Reduced Vagal Activity in Salt-Sensitive Subjects During Mental Challenge

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Background: Salt-sensitive normotensive men exhibit an enhanced pressor and heart rate (HR) response to mental stress. Stress-induced HR acceleration may result from sympathetic activation or vagal withdrawal. We studied the importance of vagal withdrawal for the increased stress responsiveness of salt-sensitive subjects.

Methods: We studied cardiovascular reactivity to mental challenge in 17 salt-sensitive healthy white male students and 56 salt-resistant control subjects who were comparable with respect to age, body mass index, and physical fitness. Salt sensitivity was determined by a 2-week dietary protocol (20 mmol v 240 mmol sodium/day). Mental stress was induced by a computerized information-processing task (manometer test). Electrocardiogram and finger blood pressure (BP; Finapres, Ohmeda, Louisville, CO) were registered continuously to determine HR and interbeat-interval length. Time and frequency domain (spectral power) based measures of respiratory-related heart rate variability (HRV) were calculated to estimate vagal cardiac control; diastolic BP reactivity was assessed to estimate peripheral sympathetic effects.

Results: Stress-induced increase in HR was higher in salt-sensitive than in salt-resistant subjects. Salt-sensitive subjects, in comparison to salt-resistant subjects, showed significantly reduced respiratory-related HRV during baseline and mental stress conditions ($P < .01$). The increase in diastolic BP during mental challenge was significantly greater in salt-sensitive subjects ($P < .05$).

Conclusions: Our findings suggest reduced vagal and increased sympathetic tone during mental challenge in salt-sensitive subjects. Altered autonomic nervous system function may contribute to later development of hypertension in salt-sensitive individuals. Am J Hypertens 2003; 16:531–536 © 2003 American Journal of Hypertension, Ltd.

Key Words: Heart rate variability, vagal activity, mental stress, sodium-dependent hypertension, blood pressure.

Enhanced cardiovascular responsiveness to mental challenge was found in subjects at future risk for the development of arterial hypertension, such as borderline hypertensives and healthy offspring of hypertensive parents.[1] Increased pressor responsiveness has also been described as a consequence of salt loading in a proportion of young normotensive individuals. Several lines of evidence suggest that these salt-sensitive individuals may be genetically prone to the development of hypertension.[2–4] We have previously shown that young normotensive salt-sensitive subjects display an elevated heart rate (HR) response to mental challenge,[5] suggesting that autonomic nervous system (ANS) factors may con-

tribute to the development of hypertension in these subjects.

In accordance, enhanced anxiety and irritability was found in salt-sensitive subjects,[6] compatible with a contribution of higher central nervous system factors. However, HR changes may result from parasympathetic or sympathetic nervous system changes and it remains unclear whether vagal withdrawal or sympathetic activation is responsible for the enhanced cardiovascular responsiveness to mental challenge described in salt-sensitive subjects.

Several investigators have shown that the high frequency component of heart rate variability (HRV) primar-

ily reflects vagal tone.[7–10] Diastolic blood pressure (BP) responses have been used as estimates of sympathetic nervous system excitement.

The aim of the present study was to examine ANS changes in salt-sensitive subjects, as compared to salt-resistant subjects, during rest and mental stress conditions.

Methods
Study Population

Seventy-three healthy white men (age range: 20 to 30 years), who responded to an advertisement posted on the university campus, volunteered for the study. All but four students of other faculties (two salt-sensitive and two salt-resistant subjects) were enrolled in medical school. Before entering the study, all subjects underwent routine physical and laboratory evaluation to ensure that none had hypertension, diabetes mellitus, hepatic, pulmonary, or renal disease, or abnormal weight (body mass index, <19 or >26 kg/m^2). All subjects had a resting diastolic BP <85 mm Hg and a systolic BP <135 mm Hg, defined by the mean of 60 oscillometric measurements (DINAMAP, Criticon, Tampa, FL) in the recumbent position. Subjects were excluded if they reported a neurologic or psychiatric disease, drug abuse (including nicotine and alcohol), vascular damage, or current medication.

