Short-term analysis of the relationship between blood pressure and urinary sodium excretion in normotensive subjects

Leonardo CENTONZA*, Giovanna CASTOLDI*, Roberto CHIANCA†, Giuseppe BUSCA*, Raffaello GOLIN*, Alberto ZANCHETTI* and Andrea STELLA*

*Istituto di Clinica Medica e Terapia Medica, Centro di Fisiologia Clinica e Ipertensione, University of Milan, Ospedale Maggiore, via F. Sforza 35, 20122 Milan, Italy, and †Istituto Auxologico Italiano – I.R.C.C.S., Milan, Italy

ABSTRACT

The aim of this study was to investigate whether, in the short term, physiological blood pressure changes are coupled with changes in urinary sodium excretion in normotensive subjects, maintained at fixed sodium intake and under controlled postural and behavioural conditions. Twelve normotensive subjects were recruited. For each subject, seven urine samples were collected at fixed time intervals during an overall 26 h period: late afternoon (16.00–20.00 hours), evening (20.00–24.00 hours), night (24.00–06.00 hours), quiet wakefulness (06.00–09.00 hours), morning (09.00–12.00 hours), post-prandial (12.00–15.00 hours) and afternoon (15.00–18.00 hours). Blood pressure was monitored by an ambulatory blood pressure device during the whole 26 h period. Each urine sample was used to measure urinary sodium excretion and glomerular filtration rate (creatinine clearance). Blood pressure, heart rate, urinary sodium excretion and glomerular filtration rate recorded in the daytime were higher than those measured during the night-time. A significant positive correlation between mean blood pressure and urinary sodium excretion was found during the night, over the whole 26 h period, and during two subperiods of the daytime: quiet wakefulness and the post-prandial period. The coefficient of the pressure–natriuresis curve was significantly decreased by postural changes. We conclude that, in normotensive subjects, blood pressure and urinary sodium excretion are coupled in the short term. The assumption of an upright posture can mask this relationship, presumably by activating neurohumoral factors.

INTRODUCTION

The relationship between blood pressure and urinary sodium excretion has been demonstrated by epidemiological studies [1,2] and by evidence provided in experimental animals [3–5]. This relationship is thought to be important in the long-term control of blood pressure [6,7]. Several factors, such as the sympathetic nervous system and circulating hormones, can modify the pressure–natriuresis curve [6–11]. According to Guyton [6,7], in essential hypertension the pressure–natriuresis curve is shifted to the right, due to the inability of the kidneys to excrete an adequate amount of sodium at normal blood pressure. The rightward shift of the curve has been confirmed in some conditions of secondary hypertension, e.g. renovascular hypertension, primary aldosteronism and polycystic kidney disease [12,13].

Experiments in rats have suggested that the cumulative effect of moment-to-moment changes in arterial pressure, being coupled to rapid changes in urine flow rate, might influence the long-term control of arterial pressure [14].

Key words: ambulatory blood pressure monitoring, normotensive subjects, pressure–natriuresis curve, urinary sodium excretion.

Abbreviations: GFR, glomerular filtration rate; HR, heart rate; MBP, mean blood pressure.

Correspondence: Professor A. Stella (e-mail Andrea.Stella@unimib.it).

© 2000 The Biochemical Society and the Medical Research Society
Human studies have given rise to different and somewhat controversial results which vary depending on the age, race and behavioural conditions of the subjects studied. When the relationship between blood pressure and urinary sodium excretion was studied in normotensive subjects and hypertensive patients [15–17], a positive correlation was found during the night-time only [15,16], or when the data were analysed by the ‘cumulative sum method’ [17]. On the other hand, in healthy normotensive children and adolescents, a positive relationship between blood pressure and sodium excretion was found in black, but not in white, subjects [18]. In addition, no correlation between blood pressure and sodium excretion was found during the daytime and throughout a 24 h period, suggesting a possible interfering effect of posture and behavioural conditions [15,16].

To better investigate whether blood pressure is closely coupled with urinary sodium excretion, a short-term analysis of the two variables was carried out in a small group of normotensive subjects, maintained under fixed sodium intake. Seven urine samples were collected at fixed time intervals during an overall 26 h period, during which blood pressure was monitored by an ambulatory blood pressure device [19]. Four of the seven periods were accurately characterized in terms of postural and behavioural conditions, whereas during the other three periods the subjects were free to attend to their usual activities.

METHODS

Twelve normotensive volunteers (eight males) recruited from the hospital staff were studied. Their mean age was 32 (range 24–48) years, and the mean body mass index was 22.7 (range 20.2–27.7). Subjects were enrolled into the protocol after clinical, instrumental (renal and urinary tract echography, standard ECG, transthoracic echocardiography) and laboratory evaluations to rule out renal, cardiovascular, hepatic or metabolic diseases and incomplete urine voiding. After 3 days at a fixed sodium intake (170 mmol/day), a 24 h urine sample was collected to measure urinary sodium excretion in order to verify that sodium balance had been achieved (Figure 1). All subjects were accurately instructed as to the protocol in order to obtain the best compliance. The local Ethics Committee approved the protocol, and all participants gave their informed written consent.

