Original Article

Sodium Intake and Cardiac Sympatho-Vagal Balance in Young Men with High Blood Pressure

Osamu TOCHIKUBO and Kiyoko NISHIJIMA

We have previously reported that a high sodium intake increases sleep-time blood pressure (BP) in young men. However, there are cases in which this relation does not apply. To account for them, we investigated the relation between sodium intake and cardiac sympatho-vagal balance (SVB) in young men with high BP. Sodium intake was estimated from the amount of urinary sodium excretion over 1 week. Twenty-four-hour (24-h) urinary sodium excretion (Salt24), 24-h ambulatory BP and ECG were obtained on the last day of the observation period. As an index of sodium intake, the expression ln(Salt24/Cr24) (Cr24, 24-h urinary creatinine excretion) was used. From power-spectral analysis of ECG-RR intervals during sleep, we obtained the LF/HF ratio between the low-frequency component (LF) and the high frequency component (HF) and used it as an index of SVB. The subjects were male medical students divided into a normal BP group (N-group; n = 103) and a high BP group (H-group; n = 26, 24-h BP > 125/75 mmHg). Mean ln(Salt24/Cr24) and LF/HF in the H-group were significantly higher than those in the N-group (LF/HF: 1.86 ± 0.44 [SD] vs. 1.37 ± 0.30, p < 0.001). The calculated discriminant function (D) for the H-group and N-group was D = 1.6x + 5y - 11, where x is ln(Salt24/Cr24) and y is LF/HF. This formula (D) resulted in high discriminant predictive accuracy (82%) between the groups. If D > 0 (the value of the cut-off line determining separation of the groups), the relation y = -0.32x + 2.2 (negative relation between y and x) was obtained. These results suggest that excessive sodium intake in combination with accentuated SVB (LF/HF) increases BP in young men. (Hypertens Res 2004; 27: 393–398)

Key Words: dietary sodium, sympathetic nervous system, young man, sleep, ambulatory blood pressure monitoring

Introduction

Blood pressure (BP) demonstrates large circadian and day-to-day variations (1–3). Large day-to-day fluctuations (4, 5) also occur in sodium intake. Various factors—age, sex, race, renal function (6–8), and sodium sensitivity (9, 10)—play a role in the effect of sodium intake on BP. Therefore, investigating the relation between BP and sodium intake necessarily entails clarifying and analyzing all these factors.

We have reported a significant correlation between sleep-BP and 24-h urinary sodium excretion (Salt24) in young men (11). However, some of the subjects did not have high BP, even though their sodium intake was excessive. It is thus likely that individual sodium sensitivity is a contributory factor to BP. Still, it is difficult to measure sodium sensitivity directly under daily clinical conditions. It has been proposed that accentuation of sympathetic nervous system activity or cardiac sympa-tho-vagal imbalance may contribute to sodium sensitivity (12, 13). The present study investigated the relations among three factors in a group of young men: sleep-BP (base-BP) (3), Salt24, and cardiac sympatho-vagal balance (SVB).

Methods

Measurement of Salt24

One week’s urinary sodium excretion was estimated according to our previously reported protocol (11). In brief, 24-h urine of subjects was collected on the first day and again a week later by means of a portable Urinemate P (Sumitomo
Measurement of 24-h BP and SVB

On the final day of the week-long observation of sodium intake, we used a multibiomedical recorder (TM2425; A&D Co., Ltd., Tokyo, Japan) to measure 24-h BP and SVB. Since we have previously reported on this method and its accuracy (3, 19), we here describe it only in brief.

Systolic BP (SBP) and diastolic BP (DBP) were measured at 30-min intervals and the ECG was recorded beat-to-beat. Power spectral analysis of the RR intervals of the ECG gave the low-frequency (LF) component (0.05 to 0.15 Hz) and the high-frequency (HF) component (0.15 to 0.40 Hz) and their ratio (LF/HF). This provided an index of sympathetic nervous activity, because HF correlates with cardiac vagal activity and LF reflects the activity of both the sympathetic and parasympathetic nervous system (20–23). It is thought that the ratio between them (LF/HF; SVB) can be used to estimate sympathetic nervous system activity to some degree (22, 23). Since the TM2425 can measure factors such as body position (standing, sitting), ambient temperature, and physical activity (acceleration), it was possible to evaluate the degree of daytime activity and nighttime sleep from these measurements. For the day on which TM2425 measurements were made, we asked all subjects to make a record of their activities, nighttime sleep, time of rising, and alcohol and tobacco consumption. Comprehensive estimation of the nighttime sleep period was made on the basis of these records, and of acceleration, temperature (since ambient temperature rises in bed), and body position. The remainder of the 24-h period was defined as daytime. Daily activities greatly influence daytime BP. During nighttime sleep, however, day-to-day fluctuations of base-BP (minimum BP during sleep) are slight (3, 24). Consequently, to analyze the mutual relations among BP, SVB, and Salt24, we employed base-BP. Referring to it as sleep-BP, we took it as the representative BP value for each individual (3). We have previously reported on the method of base-BP measurement and its precision (3, 24).

