Effects of sodium intake on cardiovascular variables in humans during posture changes and ambulatory conditions

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Among decades, the relationship between the intake of sodium and extracellular fluid volume, arterial pressure, and neuroendocrine systems has been extensively investigated (12, 13). Only a few studies, however, have focused on the relationship between the variations in sodium intake, changes in cardiac output (CO), stroke volume (SV), and the resulting renal sodium excretion. Recently, as originally proposed by Schrier (23), it has been shown that baroreceptors, which are stimulated through pulsatile changes in the arterial tree, might play an important role in long-term volume and pressure regulation through modulation of renal sympathetic nervous activity and thereby renal sodium excretion (16–18, 25). Despite this, the influence of changing the intake of dietary sodium on central hemodynamics has only been sparsely investigated.

In previous investigations, the alterations in sodium intake have often been beyond the normal physiological range, which might not be relevant for most human beings (19, 20). Furthermore, the central hemodynamic estimations have usually been performed by echocardiography (19, 20, 26, 27) with the subjects in the supine position (19, 20, 26) under strictly controlled laboratory conditions (19–22, 26, 27). Selecting the supine posture for such studies is not optimal, because it per se causes a central and intravascular volume expansion, which might mask the additional responses to changes in sodium intake. Moreover, the upright (seated) posture has been demonstrated to constitute a steady-state condition for sodium excretion in humans in contrast to supine posture (1). Therefore, when evaluating the cardiovascular adaptations to the different levels of sodium intake, this should include measurements in the upright position, which in fact is the most frequent posture for humans during most of the daytime. These considerations can explain the fact that previous studies have concluded differently regarding the existence and the magnitude of the hemodynamic responses to alterations in sodium intake.

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Therefore, we determined the central hemodynamic responses in healthy humans to variations in sodium intake within the normal physiological range during controlled postural changes in the laboratory and during more ambulatory seated conditions. The hypothesis was tested that CO and SV are increased by a more pronounced effect in the ambulatory upright seated than supine position.

MATERIALS AND METHODS

Fourteen male subjects (age 25.9 yr (range 20–29 yr), height 185.3 cm (range 172–192 cm), and weight 77.8 kg (range 59.4–89.5 kg)) participated in the experiment. All were nonsmokers, had a negative history of any medical diseases, and were healthy as indicated by routine clinical examinations and measurements of arterial pressure, electrocardiogram (unipolar), and urine test (strip) for glucose, leukocytes, erythrocytes, and protein. None of the subjects took any medication at the time of the study. Informed consent was obtained after the subjects had read a description of the experimental protocol, which was approved by the Ethics Committee of Copenhagen (KF 01–249/00) and in compliance with the Declaration of Helsinki.

The study consisted of two consecutive 5-day periods, where the subjects shifted between a low (70 mmol/24 h) and a high (250 mmol/24 h) sodium intake or vice versa in a randomized balanced fashion (Fig. 1). Urine collections for determination of 24-h renal sodium excretions were collected during the final 7 days of the 10-day study. Water intake was ad libitum, and heavy exercise was not allowed.

During the final 2 days of each 5-day period, the subjects were investigated under controlled and more ambulatory conditions, respectively.

Controlled Laboratory Measurements (Days 4 and 9)

Before the experiment, the subjects slept at the laboratory and fasted for 12 h. The subjects were awakened at 7:00 AM, and each cubital vein was instrumented with a short 18-gauge venous catheter (Venflon 2; 1.3-mm OD, length 45 mm) for blood sampling and injection of Evans blue. After emptying the bladder, the subject was weighed, seated in an arm chair, and administered 400 ml of tap water just before emptying the bladder, the subject was weighed, seated in an arm chair, and administered 400 ml of tap water just before startup of the experiment. Ambient temperature and humidity were kept at 25.0 ± 1.0°C (SE) and 28.4 ± 1.9%.

The experiment lasted 6 h. The subject was seated upright with upper body and lower legs vertical and thighs horizontal for 2 h and subsequently was placed in the supine position for 3 h and finally again in the upright seated position for 1 h. The subjects received 200 ml tap water every 60 min.

CO, heart rate (HR), and arterial pressures were measured simultaneously at hourly intervals, and the averages of duplicate measurements were used in the data presentation and statistical calculations. Left atrial (LA) diameter was determined by echocardiography.

