Clustering of Endothelial Markers of Vascular Damage in Human Salt-Sensitive Hypertension

Influence of Dietary Sodium Load and Depletion

Claudio Ferri, Cesare Bellini, Giovambattista Desideri, Elisabetta Giuliani, Luca De Siati, Sabrina Cicogna, Anna Santucci

Abstract—The contributing role of vascular endothelium in the development of hypertension-related vascular damage is well accepted. Salt-sensitive hypertension is characterized by a cluster of renal, hormonal, and metabolic derangements that might favor the development of cardiovascular and renal damage. To evaluate endothelial involvement in salt-sensitive essential hypertension, plasma levels of several markers of endothelial damage such as endothelin-1 (ET-1), von Willebrand factor (vWF), and soluble (S-) adhesion molecules E-selectin, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and 24-hour urinary albumin excretion (UAE) were measured in 39 nondiabetic, nonobese, never-treated essential hypertensive patients after intermediate (120 mmol/d), high (220 mmol/d), and low (20 mmol/d) NaCl diets. Patients were classified as salt sensitive (n = 18) or salt resistant (n = 21) according to their blood pressure responses to changes in dietary NaCl intake. Salt-sensitive hypertensives showed higher plasma ET-1 (P < 0.05), vWF (P < 0.005), and S-E-selectin levels (P < 0.04) and increased UAE (P < 0.05) than salt-resistant hypertensives. By contrast, circulating S-ICAM-1 and S-VCAM-1 concentrations were not significantly higher in salt-sensitive (596.56 ± 177.05 ng/mL and 541.06 ± 157.84 ng/mL, respectively) than salt-resistant patients (516.86 ± 147.99 ng/mL and 449.48 ± 158.91 ng/mL, respectively). During the intermediate NaCl diet, plasma ET-1 responses to oral glucose load were greater in salt-sensitive (P < 0.05) than in salt-resistant patients. A marked (P < 0.05) hyperinsulenicemic response to oral glucose load was evident in salt-sensitive but not salt-resistant patients after each diet. This study shows increased plasma levels of the endothelium-derived substances E-selectin, vWF, and ET-1 in salt-sensitive hypertensives. Our findings support the hypothesis that salt sensitivity is correlated with an increased risk for developing hypertension-related cardiovascular damage. (Hypertension. 1998;32:862-868.)

Key Words: endothelium ■ cell adhesion molecules ■ vasorelaxation ■ sodium ■ blood pressure

Salt-sensitive hypertension is characterized by a cluster of renal, hormonal, and metabolic derangements that might favor the development of cardiovascular and renal complications. In this regard, the vascular endothelium modulates platelet aggregation, adhesion molecule expression, and vascular smooth muscle cell replication, all of which contribute to atherogenesis. Interestingly, salt-sensitive hypertension is characterized by impaired endothelium-dependent vasorelaxation. Furthermore, circulating levels of the endothelial-derived peptide endothelin-1 (ET-1) are higher, while urinary ET-1 excretion is lower and more responsive to salt loading in salt-sensitive than salt-resistant patients. Urinary albumin excretion (UAE), a well-known marker of vascular damage, is associated with high plasma levels of von Willebrand factor (vWF), a glycoprotein released by damaged vascular endothelial cells. Since UAE is higher in salt-sensitive than salt-resistant hypertensives, this abnormality further suggests that hypertension-related endothelial damage is more marked in salt-sensitive than salt-resistant individuals.