Our criteria for determining hypertension were as follows: the upper limit for normal 24-h BP was taken as SBP of 125 mmHg or DBP of 75 mmHg (25). Subjects whose mean BP was higher than either of these values were included in the high-BP group (H-group; 24-h SBP $\geq$125 mmHg or 24-h DBP $\geq$75 mmHg); those with lower values were included in the normal BP group (N-group).

**Subjects**

The initial group of subjects comprised 138 male medical students aged 21–28 years. After personal interviews to investigate their family and past medical history, individuals with cardiac or renal problems were excluded from the study group. Individuals were deemed to have a family history of hypertension if primary hypertension was recognized in a parent, sibling, or grandparent. A family history of hypertension was found in 46% of the H-group and 22% of the N-group. The percentage was significantly higher in the H-group ($p<0.05$). Two subjects were excluded because their Cr24 data fell outside the 95% confidence limits of the linear relationship between Cr24 and LBM on the day when urine was collected for measurement of 24-h BP and LF/HF. One was excluded because he could not sleep on the day of the study. Three were excluded because the day-to-day fluctuation in their Salt24 exceeded 3 g/day. One was excluded because he was obese (body mass index: 36 kg/m²) and thus his upper-arm circumference (36 cm) could have caused the TM2425, with a cuff width of 12 cm, to give a falsely high measurement (26). Two subjects demonstrated extremely high LF/HF values although their sleep-SBP was low. A check of their daily records showed that they had drunk large quantities of alcohol before going to sleep and showed tachycardia during sleep (27), resulting in an extremely high LF/HF. They were therefore eliminated from the study.

This left 129 subjects. The age, height, weight, and casual BP as determined by the auscultatory method are shown in Table 1 for the N-group (n = 103) and H-group (n = 26) subjects. Auscultatory BP was taken by the standard method (two readings taken with the subject seated by a trained doctor using a mercury sphygmomanometer with 13-cm cuff size).

The Ethics Committee of Yokohama City University School of Medicine approved the study (Recognition No. 2001-36), and all subjects gave informed consent.

**Statistical Analysis**

Standard statistical methods, including non-paired $t$-test (Welch’s method), sensitivity (Sn) / specificity (Sp) test, re-
Table 1. Main Clinical Characteristics of Two Groups

<table>
<thead>
<tr>
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<th>N-group</th>
<th>H-group</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>23.0 ± 2.92</td>
<td>23.0 ± 1.88</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.7 ± 5.6</td>
<td>174.3 ± 5.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.1 ± 7.9</td>
<td>68.3 ± 10.2</td>
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<tr>
<td>24-h Urine volume (ml/day)</td>
<td>1,087 ± 481</td>
<td>1,268 ± 622</td>
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<tr>
<td>Cr (mmol/day)</td>
<td>12.9 ± 2.56</td>
<td>12.8 ± 3.09</td>
</tr>
<tr>
<td>Na (mmol/day)</td>
<td>149 ± 50.8</td>
<td>187 ± 71.2*</td>
</tr>
<tr>
<td>K (mmol/day)</td>
<td>43.9 ± 15.6</td>
<td>52.7 ± 21.7</td>
</tr>
<tr>
<td>Ca (mmol/day)</td>
<td>3.74 ± 1.49</td>
<td>3.74 ± 1.75</td>
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<tr>
<td>Mg (mmol/day)</td>
<td>5.76 ± 3.29</td>
<td>5.35 ± 3.70</td>
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<tr>
<td>Casual SBP (mmHg)</td>
<td>127 ± 9.2</td>
<td>136 ± 12.5***</td>
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<tr>
<td>DBP (mmHg)</td>
<td>75 ± 9.3</td>
<td>80 ± 11.5</td>
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<tr>
<td>HR (bpm)</td>
<td>65 ± 10.0</td>
<td>66 ± 11.1</td>
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Values are mean ± SD; *p<0.05, ***p<0.001 vs. N-group. N-group, normotensive group; H-group, high-blood pressure (BP) group; Cr, creatinine; Na, sodium; K, potassium; Ca, calcium; Mg, magnesium; SBP, systolic BP; DBP, diastolic BP; HR, heart rate.

