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Article *in* Journal of Human Hypertension · December 2002

DOI: 10.1038/sj.jhh.1001492 · Source: PubMed

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ORIGINAL ARTICLE

Salt supresses baseline muscle sympathetic nerve activity in salt-sensitive and salt-resistant hypertensives

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The objective of our study was to evaluate the role of the baroreflex control of peripheral sympathetic nervous system on the increase of muscle sympathetic nerve activity (MSNA) in salt-sensitive (SS) and salt-resistant (SR) hypertensives under low salt diet. In phase I mild-to-moderate hypertensive patients ($n=5$) received three diet periods: a first regular salt (RS1), a low salt (LS = 20 meq Na^+/day), followed by a second regular salt diet (RS2) with a 7-day duration of each. At the end of each period, sympathetic and heart rate baroreflex control were recorded. Baseline MSNA varied ($P<0.005$) from 18 ± 8 (RS1) to 32 ± 9 (LS) and to 14 ± 9 (RS2) bursts per minute (bpm). In phase II additional patients ($n=6$) were included to have baseline MSNA, sympathetic and heart rate baroreflex control evaluated at the end of the LS and RS2. For all patients ($n=11$), there was a significant decrease of MSNA from 36 ± 4 to 20 ± 8 bpm on day 7 of LS to RS2 ($P<0.05$). The response of MSNA to a salt restriction was similar for SS and SR patients, who showed a change from 32 ± 6 to 18 ± 11 and from 36 ± 9 to 17 ± 7 bpm for SS and SR on day 7 of LS and RS2 diets, respectively ($P<0.05$). MSNA baroreflex gain was similar during phenylephrine infusions at day 7 of LS and RS2 (5.1 ± 1.6 and 6.1 ± 2.9 bpm/mmHg), but it was reduced under LS during sodium nitroprusside infusion (19.5 ± 4.9 *vs* 8.9 ± 0.7 bpm/mmHg) ($P<0.05$) for the whole group. Baroreflex control of MSNA was also similar during phenylephrine infusions under LS and RS2 diets for SS (4.0 ± 0.9 and 3.3 ± 0.2 bpm/mmHg) and for SR patients (10.1 ± 2.5 and 5.6 ± 1.5 bpm/mmHg). During nitroprusside infusion, baroreflex gain was significantly greater under RS2 for SR patients (19.5 ± 2.6 bpm/mmHg) when compared to LS (11.2 ± 5.2 bpm/mmHg) and the same significant difference was observed among SS patients (14.4 ± 4.7 and 9.1 ± 3.6 bpm/mmHg under RS2 and LS diets, respectively). There was no difference in heart rate baroreflex gain between LS and RS2 diets. Data support the hypotheses that (1) sodium supresses baseline MSNA in SS and SR hypertensives and (2) sodium restriction may impair baroreflex control of MSNA in SR and SS mild-to-moderate hypertensive patients during blood pressure reductions.
Journal of Human Hypertension (2002) **16,** 843–850. doi:10.1038/sj.jhh.1001492

Keywords: blood pressure; sympathetic nervous system; salt sensitivity

Introduction

Muscle sympathetic nerve activity (MSNA) has been evaluated in hypertensives under low and high salt diets. Anderson *et al*[1] evaluated muscle sympathetic nerve activity in normotensive and borderline hypertensive patients under low salt (10 meq Na^+/day) and high salt diets (400 meq Na^+/day), and found a significant reduction under high salt regimen for both normotensive and hypertensive subjects.

More recently, Grassi *et al*[2] evaluated hypertensive patients, under the three salt regimens (regular, low and again regular) and studied the mechanisms involved in the sympathetic activation under low salt diet. They showed that sodium restriction may impair arterial baroreflex and suggested that this impairment may be responsible for the sympathetic activation.

It is well known that haemodynamic responses to high salt diet is not uniform among hypertensives.[3] In addition, it is not known whether salt-sensitive and salt-resistant hypertensives show the same MSNA response to low salt diet; and whether the arterial baroreflex impairment showed by Grassi *et al*[2] is dependent on salt sensitivity.

Therefore, the objective of the present study was to evaluate in salt-sensitive and salt-resistant hypertensive patients under low and regular salt diets: (1) baseline MSNA and (2) sympathetic baroreflex control of MSNA.