All subjects underwent phenotypic characterization regarding their BP response to a dietary salt-loading/restriction protocol as previously described.[11,12] In brief, subjects were given a standardized low-salt diet containing 20 mmol sodium, 20 mmol chloride, 60 mmol potassium, and 20 mmol calcium per day for 14 days. To this diet, a daily supplement of 22 tablets of Slow Sodium (10 mmol NaCl per tablet; CIBA-GEIGY, Horsham, United Kingdom) and placebo were each given in a randomized single-blind crossover fashion for 7 days. Dietary compliance was assessed by daily measurement of electrolyte excretion. At the end of each week, after a 30-min resting period, BP was measured for assessment of salt sensitivity in the recumbent subject during 1 h at 1-min intervals with an automatic oscillometric device (DINAMAP 1846 SX, Criticon). As in previous studies,[11,12] salt sensitivity was defined as a significant decrease in mean arterial pressure >3 mm Hg under the low-salt diet calculated as the difference between the average of the 60 readings under the high salt and low salt periods. Following the supine measurements, subjects were asked to stand upright, and BP and HR was measured during 15 min at 1-min intervals. To assess nonspecific sympathetic reactivity under low and high salt intake, BP and HR readings of the 15 min in the orthostatic position were averaged and compared to the average of the 60 readings in the supine position.

Physical fitness was estimated by subjects reports about their exercise habits and was classified as 1 point for <1 h, 2 points for 1 to 2 h, and 3 points for >2 h of physical exercise per week.

Study Protocol

All psychophysiologic tests were conducted between 8 and 12 AM, with the subjects seated comfortably in a high-backed chair in a quiet room with an ambient temperature of 20°C to 24°C. Electrodes and transducers for detection of physiologic parameters were fastened to the chest, nondominant arm, and hand. Blood pressure was continuously registered by the Finapres device (Ohmeda, Louisville, CO), attached to the middle digit of the nondominant hand. Heart rate was continuously registered by electrocardiography. Respiratory rate was continuously registered with a piezo-electric transducer that was fastened to the chest with an elastic belt.

The mental challenge test (manometer test) was performed 1 to 3 days before the salt loading/restriction protocol began. Subjects were instructed to abstain from coffee and black tea for at least 12 h before testing. Before the manometer test, subjects remained on their normal salt intake with a comparable sodium excretion between salt-sensitive and salt-resistant subjects (184.3 ± 61.5 *v* 181.6 ± 91.2 mmol within 24 h before the test). After the first instructions, a venous cannula was placed in the dominant forearm. Thereafter, subjects rested for 30 min to get accustomed to the environment. The duration of the manometer test was 8 min, and it was preceded by a resting phase of 5 min. Blood samples for catecholamine levels (measured by HPLC) and plasma renin activity (measured by radioimmunoassay) were drawn immediately before the resting phase and immediately after the manometer test.

The manometer test[13] consisted of a standardized computer-based information-processing task, performed under time pressure. All tests and instructions were presented on a computer monitor, and data entry was performed by manipulating a mouse with the dominant hand. Subjects were presented with an increasing number of 3 to 11 manometer clocks, and had to rapidly decide whether one or more hands of the clocks deviated by more than 90 degrees from the direction of an arrow shown on the top of the screen. Wrong answers were indicated by a loud acoustic signal. During the course of the test, the time allowed for the decision was subsequently shortened by 30% until the participant made a mistake. After a mistake, the time allowed for the decision was extended by 30%. This algorithm maintained an individually adapted workload. In previous studies the manometer test was judged as emotionally distressing by most participants. The test was shown to elicit reproducible BP and HR responses that are within the expected range of comparable mental challenge tests (eg, mental arithmetic).[14,15]

The protocol of the study, including the process for obtaining informed consent, was approved by the ethics committee of our hospital.