To elucidate the involvement of vascular endothelium in human salt-sensitive hypertension, plasma levels of several markers of endothelial damage, ie, ET-1, vWF, and soluble (S-) adhesion molecules E-selectin, ICAM-1, intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1 (VCAM-1), and UAE were measured in uncomplicated, nondiabetic, nonobese, never-treated essential hypertensives. Since glucose ingestion is known to modulate ET-1 and S-ICAM-1 release, all measurements were repeated after an oral glucose tolerance test. Because of interrelations among accelerated erythrocyte Na+/Li+ countertransport, cardiovascular and renal damage, and metabolic disturbances, activity of this Na+ transporter and lipid profile were also assessed. Evaluations were made after an intermediate, a low,
pressure levels were concomitant diseases or was on treatment with any drug. Blood Na\(^+\) 125 g/m\(^2\). 17 All patients were white nonsmokers. No patient had maladies, including myocardial hypertrophy (left ventricular mass echocardiograms allowed us to exclude patients with cardiac abnormalities, including myocardial hypertrophy (left ventricular mass <1.5 mmol/L and <5.8 mmol/L, respectively. Echo-Doppler examinations of limb and neck vessels excluded atherosclerotic lesions. M-mode and B-mode echocardiograms were performed at 1-week intervals. Family histories of hypertension and myocardial infarction were also evaluated, as already described. 16 Four patients were noncompliant, and 2 patients were lost during the above diet, 5 patients were noncompliant and were eliminated from the study group. The remaining 46 patients were randomly, double-blindly assigned to a high (220 mmol NaCl per day) or a low NaCl per day diet, without change in the other diet components. A daily supplement of 10 capsules containing 10 mmol NaCl each was given to all subjects to obtain 120 mmol NaCl per day. After 1 week on the above diet, 5 patients were noncompliant and were eliminated from the study group. The remaining 46 patients were randomly, double-blindly assigned to a high (220 mmol NaCl per day) or a low (20 mmol NaCl per day) NaCl intake for 2 weeks. Different NaCl diets were obtained by changing the NaCl contents of capsules, ie, 0 mmol on the low and 20 mmol on the high NaCl intake. Patients were considered compliant when Na\(^+\) excretion varied from low to high NaCl intake. Eight healthy subjects without family histories of hypertension or myocardial infarction served as controls.

**Methods**

The study was conducted in 76 never-treated essential hypertensive outpatients (age, 47.1 5.7 years), some of whom had participated in previous studies by our group. 5,7 Entry criteria were as follows: 5,7,15 age >25 and <60 years, body mass index <27 kg/m\(^2\), normal glucose tolerance and renal function, absence of macroproteinaemia, and serum triglycerides and total cholesterol <1.5 mmol/L and <5.8 mmol/L, respectively. Echo-Doppler examinations of limb and neck vessels excluded atherosclerotic lesions. M-mode and B-mode echocardiograms allowed us to exclude patients with cardiac abnormalities, including myocardial hypertrophy (left ventricular mass >125 g/m\(^2\)). 17 All patients were white nonsmokers. No patient had concomitant diseases or was on treatment with any drug. Blood pressure levels were >160/95 and <180/114 mm Hg at 4 visits performed at 1-week intervals. Family histories of hypertension and myocardial infarction were also evaluated, as already described. 16 Eleven patients were excluded for doubtful responses. The remaining 65 patients were given an isocoric diet with constant NaCl intake for 2 weeks. Diet was composed of ~50% carbohydrate, 20% fat, and 30% protein and was controlled for NaCl (120 mmol/d), Ca\(^2+\) (20 mmol/d), Mg\(^2+\) (10 mmol/d), and K\(^+\) (60 mmol/d). We required that Na\(^+\) excretion be >80 and <130 mmol/24 h. Eight patients were considered noncompliant, and the remaining 57 were admitted to the clinic for assessment of plasma glucose, insulin, ET-1, S-E-selectin, S-ICAM-1, S-VCAM-1, and vWF levels at baseline and after oral glucose load (75 g). On the same occasion, triceps, subscapular, and iliac skinfold thicknesses were evaluated by a skinfold caliper.