It was hypothesized that an altered baroreflex control of MSNA might contribute to the increase of

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activity in MSNA under a low salt diet in salt-sensitive hypertensive patients.

Material and methods

The study was approved by the Institutional Ethics Committee. A total of 16 patients were invited to be enrolled in the study. They were outpatients from the Hypertension Unit, Nephrology Division from University of São Paulo School of Medicine.

In all, 11 subjects, who were able to participate in all the phases of the study, gave their written informed consent prior to the enrollment. They were mild-to-moderate essential hypertensives ($90 < DBP < 114$ mmHg)[4] aged between 18 and 65 years, both genders, with or without left ventricular hypertrophy[5] and body mass index of < 30 kg/m^2. Secondary causes of hypertension were excluded through abdominal ultrasonography, renal radioisotopic cintilography, radioisotopic nephrogram and renal arteriography. Exclusion criteria included: diabetes mellitus, abusive alcohol intake, obesity, ischaemic cardiopathies, hepatopathies, cerebrovascular diseases and psychiatric disorders.

All subjects had blood pressure measurements done at least three times and the diagnosis of hypertension was performed using the mean of the three screening blood pressure measurements. All patients previously treated for hypertension had their antihypertensive medication withdrawn for 8 weeks. Medical histories and physical examinations were normal except for hypertension-positive family histories for 10 patients.

Only those patients, whose urinary sodium excretion was $\leqslant 50$ meq/24 h and the increase was > 100 meq/24 h when they were transferred from low to regular salt diet, were considered for the study.

The salt sensitivity was evaluated through an arbitrary criterion of mean blood pressure change of 5 mmHg measured on the 7th day of each diet. Salt-sensitive patients were considered, as those whose mean blood pressure increase was > 5 mmHg, when transferred from a low to a regular salt diet.

Experimental protocols

There was a placebo period of 8-week duration, during which patients were on regular diet and had previous antihypertensive medication withdrawn. All subsidiary examinations to exclude secondary causes of hypertension and to evaluate organ damage were performed during this phase. Patients during this phase had fortnightly visits for blood pressure measurement, clinical examination and compliance evaluation (only those patients remained on study, whose placebo tablets intake was always greater than 80%).

During the whole protocol, blood pressure measurements were done always in the morning around 0800 h in supine position. Blood pressure was measured thrice with a calibrated mercury sphygmomanometer. The average of the values was used.

Phase I

This phase consisted of 3 weeks and patients were consecutively allocated to receive three diet periods: a first regular salt, a low salt (20 meq Na^+/day), followed by a second regular salt diet with a 7-day duration each. Two regular salt diet periods were conceived in order to have a time control and the possibility to confirm data and preclude possible salt intake errors. At the end of each period, patients were submitted to the MSNA recording in the peroneal nerve by the microneurographic technique[6] have baseline MSNA recorded. Diets order was not randomized; regular was always the first offered one.

On day 7 of each diet patients were submitted to an experimental session, during which MSNA was evaluated, through direct recording of the peroneal nerve through microneurography. Prior to the beginning of the experimental session, the antecubital vein was calculated and blood samples were collected for haematocrit, haemoglobin, plasma sodium and potassium, plasma renin activity and plasma aldosterone measurements. A 30-min baseline MSNA was recorded. At the end of low salt and second regular salt diet periods, the baseline recording was followed by continuous 10-min infusions of increasing doses of phenylephrine (0.25, 0.50 and 1.0 mcg/kg/min).

After the last phenylephrine dose, there was a recovery period lasting 20–30 min, until MSNA, heart rate and blood pressure values returned to baseline levels. Continuous 10-min infusions of increasing doses of sodium nitroprusside (0.25, 0.50 and 1.0 mcg/kg/min) were again followed by a recovery period of similar duration to the first.

Heart rate was continuously recorded by EKG through chest electrodes (KD281-045072, Dayton, OH, USA) Blood pressure was continuously measured with noninvasive, automatic device (Finapress 2300, Ohmeda, Englewood, CO, USA), and minute-to-minute and respiratory movements were recorded through a pneumograph.

