Sodium Sensitivity of Blood Pressure Appearing Before Hypertension and Related to Histological Damage in Immunoglobulin A Nephropathy

Yoshio Konishi, Noriyuki Okada, Mikio Okamura, Takashi Morikawa, Michiaki Okumura, Katsunobu Yoshioka, Masahito Imanishi

Abstract—Patients with renal parenchymal disease exhibit sodium-sensitive hypertension. We examined patients with immunoglobulin A (IgA) nephropathy to determine whether this sensitivity appears before hypertension begins and whether this sensitivity is related to histological damage. Thirty-eight patients with IgA nephropathy followed a diet with an ordinary sodium level for 1 week and a sodium-restricted diet for 1 week, in random order, and were divided into 3 groups by their systemic blood pressure on the diet with an ordinary sodium level (optimal, <120/<80 mm Hg, n=15; normal to high-normal, 120 to 139/80 to 89 mm Hg, n=18; hypertensive, ≥140/≥90 mm Hg, n=5). The sodium sensitivity index was calculated as the reciprocal of the slope of the pressure-natriuresis curve drawn by linkage of 2 datum points obtained during the different diets. The scores for glomerulosclerosis and tubulointerstitial damage were evaluated semiquantitatively. The sensitivity index, glomerulosclerosis score, and score for tubulointerstitial damage were higher in patients with normal to high-normal blood pressure or hypertension than in patients with optimal pressure. The sensitivity index was significantly correlated with glomerulosclerosis (P=0.001) and tubulointerstitial damage (P=0.002). In patients with normal to high-normal pressure, sodium restriction lowered blood pressure to the optimal range and decreased proteinuria. In patients with IgA nephropathy, sodium sensitivity of blood pressure related to renal histological damage appears before hypertension. (Hypertension. 2001;38:81-85.)

Key Words: sodium ■ glomerulonephritis, IgA ■ glomerulosclerosis ■ blood pressure ■ hypertension

Hypertension is a risk factor for cardiovascular disease. Lifestyle modifications, including restriction of sodium intake, can lower blood pressure. Such restriction is particularly effective for patients with sodium-sensitive hypertension. Patients with renal parenchymal disease, including immunoglobulin A (IgA) nephropathy, exhibit sodium-sensitive hypertension as renal dysfunction progresses, because sodium excretion by the kidneys decreases. It is not known, however, when the sodium-sensitive hypertension appears.

Sodium sensitivity of the blood pressure seems to be linked with glomerular capillary hydraulic pressure in 2 animal models; this phenomenon has been examined theoretically and clinically in investigations of the pressure-natriuresis relationship. Glomerular hypertension may worsen renal dysfunction in renal diseases, according to results of animal studies. The importance of glomerular hypertension in glomerulonephritis has been suggested by studies showing that angiotensin-converting enzyme inhibitors attenuate its progress. In humans, however, there is no direct evidence from measurement of glomerular capillary pressure about the role of glomerular hypertension.

Recently, it was established that the sodium sensitivity index (SSI), the reciprocal of the slope of the pressure-natriuresis curve, shows the sodium sensitivity of blood pressure, which seems to be related to glomerular capillary pressure. In this study, using SSI, we examined patients with IgA nephropathy to determine whether sodium sensitivity of blood pressure increases before hypertension begins and whether this sensitivity is related to renal histological damage.

Methods

Subjects
Thirty-eight Japanese inpatients with IgA nephropathy were studied; the 10 men and 28 women were aged 20 to 59 years. Twenty-three of these patients were described earlier. Histological diagnosis by renal biopsies was performed immediately before the study began. Patients with other renal disease or heart disease were excluded. All patients were informed of the purpose and methods of the study before consent was obtained, and the study was approved by an institutional ethical committee.

Study Protocol
Percutaneous renal biopsy was done for all patients. Before the study began, patients ate standard meals with ~10 g/d NaCl. The study
began after the patients' condition stabilized after the biopsy. Patients were put on a low-sodium diet (~5 g/d NaCl) or one with an ordinary sodium level (~12 g/d NaCl) for 1 week at each level, in random order, with no time intervening; their systemic blood pressure on the ordinary level of sodium was used for assignment into groups. Blood pressure of the group with optimal blood pressure (n=15) was <120 mm Hg (systolic) and <80 mm Hg (diastolic). Blood pressure of the normal to high-normal group (n=18) was 120 to 139 mm Hg (systolic) and 80 to 89 mm Hg (diastolic). Blood pressure of the hypertensive group (n=5) was ≥140 mm Hg (systolic) or ≥90 mm Hg (diastolic).