Table 1. Demographic parameters of salt-sensitive and salt-resistant subjects

Parameter	Salt-Sensitive Subjects ($n = 17$)	Salt-Resistant Subjects ($n = 56$)
Age (y)	25.3 ± 3.1	25.6 ± 2.4
Body mass index (kg/m^2)	23.1 ± 2.0	22.7 ± 2.3
Physical fitness (3 categories)	1.85 ± 0.90	1.84 ± 0.80
Degree of salt-sensitivity (mm Hg)		
(MAP$_{high\ salt\ period}$ − MAP$_{low\ salt\ period}$)	$5.4 \pm 2.4*$	-2.8 ± 3.2

MAP = mean arterial pressure.

    Values are means $\pm$ SD.

    * $P < .001$ v salt-resistant subjects.

Data Analysis

All physiologic signals were continuously recorded at 1000 Hz with DOS-Software (Turbolab, Stemmer, Puchheim, FRG). The electrocardiographic and finger BP curves were analyzed off-line under visual artifact control by ALYS software (version 1.18, T. Sudhop and H. Schächinger, Basel, Switzerland). Blood pressure and HR responses to the mental task were determined by subtracting the average of the readings during the baseline period from the average of the readings during the manometer test.

Power spectral density of HR and BP was analyzed by Fourier transformation according to published standards.[16] The very low, low, and high bands were defined as 0.02 to 0.06 Hz, 0.07 to 0.14 Hz, and 0.15 to 0.4 Hz, respectively. Respiratory frequency is an important determinator of HRV[17] and was assessed by calculating the modal value of respiratory frequency tracings during each test period. The root mean square of successive differences (RMSSD) of inter-beat interval (IBI) length was calculated as a time domain-based measure of respiratory-related HRV.[18,19] Variability measures were log-transformed to achieve normally distributed parameters.

Statistical Analysis

Repeated measures analysis of variance was performed by SAS GLM-Procedure (version 8.1; SAS Inc., Cary, NC) to determine group (salt-sensitive versus salt-resistant) and stress effects (resting baseline versus mental stress) and potential interactions. A statistically significant interaction term reflects different effects of stress between groups. All data are presented as means $\pm$ standard deviation. A $P < .05$ was considered statistically significant.

Results

Baseline characteristics of salt-sensitive and salt-resistant subjects are shown in Table 1. Subjects were comparable with respect to age, body mass index, and physical fitness. By definition, the difference in mean arterial BP between the high salt and low salt periods was greater in the salt-sensitive than in the salt-resistant group.

Baseline levels of HR (69.1 ± 9.9 beats/min v 67.0 ± 10.2 beats/min), systolic BP (109.05 ± 13.09 mm Hg v 107.31 ± 14.83 mm Hg), and diastolic BP (64.50 ± 7.16 mm Hg v 63.73 ± 11.20 mm Hg) before the mental stress test were comparable between salt-sensitive and salt-resistant subjects, respectively. During the manometer test, systolic and diastolic BP increased in all subjects, but salt-sensitive subjects displayed greater heart rate (10.7 ± 9.0 beats/min v 5.9 ± 6.1 beats/min; $P < .01$) and diastolic BP responses (11.3 ± 3.7 mm Hg v 9.2 ± 3.7 mm Hg; $P < .05$) than salt-resistant subjects, and tended to display greater systolic BP responses (19.2 ± 8.5 mm Hg v 16.4 ± 8.5 mm Hg; $P < .10$).

Salt-sensitive subjects tended to display lower respiratory rates during baseline (0.233 ± 0.046 Hz) as compared to salt-resistant subjects (0.252 ± 0.039 Hz; $P = .05$). During mental stress, respiratory rate increased significantly in both study groups ($P < .0001$) but did not differ between salt-sensitive (0.306 ± 0.038 Hz) and salt-resistant subjects (0.324 ± 0.039 Hz).