CO was measured with an inert gas rebreathing method as described in detail previously (3, 11). Briefly, a closed system containing a rebreathing gas mixture of 1% SF6, 5% N2O, and 50% O2 in N2 and an infrared photoacoustic gas analyzer were used (AMIS 2001, Innovision, Odense, Denmark). The rebreathings were performed over 34 s with a gas volume of 30% of the calculated vital capacity and a breathing rate of 14 min−1. CO (effective pulmonary blood flow) was then determined from the gas concentration tracings.

During rebreathing, HR was obtained by continuous ECG recordings, which afterward were used for calculation of SV. Arterial pressures were obtained during the rebreathing procedures with automatic oscillometric equipment (Propaq 102, Protocol Systems). This equipment has previously been tested against an invasive arterial pressure monitoring system (10). The cuff for blood pressure determination was kept at the level of the fourth intercostal space when the subject was seated and at level with the midpoint at the midaxillary line when the subject was supine. The total peripheral vascular resistance (TPR) was calculated by dividing mean arterial pressure (MAP) by CO.

The LA diameter was determined by echocardiography (Aloka SSD 500, Simonsen and Well) from 3M-mode recordings obtained from the parasternal long-axis view. Printouts of the recordings were analyzed by the same investigator in a blinded fashion according to the criteria described by Feigenbaum (8).

Plasma volume (PV) was determined by the Evans blue dye dilution technique (9). In brief, after a blood draw of 3 ml, 2.5 mg of Evans blue was injected through a peripheral venous catheter. Blood samples (3 ml) were drawn at exactly 5, 7, 10, and 15 min of injection from the opposite catheter and centrifuged for 10 min at 1,500 g, and the concentration of dye thereafter was determined by spectrophotometry (Hitachi-1100 spectrophotometer).

Blood samples (20 ml) were drawn after 1 h in the seated and 1 h in the supine position. The amount of collected blood was substituted with a similar amount of isotonic saline and was immediately transferred to chilled tubes and centrifuged at 3,700 rpm for 10 min. Fresh plasma samples were afterward used for determination of plasma protein (Pprot) and electrolyte concentration (PNa and PK), osmolality (Posm), and hematocrit (Hct). Plasma for hormone concentration analyses was immediately frozen in polyethylene tubes and stored at −25°C for later analysis. Pprot was determined in duplicate by a handheld refractometer (Bellingham and Stanley, Eclipse H5–64, Turnbridge Wells, UK). Posm was measured in triplicate by freezing point depression (Advanced Osmometer, 3MO plus, Advanced Instruments, Needham Heights, MA). PNa and PK were measured by an ion-selective electrode system (KNA-2, Radiometer, Copenhagen, Denmark), while Hct was determined in quadruplicate by centrifugation of microhematocrit tubes (Brand) for 5 min at 12,600 g.

Plasma concentration of norepinephrine (NE) and epinephrine (Epi) was measured by a radioenzymatic assay as described previously (15), plasma aldosterone (Aldo) was...

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Fig. 1. Experimental protocol. Study flow chart. LAB, examinations during controlled laboratory conditions; AMB, examinations during ambulatory conditions.

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measured by radioimmunoassay with a commercially available kit (Coat-A-Count, DPC), and atrial natriuretic peptide (ANP) and ANG II were determined by radioimmunoassays as described previously (2, 24).

The 24-h urine samples were analyzed for concentration of electrolytes (PNa and PK) and osmolality by the methods described above.

**Ambulatory Measurements (Days 5 and 10)**

On the ambulatory days, the subjects visited the laboratory four times at 8:00 AM, 12:00 PM, 4:00 PM, and 8:00 PM for brief examinations. The subjects continued their normal daily activities in between. Within 10 min of arrival at the laboratory, the subjects were upright seated in an arm chair, and CO, HR, arterial blood pressures, and LA diameter were determined as described above. Approximately 30 min after arrival the subjects left the laboratory.

**Statistical Analysis**

Data are presented as means ± SE. A multifactor ANOVA (Statgraphics Plus for Windows, version 3.0) for repeated measurements with the variable as main variate and time and subjects as factors was used to evaluate the effects on a variable over time. Differences between the mean values were evaluated by a post hoc multiple range test (Newman-Keuls). To evaluate the effect of sodium intake (high vs. low) on a variable at a specific point in time, a Student’s paired two-sided *t*-test was applied. A significance level of 0.05 was chosen.