**TABLE 1. General Characteristics of Study Population**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normotensives</th>
<th>All</th>
<th>Salt Sensitive</th>
<th>Salt Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>8</td>
<td>39</td>
<td>18</td>
<td>21</td>
</tr>
<tr>
<td>Age, y</td>
<td>43.8 6.9</td>
<td>46.1 4.5</td>
<td>47.3 4.8</td>
<td>44.9 5.1</td>
</tr>
<tr>
<td>Family history of hypertension</td>
<td>...</td>
<td>20</td>
<td>13*</td>
<td>7</td>
</tr>
<tr>
<td>Family history of MI</td>
<td>...</td>
<td>15</td>
<td>11*</td>
<td>4</td>
</tr>
<tr>
<td>Body mass index, kg/m(^2)</td>
<td>23.9 1.0</td>
<td>25.1 1.2§</td>
<td>26.4 0.8¶</td>
<td>23.8 1.2</td>
</tr>
<tr>
<td>Waist/hip</td>
<td>0.87±0.04</td>
<td>0.91±0.05§</td>
<td>0.94±0.05¶</td>
<td>0.88±0.06</td>
</tr>
<tr>
<td>Subscapular skinfold thickness, mm</td>
<td>14.8±5.6</td>
<td>22.7±7.4§</td>
<td>26.0±7.1‡</td>
<td>19.6±6.8</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>134.3±8.1†</td>
<td>154.3±6.6</td>
<td>156.0±6.6</td>
<td>152.8±6.2</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>77.6±2.4‡</td>
<td>106.5±3.2</td>
<td>107.7±3.3</td>
<td>105.5±2.8</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.69±0.58</td>
<td>5.10±0.72</td>
<td>5.18±0.56</td>
<td>5.01±0.67</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.75±0.33</td>
<td>1.38±0.45§</td>
<td>1.20±0.44§</td>
<td>1.55±0.51</td>
</tr>
<tr>
<td>LDL cholesterol, mmol/L</td>
<td>2.73±0.58</td>
<td>3.45±0.72§</td>
<td>3.68±0.69§</td>
<td>3.21±0.73</td>
</tr>
<tr>
<td>VLDL cholesterol, mmol/L</td>
<td>0.22±0.08</td>
<td>0.28±0.12</td>
<td>0.31±0.13</td>
<td>0.24±0.13</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>0.95±0.21</td>
<td>1.12±0.37</td>
<td>1.27±0.12</td>
<td>0.98±0.15</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.68±0.41</td>
<td>4.93±0.37</td>
<td>5.05±0.48</td>
<td>4.83±0.71</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>75.2±18.9</td>
<td>100.2±31.5§</td>
<td>103.7±28.6§</td>
<td>96.8±25.1</td>
</tr>
<tr>
<td>HbA(_1c), %</td>
<td>5.64±1.09</td>
<td>6.36±1.23</td>
<td>6.51±1.25</td>
<td>6.22±1.24</td>
</tr>
<tr>
<td>Na(^+)/(L, countertransport, μmol/(L·h))</td>
<td>319.4±168.3†</td>
<td>618.5±140.9</td>
<td>657.1±110.2*</td>
<td>580.9±119.8</td>
</tr>
<tr>
<td>Na(^+)/K(^+)-ATPase, mmol/(L·h)</td>
<td>5.31±2.23</td>
<td>4.58±1.07</td>
<td>4.95±1.65</td>
<td>4.29±1.02</td>
</tr>
<tr>
<td>Na(^+)/K(^+)/2Cl(^-) cotransport, μmol/(L·h)</td>
<td>282.3±102.4</td>
<td>481.2±132.4§</td>
<td>571.6±120.3*§</td>
<td>389.8±131.4</td>
</tr>
</tbody>
</table>

*P<0.05 vs salt-resistant hypertensives. †P<0.001 vs other groups. §P<0.001 vs normotensives and salt-sensitive hypertensives. ¶P<0.02 vs normotensives.

and a high NaCl intake according to a random, double-blind, crossover protocol.

**Dietary NaCl Intervention Study**

Four patients were noncompliant, and 2 patients were lost during the above period. In the remaining 51 patients, salt sensitivity was assessed according to a random, double-blind, crossover protocol, as already described. 7,18 Briefly, each patient was given a 20-mmol NaCl per day diet, without change in the other diet components. A daily supplement of 10 capsules containing 10 mmol NaCl each was given to all subjects to obtain 120 mmol NaCl per day. After 1 week on the above diet, 5 patients were noncompliant and were eliminated from the study group. The remaining 46 patients were randomly, double-blindly assigned to a high (220 mmol NaCl per day) or a low (20 mmol NaCl per day) NaCl intake for 2 weeks. Different NaCl diets were obtained by changing the NaCl contents of capsules, ie, 0 mmol on the low and 20 mmol on the high NaCl intake. Patients were considered compliant when Na\(^+\) excretion was >200 and <30 mmol/24 h in urine collections obtained during the high and the low Na\(^+\) intake, respectively. Four patients were noncompliant, 2 were lost, and 1 reported gastric pain. Thus, salt sensitivity was assessed in 39 patients. UAE was measured on 24-hour urine collections used for assessing compliance to the diet. A patient was classified as salt sensitive when mean blood pressure varied ≥10 mm Hg from low to high NaCl intake. Eight healthy subjects without family histories of hypertension or myocardial infarction served as controls.

