Insulin Levels Are Similar in Obese Salt-Sensitive and Salt-Resistant Hypertensive Subjects

Brent M. Egan, Konrad Stepniakowski, Pietro Nazzaro

Abstract Evidence supports the hypothesis that hyperinsulinemia, especially in obesity, contributes to salt-sensitive hypertension by enhancing sodium retention and blunting the normal reduction of sympathetic drive and vascular resistance that occurs during a high versus low NaCl diet. To address these issues, we studied 18 obese (body mass index, >27 kg/m²) subjects younger than 45 years old with mild hypertension to determine if the salt-sensitive versus salt-resistant subset had higher insulin levels, retained more volume, and failed to suppress sympathetic drive and vascular tone normally on a high (≈200 mEq/d) versus low (20 mEq/d) NaCl diet for 7 days each. Six obese subjects were salt sensitive, with an 8.4±2.1 (SEM) mm Hg increase of ambulatory mean blood pressure on the high versus low NaCl diet. Ten obese subjects were salt resistant, with a 7.1±0.9 mm Hg reduction of ambulatory mean blood pressure on high versus low NaCl. The salt-sensitive and salt-resistant groups had similar values, respectively, for the insulin area under the curve during an oral glucose tolerance test on low (14.6±1.8 versus 14.0±1.4 mU·min/dL, P=NS) and high (10.6±1.5 versus 10.6±1.0, P=NS) salt diets. Although insulin levels were similar, insulin raised calf blood flow in salt-resistant subjects (P<.05) but not in salt-sensitive subjects on the high NaCl diet. Indexes of hyperinsulinemia, especially in obesity, contribute to salt-sensitive hypertension across age and gender subgroups.1 Evidence suggests that both salt2 and the sympathetic nervous system3-4 contribute to the elevated blood pressure (BP) in obese patients. In response to an NaCl challenge, salt-resistant (SR) subjects vasodilate5 at least partially by decreasing sympathetic drive6 and vascular α-adrenergic tone.7 Conversely, salt-sensitive (SS) individuals vasoconstrict on a high salt diet,7 maintain sympathetic drive,6 and increase vascular α-adrenergic tone.7

The hyperinsulinemia associated with obesity may be a pathogenetic common denominator by contributing to increased sympathetic drive,8 enhanced α-adrenergic reactivity,9 and greater sodium retention, even in subjects with resistance to insulin-mediated glucose disposal.9,10 SS compared with SR normotensive volunteers have a greater insulin response to oral glucose10 during a high NaCl diet. Moreover, the high NaCl diet raises insulin values in the SS subset while lowering them in the SR subgroup.12 Obese, hyperinsulinemic children retain more fluid and are more sensitive to the pressor effects of salt than lean children.11 Thus, insulin levels appear to be greater in SS than SR subjects11,12 and increase further12 rather than suppressing normally12 with NaCl loading. If the greater insulin levels, especially during a high NaCl diet, in SS versus SR subjects extend to adults with obesity and hypertension, then the SS subset would be expected to retain more volume13 and fail to both suppress sympathetic drive10 and lower vascular resistance during a high versus low NaCl diet.13 This study was designed to determine if obese SS versus SR hypertensive subjects had greater insulin levels, retained more volume, and failed to reduce sympathetic drive and decrease vascular resistance during a high versus low NaCl diet.

Methods

Human Volunteers

Thirty-one paid subjects, including 24 men and 7 women, were recruited from the Hypertension Clinic and by advertisement. Every volunteer signed a written informed consent document approved by the Human Research Review Committee. Each individual had history, physical, and laboratory examinations to exclude health problems except for obesity and hypertension. Eighteen subjects were obese (body mass index [BMI], >27 kg/m²) borderline to mild hypertensive...
patients; borderline mild hypertension was defined by BP, measured in triplicate with subjects seated on at least one of three prestudy visits, that averaged greater than 140 mm Hg systolic and/or greater than 90 mm Hg diastolic. For reference purposes, the same measurements and protocol were performed on seven lean (BMI, <25.5 kg/m²) borderline mild hypertensive and six lean normotensive control subjects younger than 45 years old.