Phase II

Consisted of 2 weeks, during which patients received a regular salt diet followed by a low salt diet (20 meq Na^+/day) with a 1-week duration each. At the end of each week, patients were submitted to microneurography and had sympathetic and heart rate baroreflex control evaluated in addition to baseline MSNA recording.

Throughout all phases of the study, patients received placebo tablet once a day and only the

sodium content of diet was manipulated; the potassium, calcium and caloric contents were unchanged. Urine samples (24 h) were collected on days 6 and 7 of both low salt and regular salt diets for urinary sodium measurement. Mean values of urinary sodium excretion ($UVNa^+$) of days 6 and 7 were used as diet adherence parameters.

On day 7 of each diet patients were submitted to experimental session, during which MSNA, and additionally baroreflex control of MSNA and heart rate were evaluated through direct recording of the peroneal nerve using microneurographic technique, and phenylephrine and nitroprusside infusions.

Sympathetic nerve recording

Efferent, postganglionic muscle sympathetic nerve traffic was recorded from the right or left peroneal nerve posterior to the fibular head, as described previously.[6] Nerve signals underwent two-stage amplification ($\times$ 70 000) band-pass filtering between 700 and 2000 Hz, and integration (0.1 s time constant) with a nerve traffic analysis system (Bioengineering Department, University of Iowa, Iowa City, USA). Integrated nerve activity was monitored with a loudspeaker, displayed on a storage oscilloscope (model 511 A Tektronix, Beaverton, OR, USA), and continuously recorded in physiologic poligraph (model RS 3800 Gould Inc, Cleveland, OH, USA; 8 channels in paper at 5 mm/min). Sympathetic bursts in the mean voltage neurogram were identified by their characteristic morphology and relation to electrocardiographic R waves and expressed in bursts per minute (bpm).

Other measurements

Plasma, and urinary sodium and potassium were measured through spectrophotometer (Instrumentation Laboratory, model IL-143, MA, USA). Plasma renin activity was measured through radioimmunoassay (CIS Bio International, Oris Group. France). Plasma aldosterone measurement was done through radioimmunoassay (Diagnostic Systems Laboratories Inc., TX, USA).

Data analysis

Baseline value of MSNA, heart rate, blood pressure under low and regular salt diets correspond to the mean of the last 5 min that immediately preceeded the first vasoactive drug infusion. These values were compared with the mean of the last 5 min of each infusion for each variable. MSNA baroreflex gain for each subject was estimated by two methods: (a) least squares linear regression of values for diastolic blood pressure and MSNA (expressed as a per cent of control) and (b) per cent ratio between MSNA change and diastolic blood pressure change.

Baroreflex responses of heart rate to blood pressure changes were based on the mean blood pressure values. Heart rate baroreflex gain for each subject was estimated by least-squares linear regression of values for mean blood pressure and heart rate, and by the ratio between heart rate change and mean blood pressure change.

The differences between diets were assessed with unpaired Student's '*t*'-test. For protocol I when baseline MSNA, mean blood pressure, urinary sodium excretion under two regular and a low salt diet periods were compared, Kruskal–Wallis and Dunn's multiple comparisons tests were used.

Correlations were analysed through Pearson's test. When muscle sympathetic nerve activity was involved, Spearman's test was used. A *P*-value of less than 0.05 was considered statistically significant.

Results

No sample size estimation was performed to indicate what magnitude of difference between the two groups could be reliably detected assuming commonly used values for α ($\leqslant 0.05$) and β ($\geqslant 0.08$)

Phase I

Five patients (women, four white patients and one mullato) with a mean age 40 $\pm$ 9 years (range: 32–55) were studied. At entry into the study, blood pressure was 152 $\pm$ 8/106 $\pm$ 5 mmHg, body weight was 67 $\pm$ 14 kg (range: 49–82 kg) and body mass index was 25 $\pm$ 3 kg/m^2. All patients had family history positive for hypertension and the mean time for diagnosis of hypertension was 6 years (range: 5 months–15 years). Patients 1, 2 and 6 presented interventricular septum beyond normality[5] and ecocardiographic values for all other subjects were normal. Serum urea and creatinine were within normal limits (28 $\pm$ 9 and 0.8 $\pm$ 0.2 mg/dl, respectively). Urinary sodium excretion varied from 191 $\pm$ 78 to 19 $\pm$ 16 to 238 $\pm$ 57 meq/24 h at the end of regular, low and again regular salt diets, respectively.