Table 2. BP, LF/HF and ln(Salt24/Cr24) of Two Groups

<table>
<thead>
<tr>
<th></th>
<th>N-group</th>
<th>H-group</th>
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<tbody>
<tr>
<td>24-h SBP (mmHg)</td>
<td>119 ± 6.1</td>
<td>132 ± 5.1***</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>69 ± 5.1</td>
<td>76 ± 5.0***</td>
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<tr>
<td>HR (bpm)</td>
<td>65 ± 7.8</td>
<td>68 ± 10.1</td>
</tr>
<tr>
<td>Night SBP (mmHg)</td>
<td>106 ± 6.4</td>
<td>113 ± 5.9***</td>
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<tr>
<td>DBP (mmHg)</td>
<td>58 ± 6.1</td>
<td>62 ± 5.6*</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>43 ± 7.4</td>
<td>55 ± 8.9</td>
</tr>
<tr>
<td>Sleep-SBP (mmHg)</td>
<td>97 ± 5.9</td>
<td>105 ± 5.9***</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>50 ± 5.9</td>
<td>55 ± 5.5**</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>46 ± 5.6</td>
<td>49 ± 6.6</td>
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<tr>
<td>LF/HF (ratio)</td>
<td>1.37 ± 0.30</td>
<td>1.86 ± 0.44***</td>
</tr>
<tr>
<td>ln(Salt24/Cr24)</td>
<td>1.70 ± 0.37</td>
<td>2.00 ± 0.38***</td>
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</table>

Values are mean ± SD; *p<0.05, **p<0.01, ***p<0.001 vs. N-group. N-group, normotensive group; H-group, high-blood pressure (BP) group; SBP, systolic BP; DBP, diastolic BP; HR, heart rate; LF/HF, ratio of low frequency/high frequency component during nighttime; Salt24/Cr24, 24-h urinary sodium excretion divided by 24-h urinary creatinine excretion.

Fig. 1. Correlations between sleep-SBP and LF/HF during nighttime (upper panel), and between sleep-SBP and ln(Salt24/Cr24) (lower panel). Dotted lines indicate the optimal cut-off lines by ROC analysis between the H-group and N-group. Sleep-SBP, systolic BP during sleep; LF/HF, ratio between low frequency component and high frequency component of ECG-RR power spectral analysis during nighttime; Salt24, 24-h urinary sodium excretion; Cr24, 24-h urinary creatinine excretion.

Values were expressed as the mean ± SD, and values of p<0.05 were considered statistically significant. A multiple statistical analysis program (Social Survey Research Information Co., Ltd., Tokyo, Japan) was used for the calculations.

Results

The H-group showed significantly higher 24-h urinary sodium excretion (p<0.05), ln(Salt24/Cr24) and LF/HF than the N-group (p<0.001) (Tables 1, 2). No significant difference was observed between the groups in terms of excretion of other minerals (Table 1). A significant correlation was observed between sleep-SBP and ln(Salt24/Cr24) (r = 0.34) and between sleep-SBP and LF/HF (r = 0.32; p<0.001) (Fig. 1). The optimal cut-off points derived from ROC analysis between the H-group and N-group were 1.60 for LF/HF (predictive accuracy = 76%, Sn = 69%, Sp = 78%) and 1.96 for ln(Salt24/Cr24) (predictive accuracy = 69%, Sn = 72%, Sp =...
Minami et al. (42) reported that abnormally increased sympathetic nervous system activity (12, 13, 41) and pressor reactivity (42) may play a large role in this phenomenon. On the other hand, Grassi et al. (43) reported that moderate dietary sodium restriction triggers sympathetic activation, and Minami et al. (44) also reported that a high-sodium diet decreased LF/HF in non-sodium-sensitive hypertensive patients. Thus the relation between sodium intake and sympathetic nervous system activity remains controversial.

In this study, we used LF/HF as a marker of cardiac SVB, because LF/HF can be measured easily in the outpatient clinic. When arterial pressure is raised, the kidney excretes more sodium and water (pressure-natriuresis (43): relationship between mean BP and renal sodium output).

Although we could not obtain the pressure-natriuresis curve in this population study, the data of each subject were plotted with ln(Salt24/Cr24) as the X-axis and LF/HF as the Y-axis (Fig. 2). Subjects in the H-group were shown to have high ln(Salt24/Cr24), and their LF/HF values fell in a high range. We then derived the discriminant function (D) for the H-group and N-group: $D = 1.6 \ln(Salt_{24}/Cr_{24}) + 5.0 \times (LF/HF) - 11$. This $D$-function showed 82% predictive accuracy (Sn = 85%, Sp = 82%) (Fig. 2).