**RESULTS**

As indicated in Fig. 2, the 24-h renal sodium excretion attained a steady state within 4 days on each intake. During the 5-day period of 75 mmol/24 h sodium intake, the renal excretion was 68 ± 7 and 57 ± 5 mmol/24 h on days 4 and 5, respectively. The excretion rates during the 250 mmol/24 h sodium intake were 233 ± 11 mmol/24 h on day 4 and 263 ± 11 mmol/24 h on day 5.

**Laboratory Measurements**

Body weight was 77.8 ± 2.0 kg on the low salt intake and 78.7 ± 2.0 kg on the high (P < 0.05). As depicted in Fig. 3, PV was significantly higher during high sodium intake (P < 0.05) in both the seated (338 ± 37 ml, 9 ± 1%) and supine (297 ± 39 ml, 8 ± 1%) position.

**Central hemodynamics.** In the seated position, CO and SV were higher during high (5.3 ± 0.2 l/min and 81 ± 3 ml) compared with low sodium intake [4.8 ± 0.2 l/min (P < 0.05) and 68 ± 3 ml (P < 0.05)], whereas HR was lower (66 ± 2 vs. 70 ± 1 beats/min, P < 0.05) (Fig. 4). As a consequence of an unaltered MAP, TPR was lower during the high sodium intake (1.20 ± 0.05 vs. 1.07 ± 0.04 mmHg·ml⁻¹·s, P < 0.05).

In the supine position all the cardiovascular responses to the changes in sodium intake were attenuated. SV was 107 ± 3 and 99 ± 3 ml (P < 0.05) on high and low sodium intake, respectively. CO (6.2 ± 0.2 vs. 6.0 ± 0.2 l/min) and HR (59 ± 2 vs. 60 ± 1 beats/min) were unaffected by the levels of sodium intake (Fig. 4). TPR was lower during high sodium intake (0.84 ± 0.03 vs. 0.89 ± 0.03 mmHg·ml⁻¹·s, P < 0.05), while MAP remained unchanged (Fig. 4).

In fact, both the relative and absolute difference in the cardiovascular variables (CO, SV, HR, TPR) induced by the change in sodium intake were more pronounced in the seated than in supine position (Fig. 5).

The LA diameter was slightly increased by the high sodium intake although this increment was only significant in the supine position (Fig. 4).

**Plasma hormones.** High levels of sodium intake suppressed the renin-angiotensin-aldosterone system (RAAS) as expected (Table 1). Plasma ANG II and plasma Aldo were significantly (P < 0.05) reduced by
high sodium intake in both the seated (18.5 ± 1.9 vs. 7.7 ± 1.4 pg/ml and 120.0 ± 21.3 vs. 52.6 ± 9.8 pg/l) and the supine position (12.1 ± 1.6 vs. 4.0 ± 0.8 pg/ml and 92.7 ± 16.3 vs. 33.9 ± 7.2 pg/l). On the same sodium intake, the two plasma hormone levels were as expected lower in the supine compared with the seated position (P < 0.05). Plasma ANP was elevated by the high compared with the low sodium intake but only in the supine position (30.0 ± 2.4 vs. 43.8 ± 2.8 pg/l, P < 0.05). The plasma NE level was, as expected, suppressed (0.16 ± 0.02 vs. 0.13 ± 0.01 ng/ml, P < 0.05) by high levels of sodium intake although this was only significant in the seated position (Table 1). Changing position from upright seated to supine further reduced the plasma NE levels (P < 0.05).

Plasma composition. The high sodium intake resulted in a significantly lower $P_{prot}$ (Fig. 2) and Hct regardless of posture. In the seated position, $P_{prot}$ was 73 ± 1 g/l during low and 68 ± 1 g/l (P < 0.05) during high sodium intake while the corresponding values for hematocrit were 46 ± 1 and 44 ± 1% (P < 0.05). The same pattern of response was observed in the supine position, where $P_{prot}$ was 69 ± 1 g/l during high and 63 ± 1 g/l during low sodium intake and Hct was 45 ± 1 and 43 ± 1% (P < 0.05). $P_{Na}$, $P_{K}$, and $P_{osm}$ varied insignificantly regardless of the variations in salt intake and posture.