As shown in Figure 2, the experimental period consisted of 26 h, during which each subject was free to attend to his or her usual activities, but had to avoid strenuous physical activities and to comply with a precise protocol during four periods. For each subject, during the consecutive 26 h, ambulatory blood pressure measurements and urine collections were obtained for seven pre-set periods: late afternoon (16.00–20.00 hours), evening (20.00–24.00 hours), night (24.00–06.00 hours), quiet wakefulness (06.00–09.00 hours), morning (09.00–12.00 hours), post-prandial (12.00–15.00 hours) and afternoon (15.00–18.00 hours). In particular, the participants were instructed to retire at 24.00 hours and to sleep until 06.00 hours, then to lie awake in their bed until 09.00 hours. At 09.00 hours, all participants got up. During the post-prandial period they maintained a sitting posture, and in the late afternoon they were in the standing position.

Urine samples were collected during each period into different plastic bottles. Samples were then frozen and later analysed to determine urine volume (ml/min), urinary sodium concentration (µmol/ml) by the potentiometric method (Nova 1; Nova Biomedical, Newton, MA, U.S.A.) and urinary sodium excretion (µmol/min). Three blood samples were withdrawn from a peripheral vein just before the beginning, in the middle and at the end of the protocol. Plasma was frozen and analysed later to measure plasma creatinine concentration, using a colorimetric method (Hitachi U1100; Hitachi, Tokyo, Japan). Creatinine clearance was used as an index of glomerular filtration rate (GFR; ml/min). Blood pressure was monitored by an Oscillometric 90207 monitor (Spacelabs Inc., Redmond, WA, U.S.A.), programmed to obtain values every 15 min during the daytime (i.e. all periods excluding 24.00–06.00 hours) and every 20 min during the night-time (i.e. 24.00–06.00 hours). Systolic, diastolic and mean blood pressure (MBP) values and heart rate (HR) were calculated. Of the daily dose of sodium (170 mmol), 70 mmol was administered during dinner (at 20.00 hours), 10 mmol during breakfast (at 09.00 hours) and 90 mmol with a meat meal during lunch (at 12.00 hours).

Data are expressed as means ± S.E.M. Differences between periods were evaluated by a two-tailed paired
RESULTS

The results of the statistical analysis of data obtained from the 12 subjects are reported in Table 1, in which the time courses of all variables measured during the seven collection periods are shown. Blood pressure and HR decreased slightly during the evening (20.00–24.00 hours), and fell markedly during the night-time (24.00–06.00 hours). During quiet wakefulness in the supine position (06.00–09.00 hours), blood pressure increased significantly compared with night-time, while HR did not change. After arising, during the morning (09.00–12.00 hours), when each subject was required to maintain upright posture while attending to his or her usual occupational activities, blood pressure increased further and HR also increased significantly. In the following period (post-prandial; 12.00–15.00 hours), when the subjects were asked to maintain the sitting position during their activities, both blood pressure and HR decreased slightly. In general, urinary sodium excretion changed in parallel with blood pressure changes, except during the post-prandial period, when urinary sodium excretion reached its highest value. GFR did not change significantly during the whole period, but it increased during the post-prandial period (after lunch). As expected, the lowest value of each variable was observed during the night-time period.

To verify whether MBP and urinary sodium excretion are linked, a simple correlation analysis was carried out for: (i) each of the seven collection periods, matching (for each subject) the corresponding MBP value and the urinary sodium excretion value, and (ii) the whole 26 h period, using for each subject the averages of MBP and urinary sodium excretion (Figure 3). A significant positive correlation between MBP and urinary sodium excretion was found for the whole 26 h period (r = 0.75, P = 0.005). When the individual periods were considered (Figure 3), a significant positive correlation was found during the night-time, during the period of quiet wakefulness (subjects in a supine position), and during the

<table>
<thead>
<tr>
<th>Table 1 Timed analysis of systemic haemodynamics and renal excretory functions in normotensive subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Values are means ± S.E.M. (n = 12) for each period of analysis for systolic blood pressure (SBP), diastolic blood pressure (DBP), MBP, HR, urinary sodium excretion (UNaV) and GFR. *Statistically significant difference (P &lt; 0.05) compared with the preceding period.</td>
</tr>
<tr>
<td>Period</td>
</tr>
<tr>
<td>16.00–20.00 hours</td>
</tr>
<tr>
<td>20.00–24.00 hours</td>
</tr>
<tr>
<td>24.00–06.00 hours</td>
</tr>
<tr>
<td>06.00–09.00 hours</td>
</tr>
<tr>
<td>09.00–12.00 hours</td>
</tr>
<tr>
<td>12.00–15.00 hours</td>
</tr>
<tr>
<td>15.00–18.00 hours</td>
</tr>
</tbody>
</table>
post-prandial period (subjects in a sitting position). In contrast, no correlation was found when subjects were carrying out their usual activities in the standing position or during the remaining three periods, which were less standardized with regard to posture and activities.