**Laboratory Measurements**

Plasma ET-1 levels were assessed by reverse-phase high-performance liquid chromatography followed by radioimmunoassay (Peninsula Laboratories). 15 Plasma vWF (Boehringer Mannheim Co), S-E-selectin (R & D Systems), S-ICAM-1 (Genzyme Diagnostics), and S-VCAM-1 (R & D) were assessed by immunoenzymatic...
methods. Insulin was assayed by radioimmunoassay (Ares Serono). Serum HDL cholesterol levels were assessed by enzymatic methods (Boehringer Mannheim), and LDL and VLDL cholesterol levels were assessed by the method of Friedewald et al.20 Erythrocyte Na\(^{+}\)/Li\(^{+}\) cotransport activities were tested as already described.20 UAE was evaluated by nephelometry.

Statistical Analysis
Differences among groups were tested for significance by 1-way ANOVA followed by post hoc analysis. Linear regression and correlation tested relations among variables. The \(\chi^2\) method tested descriptive parameters. Areas under the curve were calculated by trapezoidal integration. Statistical significance was assumed at \(P<0.05\). Data are given as mean\(\pm\)SD.

Results
Body mass index, waist-to-hip ratio, subcapular skinfold thickness, fasting insulin levels, erythrocyte Na\(^{+}/\)Li\(^{+}\) countertransport, and Na\(^{+}/K^{+}/2Cl^{-}\) cotransport activities were higher in hypertensives than in controls (Table 1). Moreover, a dyslipidemic pattern was shown by hypertensives (Table 1). Plasma vWF (hypertensives, 1.42\(\pm\)0.50 kU/L; controls, 1.04\(\pm\)0.12 kU/L) \((P=0.04)\) and S-E-selectin levels (hypertensives, 0.98\(\pm\)0.32 \(\mu\)g/L; controls, 0.67\(\pm\)0.36 \(\mu\)g/L) \((P=0.018)\) were higher in hypertensives than controls, while no differences were found for ET-1 (hypertensives, 1.30\(\pm\)0.75 pg/mL; controls, 0.76\(\pm\)0.40 pg/mL) \((P=NS)\), S-ICAM-1 (hypertensives, 553.6\(\pm\)164.8 ng/mL; controls, 491.9\(\pm\)130.7 ng/mL) \((P=NS)\), and S-VCAM-1 levels (hypertensives, 491.7\(\pm\)163.0 ng/mL; controls, 426.2\(\pm\)102.1 ng/mL) \((P=NS)\).
ng/mL ($P$=NS). UAE was higher ($P$=0.0001) in hypertensives (20.87±2.52 $\mu$g/min) than controls (15.96±2.72 $\mu$g/min). Plasma soluble adhesion molecule, vWF, and ET-1 levels were unrelated to all other variables. UAE correlated with diastolic ($r$=0.587, $P$=0.0001) and systolic ($r$=0.529, $P$=0.0001) pressure in hypertensives.

**Baseline Comparison Between Salt-Sensitive and Salt-Resistant Hypertensives**

Eighteen hypertensives were classified as salt sensitive and 21 as salt resistant. Salt-sensitive patients showed a more frequent family history of hypertension and myocardial infarction and higher body mass index, subscapular skinfold thickness, and waist-to-hip ratio than salt-resistant patients (Table 1). LDL cholesterol level was higher, while HDL cholesterol was lower in salt-sensitive than salt-resistant patients (Table 1). Postload insulin levels were higher in the first than in the second group (Figure 1). Insulin and glucose areas under the curve were greater in salt-sensitive than salt-resistant patients (Figures 1 and 2). Plasma ET-1 ($P$<0.05), vWF ($P$<0.004), and S-E-selectin ($P$=0.04) levels and UAE ($P$=0.04) were higher in salt-sensitive (ET-1, 1.56±0.85 pg/mL; vWF, 1.66±0.51 kU/L; S-E-selectin, 1.09±0.31 $\mu$g/L; UAE, 21.77±2.80 $\mu$g/min) than salt-resistant patients (ET-1, 1.08±0.56 pg/mL; vWF, 1.21±0.40 kU/L; S-E-selectin, 0.88±0.29 $\mu$g/L; UAE, 20.09±2.01 $\mu$g/min). Plasma S-ICAM-1 and S-VCAM-1 levels were similar in the 2 subgroups: S-ICAM-1 (ng/mL): salt sensitive, 596.6±177.1; salt resistant, 516.9±147.9, $P$=NS; S-VCAM-1
(ng/mL): salt sensitive, 541.1±157.8; salt resistant, 449.5±158.9. Na⁺/K⁺/2Cl⁻ cotransport and Na⁺/Li⁺ countertransport activities were higher in salt-sensitive than salt-resistant patients (Table 1). Blood pressure levels were unrelated to soluble adhesion molecule, vWf, or ET-1 concentrations in both patient groups, whereas significant correlations between UAE and blood pressure levels were observable in salt-sensitive (systolic: r=0.586, P<0.001) and salt-resistant patients (systolic: r=0.481, P=0.027; diastolic: r=0.464, P=0.034). Circulating ET-1 levels correlated with plasma vWf concentrations and Na⁺/Li⁺ countertransport activity (Figure 3), while plasma S-E-selectin correlated with vWf and ET-1 levels in salt-sensitive patients (Figure 4).

