low salt and avoid salty foods. To assess compliance with dietary salt intake, 24-h urinary sodium excretion was measured from spot urine sample on the day 5 by Tanaka's method [19]. The study continued with the subjects who had met the criteria, i.e. urinary sodium excretion < 115 mmol/day or less on salt restriction and > 165 mmol/day or more on high salt intake.

Measurement of 24-hour ambulatory blood pressure

On the day 7 of each intervention period, all participants were instructed to come to the Department of Physiology, University of Medicine 2 at 7.30 am for 24-h ABP measurement and 24-hr urine collection. ABP measurement was taken by ambulatory blood pressure monitoring (ABPM) device (Spacelabs 90207, USA). Before taking ABP measurement, resting BP was measured in both arms in sitting position by mercury sphygmomanometer. If SBP difference between the two arms was < 10 mmHg, non-dominant arm was used and if SBP difference was > 10 mmHg, arm with greater pressure was used for ABP measurement. At the first place, subject's personal data were entered into the ABPM device and 24-hr ABPM was started at 8:00 am. Frequency of measurement was set at every 30 minute interval during day and night. All subjects were instructed to record his actual awake time and asleep time and daytime and nighttime were determined for each subject based on the subject's self-report of sleeping hours. Moreover, they were also instructed to maintain their usual daily activities during 24-h period and to abstain from drinking coffee or tea, smoking and strenuous physical exercises for 24-h period. Then, the participant came back to the Department of Physiology in the next morning at 8:00 am. After the recorder had been removed, the BP results were downloaded onto a computer. If more than 25% of the measurements were artifacts or missing, the participant was asked to repeat the ABP recording for another 24 hours.

Measurement of 24-hour urinary sodium concentration

Twenty four-hour urine collection was also started at 8.00 am on the same day. Subjects were instructed in detail how to collect a 24-h urine sample and day and night urine samples. The first urine voided at 8.00 am was discarded and subsequent samples were collected in a clean dry plastic container (5 litres) using toluene as preservative. The last voided urine before going to bed was collected as daytime urine. The urine voided during the night and the first urine after getting up was collected in a separate bottle as nighttime urine. The urine collection was completed with the last urine sample voided at 8.00 am in the morning of day 8. Daytime and nighttime urine volumes were measured. About 10 ml of daytime, nighttime and 24-hour urine samples were collected in the separate tubes and stored at -20°C until analysis. Sodium concentration of the urine samples was measured by Atomic Absorption Spectrometer (GBC 932 plus, serial number A.4982, Italy).

After one-week washout period with regular meal, another session of 7-day salt restriction period started again. The same procedure and measurements were done as mentioned above. Subjects who had 24-hr urine volume 500 ml or more and excretion of creatinine 10 mg/kg/24-hr or greater met the criteria for having an adequate urine collection. Those who did not meet these criteria were requested to collect urine sample for another 24 hours.

Statistical analysis of data

All data were presented as mean ± standard deviation (SD). Student's paired "t" test was used to compare data between high salt period and salt restriction period. Independent sample "t" test was used to compare data between dippers and non-dippers. Statistical significance was set as p values of less than 0.05. Analysis of data was done by using Statistical Package for Social Science (SPSS) software version 16 (SPSS Software Inc., Chicago, IL, USA).

Results

Table 1 shows the baseline characteristics of subjects participated in this study. The mean 24-hr urinary sodium excretions were 145.8 ± 41.5 mmol/day before intervention, 200.8 ± 56.3 mmol/day during high salt intake and 86.2 ± 22.3 mmol/day during salt restriction. Circadian BP patterns of normotensive adolescents during high salt and salt restriction were depicted in figure 1. Table 2 shows comparison of arterial BP values between high salt and salt restriction period. Nighttime BP dipping expressed as percentage of daytime BP was more prominent during salt restriction than during high salt intake (SBP: $p < 0.01$; DBP: $P < 0.001$; MAP: $p < 0.001$) (Table 2).

	(Mean ± SD) (n = 36)
Age (years)	15.9 ± 0.9
Weight (kg)	51.7 ± 5.2
Height (m)	1.6 ± 0.04
BMI (kg/m^2)	19.4 ± 1.6
SBP (mmHg)	112.9 ± 6.4
DBP (mmHg)	72.3 ± 5.8
MAP (mmHg)	88.3 ± 5.2
Serum creatinine (mg/dl)	0.8 ± 0.1
Baseline 24-hr urinary Na excretion(mmol/day)	145.8 ± 41.5

Table 1: *Baseline characteristics of the subjects.*

BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure.