Physiological Measurements

BP values before the laboratory study were measured with a mercury sphygmomanometer and an appropriately sized arm cuff after subjects rested for 5 minutes in the seated position. In the laboratory, mean BP (MBP) was measured with a Dinamap 1846SX (Critikon, Inc, Tampa, Fla). The agreement between three simultaneous, opposite-arm, observer values minus Dinamap BP values was 4.2±0.5/8.9±0.4 mm Hg. Twenty-hour ambulatory BPs were obtained with an Accutracker monitor (Suntech Medical Instruments, Raleigh, NC). BP was monitored at 10-minute intervals between 6 AM and 11 PM, excluding the 4 hours during the morning when the subject was in the laboratory. BPs also were obtained at 30-minute intervals from 11 PM to 6 AM. The agreement between simultaneous, same-arm, observer readings minus Accutracker readings was 1.0±0.6/10.1±0.6 mm Hg.

Hemodynamic Measurements

Stroke volume in milliliters was measured by thoracic impedance. Cardiac output (liters per minute) was calculated as Stroke Volume/1000×Heart Rate (beats per minute). MBP with the Dinamap was obtained during each cardiac output measurement for calculation of total systemic resistance as MBP/CARDIAC Output (units). Calf blood flow (milliliters per 100 mL volume per minute) was measured with venous occlusion plethysmography.3

Biochemical Measurements

Serum insulin was measured in triplicate using a solid-phase 125I radioimmunoassay. Glucose was measured in duplicate using a glucose analyzer (Beckman Instruments, Brea, Calif). Plasma norepinephrine (picograms per milliliter) and plasma renin activity (nanograms angiotensin I per milliliter per hour) were measured by radioenzymatic assay and radioimmunoassay, respectively.3

Anthropometric Measurements and Calculations

Height and weight were obtained in lightly clothed volunteers without shoes. Triceps, biceps, subcapular, and iliac skinfold thicknesses were measured with Lange calipers (Cambridge Scientific Instruments, Cambridge, Mass). Percent body fat was calculated from the skinfold data. Abdominal (“waist”) and gluteal (“hip”) circumferences were measured with subjects standing.18

Dietary Control

Volunteers were interviewed by the Clinical Research Center (CRC) nutritionist to determine their usual diet. An isocaloric diet was designed using the NUTRITIONIST III diet analysis software (N-Squared Computing, Salem, Ore). The diet was controlled for sodium (500 mg/d), potassium (2500 mg/d), calcium (800 mg/d), and magnesium (300 mg/d). The caloric composition of the diet was 45% to 50% carbohydrate, 35% to 40% fat, and 15% protein. During the high salt period, the same diet was supplemented with eighteen 600-mg NaCl tablets daily (184 mEq Na+). Volunteers came to the CRC on alternate days to obtain all food and beverages, which were prepared by trained metabolic cooks in the CRC kitchen under the dietician’s direction. Dietary compliance was verified by 24-hour urinary sodium.

Protocol

After 5 days on a low salt diet, subjects began a 24-hour urine collection at 7 AM. Volunteers reported to the CRC at 7 AM the morning after an overnight fast and closed the urine collection. Postvoid weight was obtained, and electrodes were placed for impedance cardiography and heart rate monitoring. BP was determined in triplicate with a mercury manometer and compared with simultaneous Dinamap values. With subjects supine, a 20-gauge plastic catheter was inserted into a dorsal hand vein. The hand was placed in a box heated to 70°C to arterialize venous blood.18 Systemic hemodynamic data were obtained at 5-minute intervals over the next 30 minutes. During this time, blood for glucose and insulin was drawn in triplicate at 10-minute intervals. Aliquots of the final sample were sent for complete blood count, chemistries, plasma renin activity, and plasma norepinephrine. Glucose (75 g) in water was ingested over 2 minutes. Glucose and insulin were measured at 30, 60, 90, and 120 minutes. Before subjects left the CRC, the Accutracker BP monitor was placed.

Volunteers continued the study diet and returned the next morning to the CRC after an overnight fast. The Accutracker was removed, postvoid weight was obtained, and electrodes for impedance cardiography were placed. A venous catheter was inserted into a dorsal hand vein, and arterialized venous blood samples were drawn for glucose and insulin in triplicate at 10-minute intervals with volunteers supine. Systemic hemodynamics and calf blood flows were obtained at 5-minute intervals during this 30-minute period. Human insulin (0.1 U/kg) was given as an intravenous bolus.19 Measurements of glucose, insulin, systemic hemodynamics, and calf blood flow were obtained at 3, 6, 9, 12, and 15 minutes of the insulin tolerance test.