Phase II

Six additional patients (four women, four white patients and two black patients) with a mean age 43 $\pm$ 10 years (range: 31–54) were studied. Blood pressure at the beginning of the study was 145 $\pm$ 7/100 $\pm$ 7 mmHg. Body weight was 70 $\pm$ 13 kg (range: 59–93 kg) and body mass index was 27 $\pm$ 3 kgm^2. All patients with exception of patient 3 had family history positive for hypertension and mean time for diagnosis of hypertension was 6 years (range: 5 months–15 years). All patients had normal ecocardiographic values. Serum urea and creatinine were

Table 1 Patients' characteristics at allocation

Patient	*Age (year)*	*Gender*	*Race*	*SBP (mmHg)*	*DBP (mmHg)*	*MBP (mmHg)*	*HR (bpm)*	*Weight (kg)*	*Height (cm)*	*BMI (kg/m²)*
1[a]	35	F	W	160	112	128	84	75	166	27
2[a]	35	F	W	140	102	114	65	52	154	22
3[a]	43	F	W	142	108	119	80	59	144	28
4[a]	51	F	W	150	108	122	92	49	147	23
5	31	M	W	138	90	106	73	93	174	30
6	55	F	W	150	100	117	92	82	168	29
7	47	F	N	142	108	119	72	75	158	30
8	54	F	N	150	102	118	72	62	155	26
9	32	M	W	156	95	115	73	70	168	25
10	32	F	M	157	108	125	84	58	162	22
11	51	F	W	140	100	133	76	63	164	24
Mean	42			147	103	119	79	67	160	26
s.d.	7			8	7	7	9	14		3

Blood pressure levels refer to three consecutive measurment mean. s.d.: standard deviation. SBP: sytolic blood pressure; BDP: diastolic blood pressure; MBP: mean blood pressure; HR: heart rate; M: male; F: female; W: white patients; N: black patients; M: Mullato; BMI: body mass index.
[a]Salt-resistant patients.

within normal limits (26 ± 7 and 0.7 ± 0.1 mg/dl, respectively).

Characteristics of the 11 patients at entry into the study are listed in the Table 1.

Phases I and II

From the 11 patients enrolled in both phases, four were salt-resistant mild-to-moderate white hypertensive women (mean age 41 ± 7 years, with a blood pressure at the beginning of the study of $148 \pm 9/108 \pm 4$ mmHg). Body weight was 59 ± 11 kg and body mass index 25 ± 3 kg/m^2. Seven patients (five women: four white patients, one mullato and two black patients) with a mean age of 43 ± 11 years were salt sensitive (blood pressure of $148 \pm 7/100 \pm 7$ mmHg; body weight 72 ± 12 kg and body mass index was 27 ± 3 kg/m^2). With the exception of one salt-resistant patient, who did not know familial hypertension history, all other patients had positive histories and mean time for diagnosis of hypertension was 6 years (range: 5 months–15 years). Two salt-resistant and one salt-sensitive patients presented interventricular septum beyond normality.

For the 11 patients enrolled in both protocols, laboratory examinations were performed on two occasions: at the end of the low and the second regular salt diets. They varied between the two diets, as shown below; nevertheless, the values were similar among salt-resistant and salt-sensitive patients within each diet. From day 7 of low salt diet, significant variations occurred as follows: haematocrit varied from 43.9 ± 1.3 to $40.7 \pm 2.8\%$, haemoglobin from 14.3 ± 0.6 to 13.4 ± 0.8 mg/dl, plasma sodium from 135.8 ± 2.8 to 132.4 ± 6.2 meq/l and plasma potassium from 4.1 ± 0.3 to 3.7 ± 0.4 meq/l ($P<0.05$).

Plasma renin activity was significantly reduced from 2.9 ± 1.7 to 0.7 ± 0.8 mg/ml/h and plasma aldosterone levels from 157.5 ± 87.7 to 44.5 ± 49.7 pg/ml on day 7 of low and regular salt diets, respectively ($P<0.05$). Body weight was significantly increased at the end of regular salt diet from 66.4 ± 13.8 to 67.2 ± 13.4 kg.