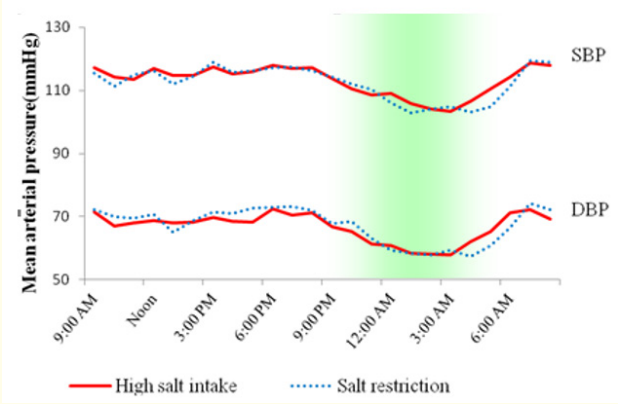

Figure 1: *Circadian pattern of SBP and DBP in response to changes in salt intake.*

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

(Mean ± SD) (n = 36)	High salt intake	Salt restriction	p value
Daytime SBP (mmHg)	116 ± 9	116 ± 6.8	0.967
Daytime DBP (mmHg)	69.8 ± 5.2	70.5 ± 4.5	0.278
Daytime MAP (mmHg)	86.2 ± 5.6	86.6 ± 4.5	0.467
Nighttime SBP (mmHg)	106.1 ± 7.7	103.8 ± 6.4	0.057
Nighttime DBP (mmHg)	60.4 ± 5	58.4 ± 4.6	< 0.05
Nighttime MAP (mmHg)	77.5 ± 5.1	75.5 ± 4.8	< 0.05
24-h SBP (mmHg)	112.8 ± 8.4	112.6 ± 6.3	0.889
24-h DBP (mmHg)	66.8 ± 4.9	67.3 ± 4.2	0.331
24-h MAP (mmHg)	83.4 ± 5.2	83.7 ± 4.4	0.645
SBP (% dipping)	8.5 ± 3.7	10.5 ± 3.5	< 0.01
DBP (% dipping)	13.4 ± 5.3	17.1 ± 6	< 0.001
MAP (% dipping)	10 ± 4.2	12.9 ± 4	< 0.001

Table 2: *Comparison of arterial blood pressure between high salt intake and salt restriction.*

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure.

During high salt intake, 17 out of 36 subjects (47.2%) were dippers (individual with a nighttime fall of mean MAP ≥ 10%) whereas 19 subjects were non-dippers (52.8%) (individual with a nighttime fall of mean MAP < 10%). During salt restriction, 13 out of 19 previously non-dippers (68.4%) changed to dippers. Finally, 30 subjects (83.3%) became dippers and only 6 (16.7%) remained as non-dippers during salt restriction. The comparison of arterial blood pressures between dippers and non-dippers during high salt intake and salt restriction were shown in table 3. Figure 2 shows nocturnal dipping of BP in dippers and non-dippers during high salt intake. Comparison of daytime and nighttime urinary sodium excretions in dippers and non-dippers during high salt intake and salt restriction were depicted in table 4.

		High salt intake		Salt restriction		
BP (mmHg)	Dipper (mean ± SD)	Nondipper (mean ± SD)	p value	Dipper (mean ± SD)	Nondipper (mean ± SD)	p value
24-h SBP	114.7 ± 8.2	111.1 ± 8.4	0.204	112.6 ± 6.4	112.7 ± 6	0.991
24-h DBP	66.2 ± 4.4	67.3 ± 5.4	0.517	67.6 ± 4	65.8 ± 5.6	0.907
24-h MAP	83.4 ± 4.9	83.4 ± 5.6	0.97	83.7 ± 4.2	83.5 ± 5.7	0.358
Daytime SBP	119.2 ± 8.6	113.1 ± 8.7	<0.05	116.3 ± 6.9	114.7 ± 6.4	0.596
Daytime DBP	70.4 ± 4.5	69.3 ± 5.8	0.557	71.2 ± 4	67.2 ± 5.9	< 0.05
Daytime MAP	87.6 ± 5.2	84.9 ± 5.9	0.163	87.1 ± 4.2	84.8 ± 6	0.277
Nighttime SBP	105.7 ± 7.8	106.4 ± 7.8	0.818	103.2 ± 6.6	107.3 ± 5	0.215
Nighttime DBP	58.1 ± 4.8	62.5 ± 4.4	<0.01	57.7 ± 4.3	62.2 ± 5	< 0.05
Nighttime MAP	75.5 ± 4.7	79.3 ± 4.8	<0.05	74.8 ± 4.4	79.5 ± 4.8	< 0.05