Time and frequency domain based measures of HRV are presented in Fig. 1 and Table 2. The time domain-based variability estimate RMSSD of IBI length revealed significant stress (time) [$F(1,70) = 57.0$; $P < .0001$] and
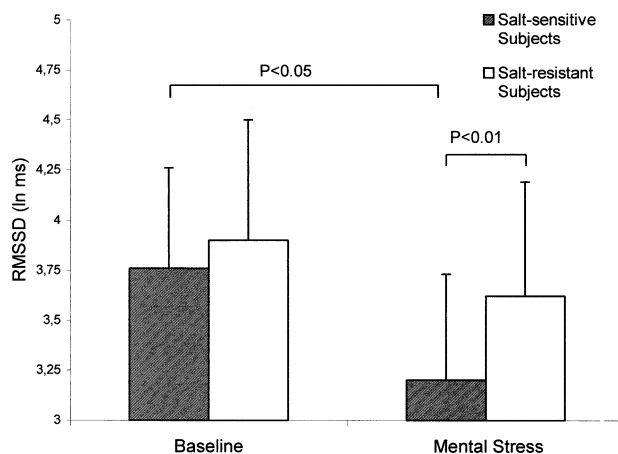
FIG. 1. Time domain-based heart rate variability (RMSSD) during baseline and mental stress in salt-sensitive and salt-resistant subjects. RMSSD = root mean square of successive differences of inter-beat intervals.

Table 2. Heart rate variability during baseline and mental stress in salt-sensitive and salt-resistant subjects

Protocol Phase/Parameter	Salt-Sensitive Subjects (n = 17)	Salt-Resistant Subjects (n = 56)
Resting baseline		
RMSSD of interbeat intervals (ln msec)	3.76 ± 0.50*	3.90 ± 0.60
HRV-Very low band (0.02–0.06 Hz; ln beats/min^2)	1.99 ± 0.70	1.97 ± 0.72
HRV-Low band (0.07–0.14 Hz; ln beats/min^2)	2.20 ± 0.56	2.09 ± 0.89
HRV-High band (0.15–0.40 Hz; ln beats/min^2)	1.94 ± 0.88	1.99 ± 1.13
Mental stress		
RMSSD of interbeat intervals (ln msec)	3.20 ± 0.53†‡	3.62 ± 0.57
HRV-Very low band (0.02–0.06 Hz; ln beats/min^2)	1.85 ± 0.81	1.85 ± 0.75
HRV-Low band (0.07–0.14 Hz; ln beats/min^2)	1.63 ± 0.61‡	1.75 ± 0.75‡
HRV-High band (0.15–0.40 Hz; ln beats/min^2)	1.12 ± 0.78†‡	1.67 ± 1.05‡

RMSSD = root mean square of successive differences; HRV = heart rate variability.
 Values are means ± SD. Between-group differences: * $P <$ .05, † $P <$ .01; intragroup differences v baseline: ‡ $P <$ .001.

group effects [$F(1,70) = 3.7$; $P <$ .05] and a significant group × stress interaction [$F(1,70) = 6.7$; $P <$ .01], indicating reduced HRV in salt-sensitive subjects during baseline and mental stress.

The analysis of spectral power-based measures showed a significant stress effect [$F(1,71) = 45.1$; $P <$ .0001] and a significant group × stress interaction [$F(1,71) = 9.1$; $P <$ .003] in the high band of HRV (0.15 to 0.40 Hz), indicating reduced HRV in salt-sensitive subjects during mental stress. No group effects and no significant interactions in the very low and low bands of HRV and in the respective bands of BP variability (BPV) could be detected, although there were significant stress effects in the low bands of HRV [$F(1,71) = 21.9$; $P <$ .0001] and BPV [$F(1,71) = 10.9$; $P <$ .001; data not shown].

Analysis of BP and HR response to upright standing after 90 min in the supine position revealed no different increases of mean, systolic, and diastolic BP or HR be-

tween salt-sensitive and salt-resistant subjects (Table 3). With respect to absolute values, only diastolic BP was slightly higher in salt-resistant subjects during low salt intake, both in supine and standing positions ($P <$ .05).