**Discussion**

Numerous epidemiological investigations (28, 29) have identified excess sodium intake as a factor in raising BP, but individual differences play a big part in this relation, as do age, sex, race, renal function, hereditary factors (2, 5–9, 30) and sodium sensitivity (9, 10). In previous population studies, the correlation coefficients between SBP/DBP and sodium intake have been very low (-0.16/-0.5 (31), 0.12/0.07 (32), 0.15/0.06 (33), 0.31/0.06 (34), -0.05/0.07 (35) and 0.27/0.14 (36)). Sodium sensitivity is affected by such factors as defects in renal sodium excretion (37), abnormally weak suppression of intrarenal renin release (38), paradoxical decrease in atrial natriuretic peptide secretion (39), and decreased renal-kallikrein activity (40). Moreover, increased sympathetic nervous system activity (12, 13, 41) and pressor reactivity (42) may play a large role in this phenomenon. On the other hand, Grassi et al. (43) reported that moderate dietary sodium restriction triggers sympathetic activation, and Minami et al. (44) also reported that a high-sodium diet decreased LF/HF in non-sodium-sensitive hypertensive patients. Thus the relation between sodium intake and sympathetic nervous system activity remains controversial.

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Although we could not obtain the pressure-natriuresis curve in this population study, the data of each subject were plotted with 24-h mean BP (average of 24-h mean BP) as the X-axis and 24-h urinary sodium excretion as the Y-axis. Only the group of subjects with higher LF/HF values (LF/HF >1.60) showed a close relationship between 24-h mean BP and 24-h urinary sodium excretion (r = 0.58, Fig. 3). This result might suggest that the slope (46) of the BP-sodium excretion relationship in young men with higher LF/HF is depressed and is a reflection of higher sensitivity to sodium.

The subjects of this study constituted a very limited group: Japanese male medical students aged 21 to 28 years. A similar study conducted on female students failed to reveal a clear connection between sodium intake and BP as shown in male students (11), and female subjects were excluded in the present study.

Large day-to-day fluctuations occur in waking-time BP (2, 3). This is why we considered base-BP (sleep-BP), on which the influence of daily activity (acceleration) is slight (24), the representative BP of each subject. To obtain an index of sodium intake, we monitored the amount of sodium excreted into the urine during 1 week. We eliminated from consideration the individuals with large day-to-day fluctuations or in whom urine sampling was inaccurate. On the day on which sleep-BP was measured, we measured the amount of sodium excreted into the urine.
excreted into the urine over 24 h and corrected it by physical build. Then we employed natural logarithms to correct BP nonlinearity between BP and Salt2. We have previously reported our grounds for this approach (11). The coefficient of correlation between SBP and ln(Salt2/Cr24) was greater than the corresponding values for SBP and Salt2, SBP and Salt2/body weight, and SBP and Salt2/Cr24 (11). Because the correlation between BP and sodium intake is nonlinear (18) (an S-curve correlation), we consider ln(Salt2/Cr24) a useful index for examining the relation between BP and sodium intake.

The present results are compatible with the finding that sodium loading suppresses the nocturnal fall in BP and this suppression is associated with elevated BP in sodium-sensitive subjects (47, 48) (middle-aged subjects with essential hypertension). Moreover, high sympathetic nervous activity (nighttime/daytime ratio of urinary noradrenaline excretion) has been suggested to play a role in the sodium sensitivity of middle-aged subjects with essential hypertension (13). The weak relationship between sleep-SBP and sodium intake may be due to the fact that the present subjects included both sodium-sensitive and non-sodium-sensitive individuals. The combination of high sodium intake and high LF/HF (which cannot be suppressed by high sodium intake and may be one of the markers for sodium sensitivity) would probably increase BP in young men (Figs. 2 and 3).

However, this study was conducted on a small, extremely limited group of subjects. Determining whether the relations we uncovered apply to other groups, both sexes, different races, hypertensives, and hypertensives with target organ damage will require further study employing more subjects.

In summary, with these groups of subjects and these measurement conditions, a significant correlation was observed between sleep-SBP and LF/HF during sleep. The discriminant function (predictive accuracy: 82%) separating the H-group and the N-group was D = 1.6 ln(Salt2/Cr24) + 5.0 ÷ (LF/HF) + 11. If D = 0 (the value of the cut-off line determining separation of the groups), the relation LF/HF = -0.32 ÷ ln(Salt2/Cr24) + 2.2 was obtained (Fig. 2). In other words, a negative relation existed between LF/HF and ln(Salt2/Cr24) in the discriminant function. Therefore, young men whose sodium intake is relatively low but whose LF/HF is high are suggested to be susceptible to hypertension. Young men whose sodium intake is high are also thought to be susceptible to hypertension, even though their LF/HF remains relatively low. If both sodium intake and LF/HF are clearly high, hypertension is considered a distinct possibility. It is thought that sodium intake and cardiac SVB operate cumulatively to raise BP in young men. The results of the present study will be useful in analyzing the relation between sodium intake and BP.

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