**Endothelium-Derived Substances and UAE Responses to NaCl Variations**

In salt-sensitive patients, changes in NaCl intake did not affect plasma S-ICAM-1, S-VCAM-1, and vWf levels, whereas they significantly influenced plasma ET-1 (intermediate, 1.56±0.85; low, 1.22±0.54; high NaCl diet, 1.78±0.63 pg/mL; P=0.002), and S-E-selectin levels (intermediate, 1.09±0.31; low, 0.91±0.35; high NaCl diet, 1.33±0.44 μg/L; P=0.02) and UAE (intermediate, 21.77±2.80; low, 19.66±2.37; high NaCl diet, 23.83±2.37 μg/min; P=0.02). In salt-resistant patients, changes in NaCl intake did not affect plasma vWf and S-E-selectin levels, whereas they influenced plasma S-ICAM-1 (intermediate, 516.86±147.99; low, 465.48±142.29; high NaCl diet, 597.38±233.40 ng/mL; P=0.03), S-VCAM-1 (intermediate, 449.48±158.91; low, 442.14±200.75; high NaCl diet, 539.33±168.06 ng/mL; P=0.02), and ET-1 levels (intermediate, 1.08±0.59; low, 1.12±0.57; high NaCl diet, 1.32±0.40 pg/mL; P=0.02) and UAE (intermediate, 20.09±2.01; low, 19.31±1.94; high NaCl diet, 20.56±2.70 μg/min; P<0.05 versus low). UAE correlated with blood pressure levels in salt-sensitive (high NaCl, systolic: r=0.486, P=0.041; diastolic: r=0.510, P=0.031; low NaCl, systolic: r=0.480, P=0.044; diastolic: r=0.516, P=0.031) and salt-resistant patients (high NaCl, systolic: r=0.481, P=0.028; diastolic: r=0.461, P=0.028; low NaCl, systolic: r=0.523, P=0.015; diastolic: r=0.453, P=0.039).

**Responses of Endothelium-Derived Substances to Oral Glucose Load During Different NaCl Diets**

After the intermediate NaCl diet, oral glucose load induced significant plasma ET-1 increments in salt-sensitive (from 1.56±0.85 to 2.34±0.87 after 120 minutes; P<0.05 versus baseline and P<0.05 versus salt-resistant patients) but not salt-resistant patients. Plasma levels of other endothelium-derived substances were not affected by the glucose challenge on all NaCl diets.

**Metabolic Parameters and Na⁺ Transporters During Low and High NaCl Diets**

The “atherogenic” pattern of circulating lipoproteins observed after the baseline diet was more evident after NaCl loading in salt-sensitive patients (Table 2). In the same subgroup, marked hyperinsulinemic responses to oral glucose load were more evident after the high than the low NaCl diet (Figure 1). Activities of Na⁺/K⁺/2Cl⁻ cotransport and Na⁺/Li⁺ countertransport during the low and the high NaCl diets are shown in Table 3.

**Discussion**

This study demonstrates that circulating levels of S-E-selectin, ET-1, vWf, and UAE are higher in salt-sensitive than salt-resistant essential hypertensive men. By contrast, circulating S-ICAM-1 and S-VCAM-1 levels were similar between the 2 groups.