Urinary sodium excretion varied from 19 ± 16 to 201 ± 73 meq Na^+/24 h ($P<0.05$) at the end of low and regular salt diet, respectively (Table 2). A significant correlation between plasma renin activity and urinary sodium excretion ($R^2=0.42$; $P<0.05$) was found under low salt diet, but not under the regular salt diet.

Blood pressure

Phases I and II

When the whole group was considered no significant blood pressure change was observed (121 ± 6, 113 ± 8, 115 ± 17 mmHg at the end of regular, low and again regular salt diets, respectively) in phase I; there also did occurred any significant blood pressure change (mean blood pressure of 110 ± 6 *vs* 101 ± 6 mmHg) at the end of the regular and the low salt diets in phase II.

Among salt-resistant patients, no blood pressure alteration was observed between day 7 of regular salt diet ($127 \pm 16/90 \pm 10$ mmHg) and low salt diet ($130 \pm 14/96 \pm 12$ mmHg). Nevertheless among salt-sensitive patients, blood pressure was significantly different from day 7 of regular salt diet ($151 \pm 23/101 \pm 13$ mmHg) to day 7 of low salt diet ($138 \pm 15/92 \pm 12$ mmHg).

Mean blood pressure values were comparable for both salt-sensitive and salt-resistant group at the end of low salt diet (106 ± 12 and 107 ± 11 mmHg), but

Table 2 Individual plasma values on day 7 of regular and low salt (20 meq Na^+/day) diets

Patient	*Low salt diet*						*Regular salt diet*					
	Ht (%)	*Hb (g/dl)*	*Na^+ (meq/l)*	*K^+ (meq/l)*	*ARP (ng/ml/h)*	*Aldo (kg/ml)*	*Ht (%)*	*Hb (g/dl)*	*Na^+ (meq/l)*	*K^+ (meq/l)*	*PRA (ng/ml/h)*	*Aldo (kg/ml)*
1	42.5	13.9	137.5	3.8	3.54	215	38.1	12.7	135.5	3.7	2.16	115.0
2	45.2	14.6	134.0	3.8	4.41	240	45.4	14.7	122.5	3.6	0.38	9.0
3	40.7	12.3	138.0	4.1	2.38	NA	28.0	12.1	138.5	3.7	0.18	NA
4	42.6	13.8	133.5	4.6	3.37	95	41.0	12.7	130.0	4.4	0.29	10.0
5	42.0	14.0	138.0	4.6	NA	NA	40.0	12.1	134.0	4.3	NA	NA
6	44.0	14.1	134.0	4.2	NA	NA	40.5	13.2	138.0	3.4	NA	NA
7	43.5	14.6	136.0	4.1	3.21	NA	41.3	13.0	136.0	3.2	1.12	NA
8	40.1	13.2	143.0	4.0	1.72	190	39.1	12.7	134.0	4.0	0.61	36.0
9	41.6	14.0	144.0	4.1	2.30	NA	42.6	13.7	138.0	4.0	0.59	NA
10	45.1	15.2	140.0	4.3	0.41	80	38.9	14.0	136.0	3.8	0.00	42.0
11	43.1	14.1	140.0	4.1	3.30	90	40.1	13.0	134.0	3.9	0.64	32.0
Mean	42.8*	13.9*	138.0*	4.2*	2.73*	151.66*	39.6	13.0	134.2	3.8	0.66	40.7
s.d.	1.6	0.8	3.5	0.3	1.18	71.32	4.3	1.7	4.6	0.4	0.64	38.9

sd: standard deviation; Ht: hematocrit; Hb: hemoglobin; Na^+: plasma sodium; K^+: plasma potassium; PRA: plasma renin activity; Aldo: plasma aldosterone. *$P<0.05$ *vs* regular salt diet.
NA: not available.

were greater for salt-sensitive patients on day 7 of regular salt diet (118 ± 13 and 101 ± 10 mmHg; $P<0.05$).

Urinary sodium excretion varied from 9.5 ± 7 and 23.4 ± 16 meq Na^+/24 h for salt-resistant and salt-sensitive patients, respectively, to 197 ± 66 and 204 ± 80 meq Na^+/24 h ($P<0.001$) at the end of low and regular salt diets respectively.