To evaluate the influence of postural changes and daily activities on the relationship between blood pressure and urinary sodium excretion, a more detailed analysis was performed for the periods that were standardized. The increments of MBP and urinary sodium excretion associated with waking up (calculated as the difference between the quiet wakefulness and night-time periods) and those associated with rising (calculated as the difference between the morning and quiet wakefulness periods) are shown in Figure 4. Increments in MBP after the transition from night-time to quiet wakefulness were significantly smaller than those measured after the transition from quiet wakefulness to arising in the morning (Figure 4, top panel). In contrast, changes in urinary sodium excretion after the transition from night-time to quiet wakefulness

---

**Figure 3** Relationship between MBP and urinary sodium excretion

Scatter plots show the correlation between MBP (mmHg) and urinary sodium excretion ($\mu$mol/min) for each subject during the whole 26 h experimental period and during the seven pre-set periods. The correlation coefficient ($r$) and its significance ($P$) are also shown for each plot.
were larger (although not significantly) than those observed after the transition from quiet wakefulness to morning (Figure 4, middle panel). Consequently, the ratio of changes in MBP and urinary sodium excretion was significantly higher during the period of quiet wakefulness than during the morning (Figure 4, bottom panel), suggesting that blood pressure increments following assumption of an upright posture are less effective in increasing urinary sodium excretion.

**DISCUSSION**

The results of the present study, carried out in normotensive subjects, show a positive correlation between blood pressure and urinary sodium excretion over a 26 h period, as well as during the daytime ($r = 0.68; P = 0.015$) and the night-time. Indeed, the diurnal variations of urinary sodium excretion generally paralleled the diurnal changes in blood pressure. These data are in line with epidemiological studies showing a correlation between blood pressure and sodium excretion [1,2,8] and support the hypothesis that the average level of blood pressure in normotensive subjects is dependent on sodium intake. Our results in normotensive subjects are consistent with previous data obtained in black normotensive adolescents [18] and in young normotensive or borderline hypertensive subjects by the ‘cumulative sum method’ [17]. On the other hand, in studies in which hypertensive subjects were also included [15,16], no correlation was found between blood pressure and sodium excretion during the daytime or over a 24 h period, whereas a positive correlation was observed during the night-time. In our study all subjects were maintained at constant sodium balance and under a controlled behavioural and postural pattern. It is possible that, in hypertensive subjects, other factors controlling urinary sodium excretion might overwhelm the main determinant (i.e. blood pressure) of urinary sodium excretion under conditions of uncontrolled sodium balance. Alternatively, an intrinsic alteration in the pressure–natriuresis curve, characterizing hypertension according to Guyton [6], may prevent pressure-dependent changes in natriuresis from becoming evident.

A more detailed analysis of our data also shows that, even in young normotensive subjects, the pressure–natriuresis relationship is lost during some periods of the day. Indeed, in the morning after arising, the relationship was not evident, while a strict correlation was observed during sleep (night-time) and during the period of quiet wakefulness. The most likely interpretation is that an upright posture and the usual daily activities activate neurohumoral factors capable of altering the pressure–natriuresis curve. In this regard our data, by showing that the pressure–natriuresis curve coefficient after arising (morning) is smaller than that calculated during the quiet wakefulness period, indicate that an upright posture and occupational activities can minimize the effects of arterial pressure changes on urinary sodium excretion. The well-known activation of the sympathetic nervous system caused by assumption of an upright posture may partly explain the relative sodium-retaining condition observed during the morning hours. Indeed, it has been demonstrated that an increase in efferent sympathetic discharge can augment sodium reabsorption by a direct action exerted at the tubular level, thus leading to a decrease in urinary sodium excretion [5,21]. In addition, activation of the sympathetic nervous system by stimulation of the renin/angiotensin/aldosterone system [5,22] can further promote sodium retention. Other mechanisms, such as a posture-mediated decrease in the levels of atrial natriuretic peptide [23], cannot be excluded.

In conclusion, these results indicate that, in normotensive subjects, blood pressure and urinary sodium excretion are coupled in the short term, and that this relationship can be altered by the activation of neurohumoral factors.
REFERENCES


16 Staessen, J. A., Birkenhager, W., Bulpitt, C. J. et al. (1993) The relationship between blood pressure and sodium and potassium excretion during the day and at night. J. Hypertens. 11, 443–447


Received 28 May 1999/20 August 1999; accepted 12 January 2000