Results

Baseline Characteristics

The obese borderline mild hypertensive, lean borderline mild hypertensive, and lean normotensive groups, respectively, were of similar age (40±1, 40±1, 42±1 years) and had a similar proportion of men and women (14/4, 5/2, 5/1). The obese hypertensive group had greater values for BMI than the two lean groups (35±1, 23±1, 24±1 kg/m², P<.001), percent body fat (P<.01), and waist-to-hip ratio (P<.001). The lean and obese hypertensive groups had higher systolic and diastolic BP values (P<.05) versus the normotensive control group (144±3/96±2, 137±3/93±3, 116±4/73±4 mm Hg).

Hemodynamic, Metabolic, and Neurohumoral Variables in Obese and Lean Subjects on High Versus Low NaCl Diets

The lean groups were combined, because their insulin metabolism and responses to salt were not different. The difference of ambulatory MBP between the high

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minus low NaCl was not significant within (Table 1) or between the obese and lean groups (−0.9±1.3 versus −1.2±1.4, P=NS). The two groups had significant changes in all five indirect measures of volume changes, including weight, urine sodium, thoracic impedance, hematocrit, and serum proteins. The insulin area under the curve (AUC) was greater in obese versus lean hypertensive subjects during high versus low NaCl. The changes in these indexes suggest similar volume expansion within SS and SR obese hypertensive subjects during high versus low NaCl. The changes in these indexes suggest similar volume expansion and a different pressure-volume relation in obese SS versus SR subjects (Fig 1). The insulin AUC values were similar in obese SS and SR subjects during both the high (10.6±1.5 versus 10.6±1.0, P=NS) and low (14.6±1.8 versus 14.0±1.4, P=NS) NaCl diets. The high versus low salt diet lowered fasting insulin and the insulin AUC within both groups. During the insulin tolerance test on high NaCl, cardiac output rose in obese SS subjects, whereas calf blood flow increased in obese SR volunteers (Fig 2). Glucose and insulin levels were comparable in both obese groups during the high and low NaCl diets. Plasma norepinephrine and plasma renin activity declined during high NaCl in both groups.

**Effects of High Versus Low NaCl Diets in the Obese Salt-Sensitive and Salt-Resistant Hypertensive Groups**

Systolic blood pressure was defined as ambulatory MBP during high salt ≥3 mm Hg above ambulatory MBP during low salt. Salt resistance was defined as ambulatory MBP during high salt greater than or equal to ambulatory MBP during low salt. During the high versus low NaCl diet, ambulatory MBP rose 8.4±2.1 mm Hg in the 6 SS (6 men, aged 42±1 years) and fell 7.1±0.9 mm Hg in the 10 SR (4 women, 6 men; aged 40±1 years) obese hypertensive patients (Table 2). Two obese patients were not classified, because the difference in their ambulatory MBP between the two diets fell between these limits. Heart rate decreased, and cardiac output tended to increase within both groups during high versus low NaCl. Total systemic resistance declined during high versus low NaCl only within SR subjects.

**Indexes of Volume Status, Including Thoracic Impedance, an Index of Changes in Central Fluid Volume,20** were consistent with volume expansion within SS and SR obese hypertensive subjects during high versus low NaCl. The changes in these indexes suggest similar volume expansion and a different pressure-volume relation in obese SS versus SR subjects (Fig 1). The insulin AUC values were similar in obese SS and SR subjects during both the high (10.6±1.5 versus 10.6±1.0, P=NS) and low (14.6±1.8 versus 14.0±1.4, P=NS) NaCl diets. The high versus low salt diet lowered fasting insulin and the insulin AUC within both groups. During the insulin tolerance test on high NaCl, cardiac output rose in obese SS subjects, whereas calf blood flow increased in obese SR volunteers (Fig 2). Glucose and insulin levels were comparable in both obese groups during the high and low NaCl diets. Plasma norepinephrine did not rise significantly during the insulin tolerance test on the high or low NaCl diet in either group (data not shown).