Table 3: *Comparison of arterial blood pressure between dippers and nondippers during high salt intake and salt restriction.*

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; MAP: Mean Arterial Pressure.

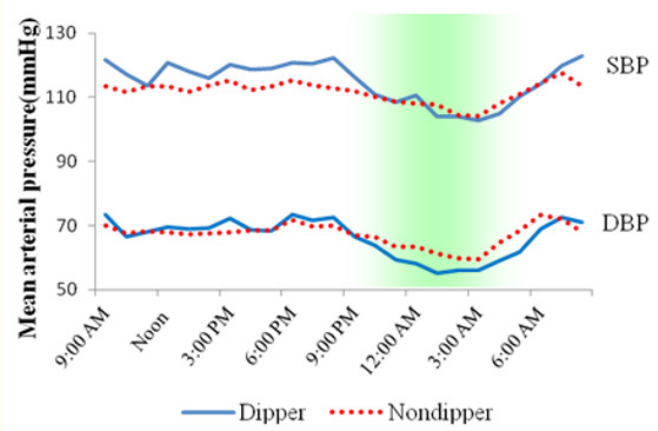

Figure 2: *Nocturnal dipping behaviour of SBP and DBP in dippers and non-dippers during high salt intake.*

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure.

		Daytime $U_{Na}V$ (mmol/h) (mean ± SD)	Nighttime $U_{Na}V$ (mmol/h) (mean ± SD)	p value
High salt intake	All (n = 36)	8.2 ± 2.7	9.1 ± 3.9	0.224
	Dippers (n = 17)	8.4 ± 2.9	7.5 ± 2.5	0.222
	Nondippers (n = 19)	7.9 ± 2.5	10.4 ± 4.4	< 0.05
Salt restriction	All (n = 36)	3.8 ± 1.2	3.2 ± 1.8	0.109
	Dippers (n = 30)	4.1 ± 1	3 ± 1.8	< 0.01
	Nondippers (n = 6)	2.3 ± 0.9	4.2 ± 1.5	< 0.01

Table 4: *Comparison of daytime and nighttime urinary sodium excretion in dippers and nondippers during high salt intake and salt restriction.*

$U_{Na}V$: Urinary Sodium Excretion; SD: Standard Deviation.

Discussion

In the present study, analysis of 24-h BP recordings demonstrated a fluctuation of BP that follows a circadian variation characterized by rising of BP during the day with a peak in early morning and decreasing steadily during the early hours of sleep. A significant decrease in nighttime BP (SBP, DBP and MAP) compare with daytime BP (SBP, DBP and MAP) ($P < 0.001$) indicated a nocturnal decline in BP. When the individual circadian BP rhythms were pooled with respect to salt intake in order to obtain a group-specific circadian rhythm of BP, the results showed that the nocturnal decline in BPs was maintained during high salt as well as salt restriction as shown in figure 1. It has been well-known that there is a balance between sympathetic and parasympathetic nervous system activity in the body with a predominant of parasympathetic nervous system activity during asleep. Sympathetic nervous system activity is decreased during sleep [20,21] and high α-sympathetic vasoconstrictor activity together with increased catecholamine concentrations has also been observed in the early morning hours [22-24]. Therefore, generally accepted mechanism for normal nocturnal decline in BP is the imbalance between sympathetic and parasympathetic nervous system tone, particularly shift from sympathetic to parasympathetic during sleep.