The increased levels of circulating substances that have been indicated as markers for vascular damage strongly support the hypothesis that salt-sensitive hypertensives are a subset at increased risk for developing hypertension-related cardiovascular diseases. Accordingly, we confirmed that the V_m, of Na⁺/Li⁺ countertransport, a well-known marker of hypertension-related renal abnormalities and insulin resistance, was higher in salt-sensitive than salt-resistant patients. Similarly, we confirmed that salt-sensitive hypertensives tended to be hyperlipemic and displayed the greatest insulin responses to oral glucose load on all diets, particularly on the high NaCl diet.

To further support our hypothesis, a positive family history for myocardial infarction was more frequent in salt-sensitive than salt-resistant patients. Although a family history of

| TABLE 2. Plasma Lipids Modifications After Dietary NaCl Intake Variations in Study Population |
|-----------------------------------------------|----------------|----------------|----------------|
|                                               | Hypertensives  | Salt Resistant | Controls       |
| High NaCl intake                              |                |                |                |
| Total cholesterol                             | 5.23±0.61      | 5.04±0.65      | 4.68±0.63      |
| HDL cholesterol                               | 1.23±0.53      | 1.61±0.56      | 1.76±0.41      |
| LDL cholesterol                               | 3.68±0.92*     | 3.23±0.81      | 2.71±0.64      |
| VLDL cholesterol                              | 0.33±0.11†     | 0.20±0.12      | 0.21±0.09      |
| Triglycerides                                 | 1.54±0.18§     | 1.11±0.23      | 1.01±0.32      |
| Intermediate NaCl intake                      |                |                |                |
| Total cholesterol                             | 5.18±0.56      | 5.01±0.67      | 4.69±0.58      |
| HDL cholesterol                               | 1.20±0.44†     | 1.55±0.51      | 1.75±0.33      |
| LDL cholesterol                               | 3.68±0.69‡     | 2.31±0.73      | 2.73±0.58      |
| VLDL cholesterol                              | 0.31±0.13      | 0.24±0.13      | 0.22±0.08      |
| Triglycerides                                 | 1.27±0.12      | 0.98±0.15      | 0.95±0.21‡     |
| Low NaCl intake                               |                |                |                |
| Total cholesterol                             | 5.21±0.58      | 5.09±0.63      | 4.63±0.71      |
| HDL cholesterol                               | 1.19±0.47      | 1.59±0.58      | 1.72±0.48      |
| LDL cholesterol                               | 3.73±0.88*     | 3.27±0.84      | 2.74±0.65      |
| VLDL cholesterol                              | 0.28±0.12      | 0.23±0.19      | 0.18±0.10      |
| Triglycerides                                 | 1.36±0.21      | 1.09±0.24      | 1.04±0.33‡     |

Values are millimoles per liter.

*P<0.05 vs controls.

†P<0.005 vs salt-resistant hypertensives.

‡P<0.002 vs other groups.

§P<0.001 vs other diets.
coronary artery disease does not imply per se that individual cardiovascular risk is increased, a familial clustering of hypertension and early myocardial infarction has recently been observed in unselected hypertensives, in salt-sensitive hypertensives with delayed renal and endocrine responses to saline infusion, and in non-modulators, a subset marked interaction with the natural ligand sialyl-Lewis x increased S-E-selectin expression by endothelial cells and lates leukocyte adhesion to the endothelium. Accordingly, and severe essential hypertensives.

Thus, these findings S-E-selectin and vWf levels were directly correlated in mild hypertension-related vascular damage. Moreover, plasma S-ICAM-1 and S-VCAM-1 in glucose-intolerant essential hypertensives. Thus, different signal mechanisms could activate selectins but not cellular adhesion molecules in essential hypertension. Consistently, plasma S-E-selectin but not S-ICAM-1 and S-VCAM-1 levels increased with high NaCl diet in salt-sensitive patients.

Another interesting result is the ET-1 increments observed after oral glucose load in salt-sensitive patients. This finding could be due to the stimulatory action of insulin on ET-1 release and suggests that ET-1 favors insulin resistance in salt-sensitive individuals. Indeed, insulin-mediated glucose uptake is also due to endothelium-dependent vasorelaxation. Thus, insulin-related ET-1 increase could counteract the vasodilatory action of insulin. Accordingly, a negative correlation between insulin-stimulated glucose uptake and plasma ET-1 levels has been demonstrated in type 2 diabetics.