**Discussion**

The principal difference between the obese SS and SR subjects was a failure of the SS subset to vasodilate on a high compared with low NaCl diet. The subnormal vasodilator response to NaCl is a characteristic of SS subjects observed in previous studies. The explanation for the differential adjustment of vascular resistance in obese SS versus SR subjects in response to NaCl is not likely explained by insulin levels per se, because insulin values were not different in SS versus

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**Table 1. Within-Group Comparisons of Selected Variables in Obese Hypertensive and Lean Volunteers on Low and High NaCl Diets**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Low Salt</th>
<th>High Salt</th>
<th>Low Salt</th>
<th>High Salt</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBP, mm Hg</td>
<td>106±2</td>
<td>106±2</td>
<td>90±3</td>
<td>96±3</td>
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<tr>
<td>MBP, mm Hg</td>
<td>62±2</td>
<td>62±2</td>
<td>90±3</td>
<td>89±3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>73±3</td>
<td>65±2*</td>
<td>61±2</td>
<td>57±1*</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>6.0±0.3</td>
<td>6.6±0.3†</td>
<td>5.4±0.4</td>
<td>5.8±0.3</td>
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<tr>
<td>TSR, µL</td>
<td>16.3±0.6</td>
<td>15.3±0.9†</td>
<td>17.0±1.1</td>
<td>16.1±1.1</td>
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<tr>
<td>Weight, kg</td>
<td>101.6±5.3</td>
<td>103.1±5.4†</td>
<td>70.8±2.0</td>
<td>71.8±2.1*</td>
</tr>
<tr>
<td>uNa*, mEq/d</td>
<td>19±3</td>
<td>219±14*</td>
<td>15±5</td>
<td>235±13*</td>
</tr>
<tr>
<td>Zc, Ω</td>
<td>22.9±1.0</td>
<td>20.9±0.8*</td>
<td>26.3±0.9</td>
<td>23.8±0.7*</td>
</tr>
<tr>
<td>Hct, %</td>
<td>43±1</td>
<td>40±1*</td>
<td>43±1</td>
<td>40±1*</td>
</tr>
<tr>
<td>TP, g/dL</td>
<td>7.2±0.1</td>
<td>6.7±0.2*</td>
<td>7.1±0.1</td>
<td>6.6±0.1*</td>
</tr>
<tr>
<td>Ins*, µU/mL</td>
<td>20.2±2.9</td>
<td>13.4±1.2†</td>
<td>8.4±0.6</td>
<td>7.3±0.8</td>
</tr>
<tr>
<td>Gluc, mg/dL</td>
<td>97±2</td>
<td>95±2†</td>
<td>89±2</td>
<td>87±3</td>
</tr>
<tr>
<td>InsAUC, mU/min/dL</td>
<td>13.7±1.0</td>
<td>10.7±0.9†</td>
<td>7.4±4.0</td>
<td>5.6±2.3‡</td>
</tr>
<tr>
<td>GlucAUC, g/min/dL</td>
<td>19.1±0.5</td>
<td>19.2±0.7</td>
<td>17.6±0.6</td>
<td>17.8±0.8</td>
</tr>
<tr>
<td>PRA, ng Ang (mL)/h</td>
<td>7.10±1.27</td>
<td>1.49±0.39†</td>
<td>3.98±0.51</td>
<td>0.71±0.09†</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>339±35</td>
<td>229±20*</td>
<td>288±15</td>
<td>198±13*</td>
</tr>
</tbody>
</table>

MBP indicates mean blood pressure; a, ambulatory; lo, laboratory observer; id, laboratory Dinamap; HR, heart rate; bpm, beats per minute; CO, cardiac output; TRS, total systemic resistance; uNa*, 24-hour urine Na+; Zc, thoracic impedance; Hct, hematocrit; TP, total serum protein; Ins, insulin; t, fasting; Gluc, glucose; AUC, area under the curve; PRA, plasma renin activity; Ang I, angiotensin I; and NE, plasma norepinephrine. Data are mean±SEM.