Although there was no significant difference in 24-h SBP, DBP and MAP between high salt and salt restriction, relative nighttime fall in BP, as expressed in percentage of the daytime BP, was significantly different between high salt and salt restriction in the present study. Percentage of dipping of SBP, DBP and MAP during salt restriction were significantly greater than those of BPs during high salt intake (Table 2). These results of the present study indicated that degree of nocturnal BP fall was affected by changes in salt intake with diminished nocturnal fall of BP during high salt intake in young normotensive subjects. Contrary to the present finding, some studies reported that the percent nighttime fall of MAP was unaffected by changes in salt intake in normotensive subjects [12,13]. However, studies regarding salt intake and nocturnal dipping of BP in hypertensive subjects reported that percent nighttime fall of MAP was affected by changes in salt intake [6,8-10]. During high salt intake, sympathetic activity significantly decreased as indexed by the urinary excretion of catecholamines, metanephrines and vanillylmandelic acid as BP and blood volume rose [25]. According to a mechanism described by Birkenhager and Meiracker [26], decreased sympathetic activity during upright position in the daytime causes venous pooling in the lower part of the body, which is associated with low renal perfusion pressure. During lying position in nighttime, increased venous return causes an increase in stroke volume, cardiac output and BP and thus reducing nocturnal BP dipping. In contrast, during the low salt intake, sympathetic activity increased significantly as BP and blood volume fell [25]. On this regards, degree of nocturnal BP fall in response to changes in salt intake observed in the present study might be due to changes of sympathetic activity.

In the present study, 52.8% of the subjects (19 out of 36) were non-dippers during high salt intake and 13 out of 19 previously non-dippers (68.4%) changed to dippers during salt restriction. The remaining 6 (16.7%) normotensive participants were still non-dippers even at relatively low dietary sodium intake. It can be concluded that nocturnal dipping of BP was changed with respect to salt intake and salt restriction can restore non-dipping pattern of BP to a dipping pattern in normotensive adolescents. Contrary to the present finding, Damasceno., *et al.* (2000) and Simonetti., *et al.* (2010) stated that nocturnal dipping of BP was unaffected by changes in salt intake in normotensive subjects [12,13]. However, in hypertensive subjects, circadian rhythm of BP shifted from a non-dipper to a dipper pattern in response to changes in salt intake [6,7,9].

In the present study, during high salt intake, daytime SBP of non-dippers was significantly lower than that of dippers ($p < 0.05$) while nighttime SBP between them was not different. On the other hand, nighttime DBP of non-dipper was significantly higher than that of dippers ($p < 0.05$) whereas there was no significant difference in daytime DBP of dippers and non-dippers (Table 3). This result indicated that non-dippers showed higher nighttime DBP and MAP compared with dippers during salt restriction and high salt intake. Moreover, non-dipper showed lower daytime SBP during high salt intake and lower daytime DBP during salt restriction (Figure 2).

It has been well-known that urinary sodium excretion shows a diurnal variation with maximum excretion during the day and minimum excretion at night in healthy people [27]. Accordingly, daytime $U_{Na}V$ was significantly higher than nighttime $U_{Na}V$ in dippers of present study. However, in non-dippers, nighttime $U_{Na}V$ was significantly higher than daytime $U_{Na}V$ during high salt intake ($p < 0.05$) as well as salt restriction ($p < 0.01$). Moreover, 13 out of 19 non-dippers (68.4%) changed to dippers with concomitant decrease in nighttime $U_{Na}V$ during salt restriction ($p < 0.05$). The rest 6 subjects were still non-dippers and their nighttime $U_{Na}V$ continued to increase in spite of reduction in salt intake (Table 4). On the other hand, night/day ratio of $U_{Na}V$ was significantly higher in non-dipper than that of dipper during high salt intake and salt restriction (Figure 3). This result indicated that the diurnal rhythm of sodium output was found to be reversed in non-dippers.

It was also observed that night/day ratio of $U_{Na}V$ was significantly and negatively correlated with %MAP dipping during salt restriction ($r = -0.46$, $p < 0.01$) and high salt intake ($r = -0.38$, $p < 0.05$) (Figure 4). All these findings taking into account, it can be concluded that non-dipping of BP might be due to increased nighttime natriuresis.