MSNA

Figure 1 shows individual baseline MSNA recorded at the end of low and regular salt diets. Figure 2 shows baseline recording of MSNA in salt-sensitive (panel a) and salt-resistant (panel b) hypertensive patients under low and regular salt diets.

Phase I
MSNA at the end of the regular salt diet was 18 ± 8 bpm and increased to 32 ± 9 bpm with salt restriction ($P<0.05$). When the usual salt content was again offered to the patients, their MSNA returned to baseline levels (14 ± 9 bpm) at the end of the regular salt diet period ($P<0.05$).

Phase II
MSNA was significantly reduced from 36 ± 4 bpm on day 7 of the low salt diet to 20 ± 8 bpm on the same day of regular salt diet ($P<0.05$). Reduction was observed in all patients and it varied from 9 to 89%. No correlation was found between urinary sodium excretion and MSNA, nor between it and plasma renin activity under any diet.

Baseline MSNA was similar for both salt-sensitive and salt-resistant groups under both diets. Salt-sensitive patients showed a change from 32 ± 6 to 18 ± 11 bpm on day 7 of low and regular salt diets, respectively ($P<0.05$), whereas MSNA of salt-resistant subjects varied from 36 ± 9 to 17 ± 7 bpm ($P<0.05$). Only among salt-sensitive patients an inverse and significant correlation between MSNA and diastolic blood pressure was found ($R^2=0.67$; $P<0.05$).

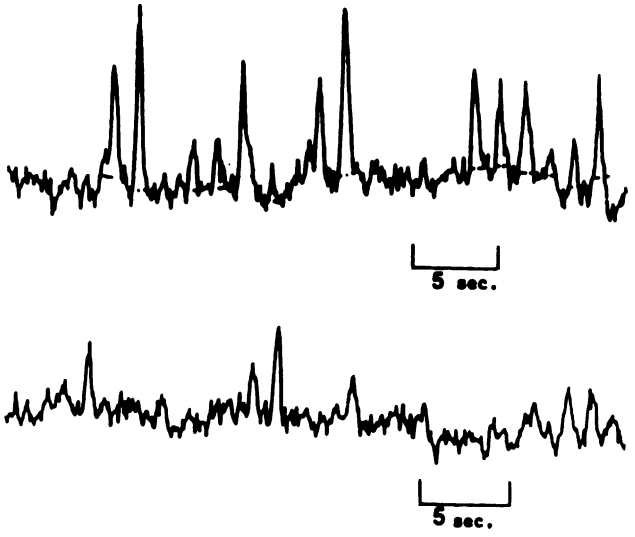

Figure 1 Baseline recording of MSNA from hypertensive patient (CGS) under low and regular salt diets. Upper part: low salt diet; BP = 125 × 81 mmHg, HR = 65 bpm, MSNA = 42 bpm. Lower part: regular salt diet; BP = 115 × 83 mmHg, HR = 69 bpm, MSNA = 15 bpm.

Baroreflex

Data for baroreflex control of MSNA and heart rate were collected from the 11 patients included in both

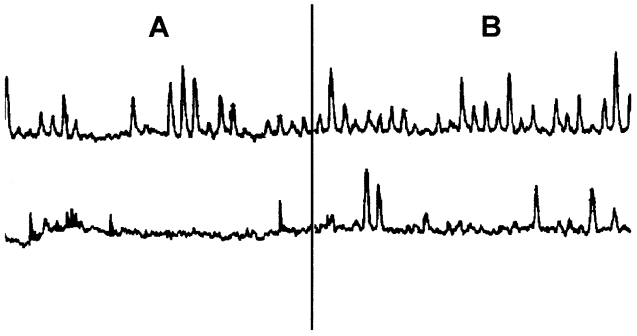

Figure 2 Baseline recording of MSNA of salt-sensitive (A) and salt-resistant (B) hypertensive patients under low and regular salt diets.

protocols. Baroreflex evaluations were performed on day 7 of low and regular salt diets.

Under low salt diet there was a progressive, significant decrease in MSNA for each phenylephrine dose, beginning with the first one. Phenylephrine 0.25 mcg/kg/min reduced sympathetic activity from 33 ± 7 to 22 ± 8 bpm ($P<0.05$). A further decrease to 17 ± 9 bpm was observed with phenylephrine 0.50 mcg/kg/min ($P<0.05$) and to 14 ± 9 bpm with phenylephrine 1.0 mcg/kg/min min ($P<0.0001$). These changes (−31, −54, −64%) were followed by blood pressure alterations. However, these were not significant (88 ± 14 to 100 ± 16 mmHg at baseline and after phenylephrine 0.1 mcg/kg/min).