In addition, we analyzed neurohumoral measures of the adrenergic tone. Plasma catecholamine levels neither differed between salt-sensitive and salt-resistant subjects before mental challenge (norepinephrine: 178.4 ± 86.6 v 217.8 ± 85.4 pg/mL, epinephrine: 40.6 ± 17.5 v 38.3 ± 20.3 pg/mL) nor after mental challenge (norepinephrine: 184.9 ± 99.1 v 229.3 ± 87.7 pg/mL, epinephrine: 38.4 ± 17.7 v 46.3 ± 20.8 pg/mL). Renin activity was lower in salt-sensitive than in salt-resistant subjects before mental challenge (1.09 ± 0.74 v 1.47 ± 0.83 μg Ang I/L/min; $P <$ .05), and was comparable after mental challenge (1.35 ± 0.78 v 1.67 ± 0.90 μg Ang I/L/min). Only in salt-resistant subjects, renin activity was significantly higher after mental challenge than before

Table 3. Blood pressure and heart rate in supine and standing position in salt-sensitive and salt-resistant subjects

Protocol Phase/Parameter	Salt-Sensitive Subjects* (n = 17)		Salt-Resistant Subjects (n = 56)	
	Low Salt Period	High Salt Period	Low Salt Period	High Salt Period
Supine position				
Systolic BP (mm Hg)	109.7 ± 8.3	113.9 ± 7.5	111.7 ± 10.9	110.5 ± 9.5
Diastolic BP (mm Hg)	54.7 ± 4.8†	58.3 ± 5.3	58.8 ± 5.7	57.9 ± 5.6
MAP (mm Hg)	75.7 ± 4.9	80.0 ± 6.3	78.6 ± 8.3	78.3 ± 6.2
Heart rate (beats/min)	56.2 ± 7.1	55.0 ± 6.4	59.1 ± 9.4	56.0 ± 8.9
Standing position				
Systolic BP (mm Hg)	110.1 ± 12.3	115.7 ± 10.9	114.4 ± 11.2‡	113.8 ± 9.8‡
Diastolic BP (mm Hg)	61.0 ± 5.1†§	63.3 ± 7.3‡	65.4 ± 6.4§	65.7 ± 7.2§
MAP (mm Hg)	83.4 ± 6.9§	87.3 ± 8.2§	87.1 ± 7.3§	87.0 ± 7.8§
Heart rate (beats/min)	79.7 ± 9.1§	75.8 ± 9.4§	81.0 ± 10.5§	76.5 ± 11.2§

BP = blood pressure; MAP = mean arterial pressure.
 Values are means ± SD.
 * In salt-sensitive subjects, all BP values were higher during high salt periods, all $P <$ .05. Between-group differences, within same dietary regimen: † $P <$ .01; intragroup differences v supine position: ‡ $P <$ .01, § $P <$ .001.

mental challenge ($P < .05$). Aldosterone and hematocrit levels at baseline were not different between study groups (data not shown).

Discussion

In a previous study, we have shown that salt-sensitive normotensive subjects display an increased pressor and HR response to mental stress.[6] In the present study, we extend these findings by demonstrating that salt-sensitive subjects, compared to salt-resistant subjects, also display a reduced vagal activity during baseline and mental stress, as demonstrated by the finding of a significant reduction of respiratory related HRV in the time (RMSSD) and frequency domains (high band HRV).

The finding of a reduced vagal tone under mental stress is well in line with previous reports on stress-related HRV in healthy volunteers and postinfarct patients.[20,21] Decreased vagal tone has been shown in established hypertension,[22] as well as borderline hypertension.[23] The reduction of vagal tone in salt-sensitive subjects in the present study may partly explain their higher HR and BP responses under mental challenge. Withdrawal of vagal tone as the cause of enhanced cardiovascular reactivity is well in line with the hypothesis that the low HR of humans under resting condition predominantly results from a strong parasympathetic cardiac input.[24]

It may be criticized that the slightly lower respiratory rate of salt-sensitive subjects during the resting baseline could have biased the results. However, the lower respiratory rate observed in the salt-sensitive group would have favored increased RMSSD of IBI—just the opposite of what was actually detected.