*P<.05, †P<.01, ‡P<.001, low vs high salt, paired t test.
TABLE 2. Within-Group Comparisons of Selected Variables in Salt-Sensitive and Salt-Resistant Obese Hypertensive Subjects on Low and High NaCl

<table>
<thead>
<tr>
<th>Variable</th>
<th>Salt-Sensitive (n=6)</th>
<th>Salt-Resistant (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Salt</td>
<td>High Salt</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>94±2</td>
<td>102±4*</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>135±3</td>
<td>143±4</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>88±3</td>
<td>91±4</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>103±2</td>
<td>108±3</td>
</tr>
<tr>
<td>MBP, mm Hg</td>
<td>93±2</td>
<td>96±3</td>
</tr>
<tr>
<td>HR, bpm</td>
<td>69±4</td>
<td>62±4*</td>
</tr>
<tr>
<td>CO, L/min</td>
<td>6.2±0.4</td>
<td>6.8±0.5</td>
</tr>
<tr>
<td>TSR, U</td>
<td>15.4±0.7</td>
<td>15.1±1.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>107.3±6.4</td>
<td>108.7±6.2*</td>
</tr>
<tr>
<td>uNa+, mEq/d</td>
<td>19±4</td>
<td>189±27†</td>
</tr>
<tr>
<td>Z, Ω</td>
<td>22.2±1.6</td>
<td>20.1±1.0*</td>
</tr>
<tr>
<td>Hct, %</td>
<td>43±1</td>
<td>40±1*</td>
</tr>
<tr>
<td>TP, gl/dL</td>
<td>7.2±0.1</td>
<td>6.6±0.2†</td>
</tr>
<tr>
<td>Ins, µU/mL</td>
<td>18.4±2.7</td>
<td>13.1±1.9‡</td>
</tr>
<tr>
<td>Gluoc, mg/dL</td>
<td>102±5</td>
<td>97±3‡</td>
</tr>
<tr>
<td>InsAUC, µU-min/dL</td>
<td>14.6±1.8</td>
<td>10.6±1.5‡</td>
</tr>
<tr>
<td>GluAUC, g-min/dL</td>
<td>18.4±0.9</td>
<td>17.9±0.9</td>
</tr>
<tr>
<td>PRA, (ng Ang l/mL)/h</td>
<td>5.94±1.75</td>
<td>2.17±1.17*</td>
</tr>
<tr>
<td>NE, pg/mL</td>
<td>371±79</td>
<td>271±53‡</td>
</tr>
</tbody>
</table>

MBP indicates mean blood pressure; a, ambulatory; SBP, systolic blood pressure; lo, laboratory observer; DBP, diastolic blood pressure; id, laboratory Dinamap; HR, heart rate; bpm, beats per minute; CO, cardiac output; TSR, total systemic resistance; uNa+, 24-hour urine Na+; Z, thoracic impedance; Hct, hematocrit; TP, total serum protein; Ins, insulin; f, fasting; Gluc, glucose; AUC, area under the curve; PRA, plasma renin activity; Ang I, angiotensin I; and NE, plasma norepinephrine. Data are mean±SEM.

*P< .05, †P< .01, ‡P< .001, low vs high salt, paired t test.

SR obese hypertensive subjects on either the high or low NaCl diet. Moreover, the obese hypertensive group, despite higher plasma insulin concentrations, was not more salt sensitive than the lean group.

Although insulin levels were similar in obese SS and SR hypertensive subjects, the hemodynamic responses during the insulin tolerance test diverged during the high NaCl diet, with increases of cardiac output in SS subjects and elevations of calf blood flow in SR subjects (Fig 1). The insulin and glucose AUC values during the insulin tolerance test were nearly identical in the two groups. Moreover, the modest hypoglycemia was not sufficient to induce a significant rise of plasma catecholamines in either group. The differences in the acute hemodynamic response to an equivalent hyperinsulinemic stimulus may serve as a marker for pathophysiological differences underlying the abnormal adjustment of vascular resistance to dietary NaCl in SS versus SR subjects. For example, the vascular actions of insulin appear to be mediated in part by β-receptors,21 perhaps by enhancing the cyclic AMP response to β-agonists.22 A high versus low salt diet decreases both the number of high-affinity β-receptors on lymphocytes and the regional vasodilator response to isoproterenol in hypertensive subjects but has the opposite effect in normotensive subjects.23 The impaired response of calf blood flow to acute hyperinsulinemia in obese SS subjects may also reflect abnormalities in endothelium-dependent vasodilation that could affect the hemodynamic actions of insulin.24