At the same experimental session, sodium nitroprusside infusions determined significant MSNA increase from 33 ± 7 to 52 ± 15 bpm starting with the second dose and further increase to 57 ± 16 bpm during sodium nitroprusside 1.0 mcg/kg/min. No blood pressure changes were observed.

Under regular salt diet beginning with the second phenylephrine dose, there was a significant reduction in MSNA from 17 ± 8 to 9 ± 7 (0.50 mcg/kg/min) and to 6 ± 7 bpm (1.00 mcg/kg/min). Only the third sodium nitroprusside infusion determined significant increase from 17 ± 8 to 41 ± 16 bpm. No blood pressure changes were observed.

Baroreflex gain of MSNA

The gain in the arterial baroreflex control of MSNA estimated by the ratio per cent of control level of peripheral sympathetic nerve activity bpm diastolic blood pressure change (mmHg) was similar during phenylephrine infusions under both low and regular salt diets (5.1 ± 1.6 and 6.1 ± 2.9 bpm/mmHg). However, during sodium nitroprusside infusion, the baroreflex gain was significantly greater under regular (19.5 ± 4.9 bpm/mmHg) than under low salt diet (8.9 ± 0.7 bpm/mmHg).

The per cent changes in MSNA obtained with phenylephrine and sodium nitroprusside infusions under low salt and regular salt diets were similar. The same was observed with blood pressure changes.

The gain of the arterial baroreflex control of MSNA was similar during phenylephrine infusions under both regular and low salt diets for both salt-sensitive (3.36 ± 0.25 and 4.0 ± 0.85 bpm/mmHg) and salt-resistant patients (5.6 ± 1.5 and 10.1 ± 2.5 bpm/mmHg) During phenylephrine infusions no significant changes were observed among both salt-resistant and salt-sensitive groups under regular salt diet (5.6 ± 1.5 and 3.3 ± 0.25 bpm/mmHg), or under low salt diet (10.1 ± 2.5 and 4.0 ± 0.9 bpm/mmHg).

However, during sodium nitroprusside infusions the baroreflex gain was significantly greater under regular salt diet for salt-resistant (19.5 ± 2.6 bpm/mmHg) than under low salt diet (11.2 ± 5.2 bpm/mmHg). The same significant difference was observed among salt-sensitive patients (14.4 ± 4.7 and 9.1 ± 3.6 bpm/mmHg under regular and low salt diets, respectively). No change between salt-resistant and salt-sensitive patients were detected within each diet.

The per cent changes in MSNA obtained with phenylephrine and sodium nitroprusside infusions under low salt and regular salt diets were similar for salt-sensitive and salt-resistant groups. The same was observed with blood pressure changes.

Baroreflex control of heart rate

Responses to phenylephrine and sodium nitroprusside infusions

No significant heart rate or blood pressure changes were observed during phenylephrine and sodium nitroprusside infusions under low salt and regular salt diets for the whole group, as well as for salt-sensitive and salt-resistant patients.

Baroreflex gain

Heart rate baroreflex gain estimated by the ratio heart rate change/mean blood pressure change during phenylephrine infusions was similar under low regular and salt diets (1.2 ± 0.2 and 1.1 ± 0.3 bpm/mmHg, respectively). Similar values were found for both low salt and regular salt diet during sodium nitroprusside infusions (2.3 ± 0.5 and 3.0 ± 0.1 bpm/mmHg, respectively.

Discussion

The main finding of the present study was that sodium suppressed baseline MSNA in salt-sensitive and salt-resistant hypertensives and did not influence baroreflex control of MSNA.

These findings were obtained in baroreflex evaluations through continuous infusions of increasing doses of phenylephrine and sodium nitroprusside. The infusion of each dose lasted 10 min and values for MSNA, blood pressure and heart rate obtained

during the last 5 min of each dosing period were compared with the baseline values. This methodology was employed by Rea and Hamdan,[7] who evaluated baroreflex gain in borderline hypertensives and normotensive, and by Grass *et al*[8] in lean and obese subjects. There are no studies in the literature that compare MSNA baroreflex control evaluated through both infusion method and 'bolus' injection. Through infusion method evaluation, Rea and Hamdan[7] found no difference in MSNA baroreflex control between normotensives and borderline hypertensives. Meyrelles *et al*[9] in our lab employed 'bolus' injection and obtained similar results.