Diastolic BP reactivity during mental stress was enhanced in salt-sensitive subjects, suggesting enhanced peripheral sympathetic effects. Enhanced peripheral sympathetic reactivity in normotensive salt-sensitive subjects was also demonstrated in former studies that showed an enhanced pressor response to noradrenaline infusion.[25,26] Some investigators suggest low frequency (LF) HRV to reflect sympathetic cardiac activity.[18] Contrasting to the increase of diastolic BP, in the present study there was a significant decrease of LF HRV that tended to be greater in salt-sensitive subjects (-26%) than in salt-resistant subjects (-16%). However, literature on stress-induced changes of low band HRV is inconsistent. With respect to the LF band, published data are not conclusive, and it remains unclear whether a decrease or increase of LF HRV during mental challenge is to be expected. Controversial findings have been reported. Spectral analysis techniques revealing non-normalized power results (such as the technique used by our study group) indicated significantly decreased LF HRV during mental stress[27,28] or nonsignificant decreases.[29] In case of normalized spectral power units, results are also inconsistent. Some found normalized LF HRV to remain unchanged during mental stress,[30] others found increases in normalized LF HRV

during mental stress.[31] The latter finding may be potentially explained by altered breathing patterns induced by mental stress tests using verbal activities.[32] In the present study, there was no significant difference between salt-sensitive and salt-resistant subjects in the reduction of the LF band during the manometer test. Thus we avoid speculating on potential differences in cardiac sympathetic tone. Yet, another possible explanation for conflicting results with respect to sympathetic cardiac activity in salt-sensitive subjects could be that their defect is located in the adrenoreceptor sensitivity rather than in central sympathetic output, as proposed by Skrabal and co-workers.[2] On the other hand, an increase of sympathetic muscle nerve activity under reduced sodium intake was found in hypertensive and normotensive subjects, which was attributed to an impaired baroreflex control.[33,34] Unfortunately, the relation of sympathetic reactivity to sodium sensitivity is not reported in these studies; therefore, comparisons to our results are difficult.

Thus, our study shows that the withdrawal of vagal activity under mental stress is more pronounced in salt-sensitive compared to salt-resistant subjects. As the subjects in the present study were normotensive volunteers, this implies that the tendency to markedly withdraw vagal tone precedes the hypertensive state, and may thus play a causal role in the later development of hypertension in salt-sensitive subjects. Decreased vagal tone has been shown in established hypertension,[14] as well as borderline hypertension.[15]

We may speculate that the withdrawal of vagal tone in salt-sensitive subjects is one of the mediators through which enhanced negative affect (eg, elicited by mental challenge) can lead to enhanced cardiovascular reactions. In a recent publication,[35] we reported an association between enhanced cardiovascular responsiveness and enhanced affective startle modulation in salt-sensitive subjects, suggesting an enhanced neurovegetative output from the amygdala. Perhaps the output of the amygdala is not only mediated by sympathetic neural efferences, as suggested by Holand et al,[36] but also by modulation of vagal efferences.

As possible limitations of our study, it should be noted that reports on reproducibility of salt sensitivity classification as well as reproducibility of cardiovascular reactions to mental stress are inconsistent. Nevertheless, in our own laboratory a good reliabilitiy of classification of salt sensitivity,[37] as well as a good reliabilitiy of cardiovascular reactivity to mental stress[13–15] were demonstrated. Furthermore, it should be said that the interpretation of reduced HRV as a reflection of vagal withdrawal is somewhat speculative and was not confirmed by experiments with vagolytic drugs in this pilot study.

In summary, in this study we provide evidence for reduced respiratory sinus arrhythmia during baseline and mental challenge in salt-sensitive subjects. The reduction of high band HRV suggests diminished vagal activity. Diminished vagal activity under mental challenge, to-

gether with enhanced sympathetic reactivity, may contribute to the later development of hypertension in salt-sensitive individuals.

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