Insulin levels were not different in obese SS versus SR subjects and declined similarly during high versus low NaCl. Although these data contrast with the report of Sharma et al,12 the findings coincide with our previous

Fig 1. Plot shows ambulatory mean blood pressure (MBP) vs 24-hour urine sodium excretion for both salt-sensitive (SS) (○) and salt-resistant (SR) (●) obese hypertensive subjects on low and high NaCl diets.
Egan et al. Insulin and Salt Sensitivity in Obese Hypertensive Subjects

Fig 2. Top, Bar graphs show cumulative changes of cardiac output (CO) and calf blood flow (CBF) from baseline vs measurements at 3, 6, 9, 12, and 15 minutes after 0.1 U/kg IV insulin for obese salt-sensitive (SS), obese salt-resistant (SR), and lean volunteers. Data are provided for both low (open bars) and high (cross-hatched bars) salt diets. *Significant ($P<.05$) change in that variable from baseline values on the same diet. Bottom, Line graphs show values for glucose and insulin at baseline and throughout insulin tolerance test for obese SS, obese SR, and lean volunteers. High vs low NaCl diet did not significantly alter glucose or insulin values during insulin tolerance test within any of the three groups.

observations.$^{13}$ Lower insulin levels during high versus low NaCl were observed in another study of SS adult hypertensive subjects.$^{25}$ The explanation for the contrasting effects of dietary NaCl intake on insulin values is not known but may be explained by differences in subject selection, because the study by Sharma et al.$^{12}$ included only young normotensive subjects.

The data suggesting that hyperinsulinemia is not directly responsible for salt sensitivity in obese hypertensive subjects (Tables 1 and 2) agree with studies by Hall et al.$^{26}$ This group could not induce SS hypertension in normal dogs or exacerbate hypertension in reduced renal mass or angiotensin-infused dogs with 1 month of euglycemic hyperinsulinemia and high NaCl diets. Rocchini and colleagues$^{11}$ found that plasma insulin concentrations coincided with the amount of volume retention and the rise of BP in obese children on high versus low NaCl diets.$^{11}$ The hyperinsulinemia and SS in obese children resolved with weight loss.$^{27}$

Insulin has some actions that could raise BP, whereas other effects could lower BP.$^{28}$ Resistance to the vaso-depressor actions of insulin may be essential to the expression of its pressor effects. If correct, then normal dogs would remain sensitive to the multiple actions of insulin with no net effect on BP.$^{26}$ Insulin-resistant children may be less responsive to the depressor actions of insulin, thereby favoring its pressor effects, including sodium retention$^{11}$ and sympathetic activation.$^{8-10}$ However, in our study the SS and SR obese hypertensive groups had nearly identical insulin values, suggesting similar degrees of insulin resistance.$^{39}$ Differences in the ages of volunteers and duration of NaCl restriction may contribute to the divergent findings.

The SS and SR subgroups had similar increases of weight and other indexes of volume expansion measured on isocaloric diets after an overnight fast and voiding. Dahl SS and SR rats also have similar sodium retention on high versus low salt diets.$^{30}$ However, a rise in BP induces a pressure natriuresis.$^{30}$ Thus, the quantitatively normal volume expansion during the high NaCl diet in the SS subset indicates a disturbed pressure-volume relation (Fig 1).

Plasma norepinephrine declined significantly during high versus low salt in both the SS and SR obese hypertensive subjects. Mean values for heart rate also tended to fall similarly in both groups. Thus, reduction in these indexes of sympathetic drive with NaCl loading does not distinguish between the SS and SR subsets. Some evidence indicates that the normal reduction of sympathetic activity during high NaCl is impaired in SS subjects.$^{6}$ Potential explanations for the dichotomous results include limitations of plasma norepinephrine as an index of sympathetic nerve activity,$^{8}$ differences in study design, and variations in demographic characteristics.