Ambulatory Measurements

CO and SV were higher throughout the day comparing high (5.9 ± 0.1 l/min and 84 ± 3 ml) with low [5.3 ± 0.2 l/min (P < 0.05) and 69 ± 3 ml (P < 0.05)] sodium intake. HR remained lower (71 ± 2 vs. 77 ± 2 beats/min, P < 0.05) while MAP was unaltered by the high sodium intake. TPR decreased from 1.08 ± 0.04 to 0.96 ± 0.03 mmHg·ml$^{-1}$·s (P < 0.05) during the high sodium intake, while LA diameter slightly increased as an average over the whole day (Fig. 6).

Comparing the measurements during the 2 days, CO was significantly higher (P < 0.05) as a result of higher HR (P < 0.05), while SV remained unchanged during the ambulatory day. MAP and LA diameter were unchanged while the calculated TPR was lower (P < 0.05).

DISCUSSION

The main findings of this study are that an increase in sodium intake within the normal physiological range increases CO and SV and lowers HR and that these changes are more pronounced in the seated than in the supine position. When seated, the hemodynamic changes appear to be of the same magnitude during both the controlled laboratory and the more ambulatory conditions.
In this study sodium intake was varied within the normal physiological range, and we examined the subjects in both the upright seated and supine posture. The hemodynamic changes were more pronounced in the upright seated position, which is noteworthy because the upright posture is the most common in humans during daytime. Furthermore, recent studies (1) have shown that the supine posture does not provide a steady-state condition for renal sodium and water excretion, for which reason this posture should be avoided when evaluating these changes. Therefore, we believe that the upright seated position, which represents a more normal physiological condition than the passive supine, should be preferred in this type of clinical investigation. When shifting body position from upright seated to supine, central blood volume is expanded by translocation of blood from the caudal parts of the body to the thoracic cavity. In addition, intravascular volume is increased as a result of a simultaneous shift of fluid from the interstitial to the intravascular space (14). Therefore, in the supine position the cardiac chambers are distended and the filling pressures increased, resulting in a higher SV. Under these conditions, the modest volume changes caused by alterations in sodium intake might only induce minor additive cardiovascular changes. This notion is confirmed in the present study, where all of the changes in central hemodynamics caused by variations in sodium intake were significantly attenuated by the supine position.

Our findings are in accordance with results of previous investigations, where no cardiovascular adaptations were demonstrated in the supine position, when the sodium intake changed within the normal physio-
logical range (19, 20, 26). In contrast, Volpe et al. (27) examined a subgroup of healthy subjects in the seated position during two consecutive 6-day periods with a shift in sodium intake from 100 to 250 mmol/day. This increase in sodium intake induced hemodynamic changes, which were very similar to the findings in our study, i.e., SV increased by 25% as a consequence of a higher CO, while HR was unaltered. Similarly, Omvik and Lund-Johansen (21) showed in borderline hypertensives that 9 mo of sodium restriction from an intake of 209 to 134 mmol/24 h significantly decreased the SV index by 9% in seated subjects, whereas no change occurred when they were supine. In a later study by the same group (22), no cardiovascular changes were observed during a moderate reduction (20%) in sodium intake. Hence, it is likely that the apparent contradictory conclusions regarding hemodynamic responses to variations in sodium intake are partly caused by the magnitude of sodium ingestion and partly by the different postures during examination.

To our knowledge, no investigators have determined CO during ambulatory conditions, where the subjects continue their normal activities in between the examinations. In the present study, the differences in CO, HR, and SV induced by the different levels of sodium intake were the same regardless of whether the measurements were performed during controlled laboratory or more ambulatory conditions. The slightly higher CO during the ambulatory compared with controlled laboratory conditions was a result of an increase in HR, for which reason the absolute values of SV were comparable (68 ± 3 and 69 ± 3 ml during low salt intake and 84 ± 3 and 81 ± 3 ml during high). Thus measurements of SV during extracellular fluid volume changes do not require standardized conditions because SV remains relatively constant after a very short period of seated rest.

The regulation of extracellular fluid volume is complex. Despite extensive investigations, it is far from understood. Traditionally, three types of mechanisms have been described to detect and respond to changes in extracellular fluid volume (4, 5): 1) cardiopulmonary (low pressure) mechanoreceptors, which detect transmural wall stress and respond by modulating renal sodium excretion through control of efferent renal sympathetic nervous activity and the renin-angiotensin-aldosterone axis (7); 2) nonneural mechanoreceptors in specific cells of the heart, the vascular epithelium, and smooth muscle cells, which respond to stretch by releasing natriuretic peptides (ANP, brain natriuretic peptide) to induce a natriuresis; and 3) physical factors such as colloid osmotic pressure and mean arterial pressure.