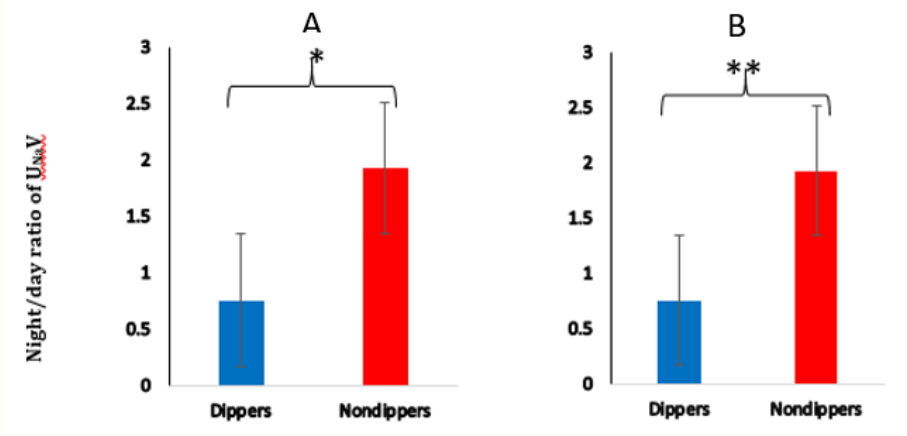

Figure 3: *Night/day ratio of urinary sodium excretion in high salt intake (Panel A) and salt restriction (Panel B).*

**Indicates significant difference at p < 0.05.*

***Indicates significant difference at p < 0.01.*

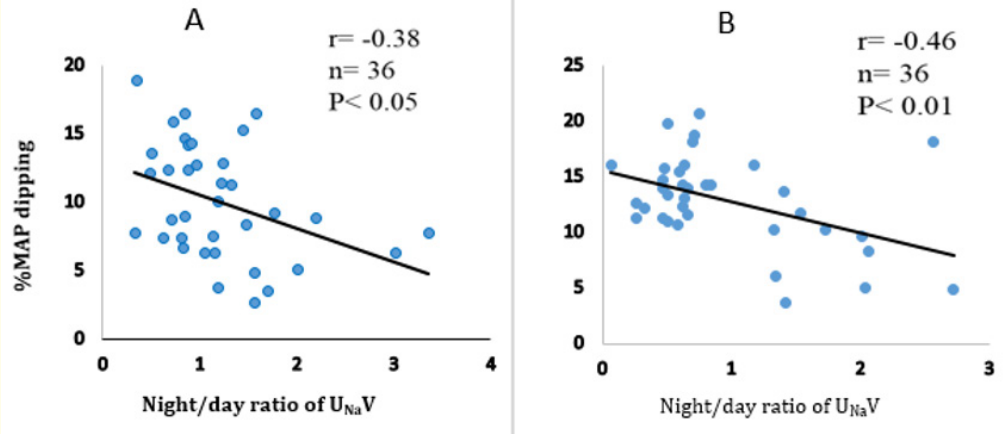

Figure 4: *Correlation between night/day ratio of UNaV and %MAP dipping during high salt intake (Panel A) and salt restriction (Panel B).*

Previous studies demonstrated that when daytime sodium excretory capacity of some individuals is insufficient, a greater proportion of sodium must be excreted at night to maintain overall sodium balance [28,29]. They hypothesized that if daytime sodium excretion is insufficient, pressure natriuresis will occur in the nighttime resulting in non-dipping pattern of BP. Thus, when sodium excretory requirements fall within the limit of individual's excretory capacity during the day, there is no need to excrete more sodium at night, maintaining a normal BP dipping pattern. This concept could explain the observed finding of the present study, i.e. increased nighttime sodium excretion concomitant with attenuated nighttime MAP dipping in non-dippers. In the present study, non-dippers have night/day

ratio of $U_{Na}V > 1$, therefore BP is adjusted upward at night to maintain overall sodium balance by pressure natriuresis, whereas dippers have night/day ratio of $U_{Na}V < 1$, indicating that they maintained sodium balance by excreting a greater proportion of sodium during the day.

Conclusion

The present study demonstrated that high salt intake would induce attenuated nocturnal dipping of BP with concomitant changes in enhanced nighttime natriuresis and that modest salt reduction would restore normal dipping pattern of BP and normal pattern of urinary sodium excretion. It can be concluded that nocturnal dipping of BP was changed with respect to salt intake even in healthy normotensive adolescents and non-dipping of BP might be due to increased nighttime natriuresis. This study pointed out homeostatic significance to maintain sodium balance and the physiological adaptation of BP in response to changes in salt intake.

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Conflict of Interests

There is no conflict of interests.

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