Although the “window” demarcating the SS and SR obese hypertensive subjects was only 3 mm Hg, the
average difference between the two groups for the change of MBP during high versus low NaCl diets was 15 mm Hg. Unfortunately, established standards do not exist for defining SS status in clinical studies.33 The lack of standardization reflects in part the continuous rather than dichotomous BP responses to salt. Of note, a constant sequence of 1 week on low salt followed by 1 week on high salt has been suggested for assessing SS status.31 In fact, several well-known studies used the fixed-sequence approach.32–36 Although the constant sequence of low and high salt diets has the potential for an order effect, this design ensures that the SS and SR subgroups received the same dietary sequence. The absence of standards for determining salt sensitivity also extends to multiple aspects of the BP data. For example, criteria have not been established on the use of automated versus observer measurements; clinic (laboratory) versus ambulatory data; the selection of systolic, diastolic, or MBP; or the difference in BP between the high and low NaCl diet that constitutes salt sensitivity. Ideally, all of these different conditions would consistently identify the same individuals as either SS or SR. One report indicates that salt sensitivity based on laboratory BP data was not apparent when the ambulatory data from these same individuals were examined.37

To our knowledge, this is the first study to provide ambulatory and laboratory BP data as well as both automated and observer-measured BP in the laboratory setting with subjects on high and low NaCl diets. Although the variability of BP outside the controlled environment of the laboratory is greater, one BP reading per hour provides a reliable estimate of the 24-hour MBP obtained from intra-aerial monitoring.38 The volunteers in our study had multiple BP measurements each hour. Consequently, the estimate of MBP over 24 hours probably represents their actual MBP. Ambulatory BPs appear to be more reproducible than clinic (laboratory) BPs.39 The changes of observer-measured MBP in the laboratory during high versus low NaCl diets within the SS and SR subsets, although not statistically significant, were directionally similar to the changes in ambulatory MBP. The difference in MBP calculated from the observer BP data on the high minus low NaCl diet was significantly different between the SS and SR subgroups.

In summary, the SS and SR subgroups probably represent distinct physiological subsets characterized by a differential adjustment of vascular resistance in response to a similar volume expansion. Differences in the hemodynamic response to acute hyperinsulinemia in SS versus SR subjects may serve as a marker for mechanisms underlying the maladjustment of vascular resistance to a high NaCl diet in SS individuals.

Acknowledgments

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References

7. Egan BM, Petrin J, Hoffmann RG. NaCl induces differential changes of MBP, systolic, diastolic, or MBP; or the difference in BP between the high and low NaCl diet that constitutes salt sensitivity. Ideally, all of these different conditions would consistently identify the same individuals as either SS or SR. One report indicates that salt sensitivity based on laboratory BP data was not apparent when the ambulatory data from these same individuals were examined.37

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7. Egan BM, Petrin J, Hoffmann RG. NaCl induces differential changes of MBP, systolic, diastolic, or MBP; or the difference in BP between the high and low NaCl diet that constitutes salt sensitivity. Ideally, all of these different conditions would consistently identify the same individuals as either SS or SR. One report indicates that salt sensitivity based on laboratory BP data was not apparent when the ambulatory data from these same individuals were examined.37

To our knowledge, this is the first study to provide ambulatory and laboratory BP data as well as both automated and observer-measured BP in the laboratory setting with subjects on high and low NaCl diets. Although the variability of BP outside the controlled environment of the laboratory is greater, one BP reading per hour provides a reliable estimate of the 24-hour MBP obtained from intra-aerial monitoring.38 The volunteers in our study had multiple BP measurements each hour. Consequently, the estimate of MBP over 24 hours probably represents their actual MBP. Ambulatory BPs appear to be more reproducible than clinic (laboratory) BPs.39 The changes of observer-measured MBP in the laboratory during high versus low NaCl diets within the SS and SR subsets, although not statistically significant, were directionally similar to the changes in ambulatory MBP. The difference in MBP calculated from the observer BP data on the high minus low NaCl diet was significantly different between the SS and SR subgroups.

In summary, the SS and SR subgroups probably represent distinct physiological subsets characterized by a differential adjustment of vascular resistance in response to a similar volume expansion. Differences in the hemodynamic response to acute hyperinsulinemia in SS versus SR subjects may serve as a marker for mechanisms underlying the maladjustment of vascular resistance to a high NaCl diet in SS individuals.

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