In the present study, data show that the gain in the baroreflex control of peripheral sympathetic nerve activity was similar for both diets for blood pressure increases. However, for hypotensive stimulae it was significantly reduced under a low salt diet. These findings support the data of Takeshita and Ferrario,[10] found a reduced baroreflex control of renal sympathetic nerve activity in salt-depleted dogs and corroborates the Grassi *et al*[2] data, who showed a reduction in the sensitivity of the baroreflex control of MSNA.

The relationship between salt and hypertension has been extensively demonstrated by epidemiologic, experimental and clinical studies.[11–13] Salt has been shown to alter neural control of cardiovascular function in dogs[10] and Dahl salt-resistant rats.[14] These alterations in neurogenic control involved peripheral adrenergic[11,12] and central neural[10] mechanisms. Takeshita and Ferrario[10] demonstrated reduced baroreflex control of renal sympathetic nerve activity in salt-depleted dogs. Ferrari and Mark[14] observed that high salt diet potentiates afferent arterial baroreceptor function in Dahl salt-resistant rats under high salt diet and suggested that this phenomenon was not related to aortic distensibility and was probably the result of sensitization of baroreceptor by high salt diet.

It is known that angiotensin II diminishes baroreflex sensitivity[15] and that renin–angiotensin–aldosterone system blockade potentiates baroreflex sensitivity in normal subjects.[16] Munakata *et al*[17] compared the heart rate baroreflex gain in mild-to-moderate essential hypertensives with aldosteronism patients prior to and after adrenalectomy. They showed that patients with aldosteronism had increased baroreflex sensitivity and this sensitivity was present in approximately 40% after adrenalectomy. They suggested that the angiotensin II generation suppression could contribute to the increased heart rate baroreflex gain.

Although we did not perform central venous pressure measurements for ethical reasons, our data showed that the renin–angiotensin–aldosterone system was effectively suppressed with the volume expansion induced by regular salt diet. This suppression could have contributed to the increased MSNA baroreflex gain. Another possibility could be that the hyperactivity of the renin–angiotensin–aldosterone system determined by low salt diet could lead to a sensitivity reduction of the MSNA baroreflex.

Another possibility that has to be taken into consideration is that the reduced baroreflex gain of MSNA during low salt intake might be because of the difference in nitric oxide production during various diets. The nitric oxide production was not the objective of the study and therefore nitric oxide was not measured.

In the present study, the increased MSNA under low salt diet corroborates Anderson *et al*[1] results. They showed a reduction under regular salt diet, which occurred without blood pressure changes. The cardiopulmonary baroreflex was not evaluated. However, it is known to be activated during volume expansion. Since our low salt diet was effective in inducing volume restriction (as demonstrated by body weight decrease, increase of hematocrit, hemoglobin, plasma sodium and potassium, plasma renin activity and plasma aldosterone levels) the sympathoexcitatory influence of cardiopulmonary baroreflex should be taken into consideration as one of the mechanisms involved in the MSNA increase.

One limitation of our study is that blood pressure was not significantly reduced by sodium restriction. Nevertheless, the same was reported by Anderson *et al*[1] and Grassi *et al*.[2] The latter suggested that impairment of the baroreflex induced by sodium restriction may oppose, via a sympathetically mediated vasoconstriction, the blood pressure lowering effect of the low sodium diet.

A second limitation of our study is the small size of the sample. This makes it difficult to draw some conclusions, mainly with regard to the gain of the arterial baroreflex control of MSNA among salt-sensitive and salt-resistant patients under different diets, because although the absolute values obtained were different, the difference between them was not statistical.

In conclusion our data suggest that

(1) Sodium suppress baseline MSNA in salt-sensitive and salt-resistant hypertensive patients; and
(2) Sodium restriction may impair baroreflex control of MSNA in salt-resistant and salt-sensitive mild-to-moderate hypertensive patients during blood pressure reductions.

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