Fig. 6. Central hemodynamic variables during the ambulatory day on low (open bars) and high sodium intake (filled bars). A: CO. B: HR. C: SV. D: TPR. E: MAP. F: LA diameter. *Statistically significant difference of the variable on low vs. high sodium intake (P < 0.05). †Statistically significant difference at different times during the day compared with 8:00 AM (P < 0.05).
pressure, which are modulated by changes in extracellular fluid volume and which may govern renal sodium handling (4, 6, 14). The results of the present study confirm some of these already-known mechanisms for renal sodium handling. The high sodium intake markedly increased plasma and extracellular fluid volume, which in turn suppressed the renin-angiotensin-aldosterone axis and reduced plasma NE, whereas plasma ANP increased. We observed in accordance with previous investigators (19–22, 26, 27) that mean arterial pressure was unaffected by the changes in sodium intake within the normal physiological range. The pressure-natriuresis hypothesis, however, predicts that renal sodium excretion can vary considerably with only minimal changes in mean arterial pressure, when the neurohormonal natriuretic (e.g., ANP) and antinatriuretic (e.g., RAAS) systems function normally (4). Finally, our results confirm previous findings from our laboratory that hemodilution during volume loading might initiate a natriuresis (14). We actually observed that PV increased and P_prot decreased by approximately 7–9% during the high salt intake. It is therefore conceivable that hemodilution and a decrease in plasma colloid osmotic pressure constitute stimuli for the augmented renal sodium output when changing from low to high sodium intake.

A possible role for arterial high-pressure baroreceptors (responding to transmural stretch) in long-term regulation of the arterial pressure and body fluid volumes has previously been rejected because the receptors have been assumed to adapt and reset rapidly (4). Recently, however, the importance of chronic baroreceptor stimulation has been underscored in both animal and human studies. Smit et al. (25) observed that bilateral carotid sinus denervation after bilateral carotid body tumor resection increased the long-term levels and variability of arterial pressure. Lohmeier et al. (17, 18) in systematic studies of unilaterally renal-denervated splintbladder dogs demonstrated that baroreceptor denervation during ANG II-induced hypertension resulted in an attenuated suppression of the renal sympathetic nervous activity, which resulted in a reduced renal sodium output. Furthermore, long-term increments of sodium intake persistently reduced renal sympathetic nervous activity (16), thereby promoting renal sodium excretion.

In our study, sodium loading augmented cardiac forward flow (CO and SV), which in turn might have stimulated the arterial baroreflexes through increased pulsation. Additionally, plasma NE, which mainly derives from kidney and muscle tissue, was reduced during the high levels of sodium intake. Therefore, as originally proposed by Schrier (23), it is conceivable that the relatively large changes in SV and thereby in pulsatile arterial high-pressure baroreflexor stimulation could promote renal sodium excretion through reduction in renal sympathetic nervous activity. Additional studies, however, concerning the relation between sodium intake, arterial baroreceptors, and renal sympathetic nervous activity are needed to further explore this possibility.

In conclusion, the results of this study indicate that increments in sodium intake within the normal physiological range in humans lead to PV expansion, which in turn increases CO and SV and lowers HR. The hemodynamic changes are more pronounced in the seated than in supine position and are readily detectable during ambulatory, noncontrolled conditions. The results indicate that SV or CO through arterial baroreceptor stimulation could constitute stimuli for the higher renal sodium excretion induced by the high sodium intake.

**Perspectives**

In this study we have demonstrated that CO, HR, and SV vary considerably within the normal physiological range of sodium intake. In the upright seated position, we observed that the hemodynamic changes were independent of whether the subjects were under controlled or more ambulatory conditions. Therefore, studies on the hemodynamic responses to long-term volume loading (e.g., sodium intake) should include measurements in the upright position, which is the most relevant physiological body position in human during daytime.

Results of this study also imply that arterial filling and hemodilution might be important factors for initiating the natriuresis of high sodium intakes. In future studies, the cardiovascular effects of sodium intake in different groups of patients characterized by fluid and sodium retention (e.g., heart failure, cirrhosis) should be addressed. The possibility of ambulatory monitoring of CO gives offspring to many future studies, e.g., 24-h monitoring of CO and arterial pressures, to determine cardiovascular function in congestive heart failure.

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