With regard to the elevated activities of Na+/K+/2Cl⁻ cotransport and Na+/Li⁺ countertransport in salt-sensitive patients, similar data were previously obtained in such patients. Overactivity of Na+/K+/2Cl⁻ cotransport was increased by a high NaCl diet, thereby indicating that this Na⁺ transporter could affect individual pressor susceptibility to “inappropriate” NaCl intake. Data from Milan hypertensive rats and essential hypertensives suggest that the elevated V̇max of Na+/K+/2Cl⁻ cotransport reflects its elevated activity at the renal tubular level, which in turn enhances Na⁺ reabsorption and pressor sensitivity to NaCl intake. Similarly, the increased V̇max of Na+/Li⁺ countertransport, which represents the in vitro mode of operation of Na⁺/H⁺ antiport, could be present in vascular smooth muscle and renal tubular cells and lead to hypertension by increasing contractility and Na⁺ reabsorption.

In conclusion, we demonstrated increased circulating S-E-selectin, vWf, and ET-1 levels and UAE in salt-sensitive hypertensives. These patients also displayed increased insulin responses to oral glucose load, elevated circulating LDL cholesterol levels, and accelerated V̇max of Na+/Li⁺ counter-

### TABLE 3. Erythrocyte Sodium Transport Systems Modifications During Dietary NaCl Intake

<table>
<thead>
<tr>
<th>Variations in Study Population</th>
<th>Hypertensives</th>
<th>Salt Sensitive</th>
<th>Salt Resistant</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High NaCl intake</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺/Li⁺ countertransport, μmol/(L · h)</td>
<td>672.3±161.3*</td>
<td>610.2±156.8*</td>
<td>402.9±151.4</td>
<td></td>
</tr>
<tr>
<td>Na⁺/K⁺-ATPase, mmol/(L · h)</td>
<td>4.71±1.02</td>
<td>4.32±1.49</td>
<td>4.96±2.84</td>
<td></td>
</tr>
<tr>
<td>Na⁺/K⁺/2Cl⁻ cotransport, μmol/(L · h)</td>
<td>612.9±118.2*†</td>
<td>437.8±124.5*</td>
<td>296.2±98.3</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate NaCl intake</strong></td>
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<td></td>
</tr>
<tr>
<td>Na⁺/Li⁺ countertransport, μmol/(L · h)</td>
<td>657.1±110.2†</td>
<td>580.9±119.8*</td>
<td>319.4±168.3</td>
<td></td>
</tr>
<tr>
<td>Na⁺/K⁺-ATPase, mmol/(L · h)</td>
<td>4.96±1.65</td>
<td>4.29±1.02</td>
<td>5.31±2.23</td>
<td></td>
</tr>
<tr>
<td>Na⁺/K⁺/2Cl⁻ cotransport, μmol/(L · h)</td>
<td>571.6±120.3†</td>
<td>389.8±131.4</td>
<td>282.3±102.4</td>
<td></td>
</tr>
<tr>
<td><strong>Low NaCl intake</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na⁺/Li⁺ countertransport, μmol/(L · h)</td>
<td>601.3±182.8*</td>
<td>604.7±166.7*</td>
<td>391.7±166.2</td>
<td></td>
</tr>
<tr>
<td>Na⁺/K⁺-ATPase, mmol/(L · h)</td>
<td>4.82±1.39</td>
<td>4.15±1.73</td>
<td>5.12±1.96</td>
<td></td>
</tr>
<tr>
<td>Na⁺/K⁺/2Cl⁻ cotransport, μmol/(L · h)</td>
<td>604.9±124.6†</td>
<td>412.3±118.6</td>
<td>302.2±118.3</td>
<td></td>
</tr>
</tbody>
</table>

*P<0.001 vs controls. †P<0.001 vs salt-resistant hypertensives.
transport. Our findings strongly support the hypothesis\(^1\) that an increased blood pressure sensitivity to NaCl intake is correlated with an elevated risk for developing cardiovascular and renal sequelae of hypertension.

**References**

Clustering of Endothelial Markers of Vascular Damage in Human Salt-Sensitive Hypertension: Influence of Dietary Sodium Load and Depletion
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