The 2 study diets contained the same amount of protein (1.2 g/kg body wt daily) and calories (35 kcal/kg daily). Patients were asked to maintain usual levels of physical activity and to refrain from drugs 1 week before and during the study. On each of the last 3 days of the 2 diets, 24-hour urine collection was performed, and the urine was assayed for sodium and protein. On the last day of each diet, a 24-hour record of blood pressure was taken with an automatic monitor by oscillometry (Ambulatory Blood Monitoring System, A&D Co) with hourly measurements. The mean arterial pressure (MAP) was calculated by addition of one third of the pulse pressure to the diastolic pressure, and the mean of these 24 values for each

### TABLE 2. Urinary Excretion of Protein and Urea Nitrogen, Systemic Blood Pressure, and Renal Function During Diets With an Ordinary or Low Sodium Level

<table>
<thead>
<tr>
<th>Renal and Other Results</th>
<th>Sodium Level</th>
<th>Optimal (&lt;120/80)</th>
<th>Normal to High-Normal (120–139/80–89)</th>
<th>Hypertensive (≥140/≥90 [either])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary excretion of protein, mg/d</td>
<td>Low</td>
<td>144 (76, 359)*</td>
<td>420 (318, 1148)*</td>
<td>1202 (992, 1359)*</td>
</tr>
<tr>
<td></td>
<td>Ordinary</td>
<td>312 (112, 395)*</td>
<td>640 (380, 1682)*</td>
<td>1944 (1227, 2104)*</td>
</tr>
<tr>
<td>Urinary excretion of urea nitrogen, mmol/d</td>
<td>Low</td>
<td>2313±467</td>
<td>2402±478</td>
<td>2409±310</td>
</tr>
<tr>
<td></td>
<td>Ordinary</td>
<td>2167±432</td>
<td>2349±521</td>
<td>2374±428</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>Low</td>
<td>107±7†</td>
<td>118±10†</td>
<td>128±8†</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>Low</td>
<td>69±6‡</td>
<td>77±7†</td>
<td>84±8‡</td>
</tr>
<tr>
<td>Creatinine clearance, mL/min</td>
<td>Low</td>
<td>118±14</td>
<td>103±27</td>
<td>104±15</td>
</tr>
<tr>
<td>Effective renal plasma flow, mL/min</td>
<td>Low</td>
<td>570±110</td>
<td>572±279</td>
<td>551±290</td>
</tr>
</tbody>
</table>

Values are mean±SD, except for urinary excretion of protein, given as median followed in parentheses by 25th and 75th percentiles. P values given in the body of the table are for differences in the same group on the 2 diets.
*P<0.05 among the 3 groups.
†P<0.05 between optimal and high-normal groups.
‡P<0.05 between optimal and hypertensive groups.
§P<0.05 between high-normal and hypertensive groups.
final day is given here. On the same day, the effective renal plasma flow and creatinine clearance were calculated by the standard clearance technique with para-aminophippurate and endogenous creatinine as markers. The renal clearance was standardized for a body surface area of 1.73 m². Patients are described in Table 1.

**Plotting of Pressure-Natriuresis Relationship and SSI**

Pressure-natriuresis curves were generated by plotting of urinary sodium excretion on the ordinate as a function of MAP on the abscissa. When a linear relation between them is assumed, a curve for a patient can be drawn by linkage of the 2 datum points obtained when the patient’s sodium balance is in a steady state during the 2 diets with different amounts of sodium. The SSI equals the reciprocal of the slope.

**Histological Study**

Sections of biopsy specimens were stained with periodic acid–Schiff or periodic acid–Schiff–methenamine silver. Biopsy specimens of all subjects had ≥10 glomeruli. All specimens were evaluated independently by 2 investigators unaware of the SSI of that patient. The severity of glomerulosclerosis and tubulointerstitial damage was evaluated semiquantitatively. The scoring for glomerulosclerosis was as described by our previous study. Individual glomeruli in biopsy specimens were examined, and the severity was graded from 0 to 4 to express the percentage of that glomerulus affected. Injury scores were then calculated by multiplication of this grade of 0 to 4 for individual glomeruli by the percentage of glomeruli with the same degree of injury. The severity of the injury for each tissue specimen was obtained by the addition of these injury scores. The severity of tubulointerstitial damage for each specimen was scored as the percentage of the area of the cortex affected by tubulointerstitial damage.

**Statistical Analysis**

Values are expressed as mean ± SD except for the urinary excretion of protein, scores for histological damage, and the SSI, which are expressed as medians with the 25th to 75th percentiles because values were not in a normal distribution. The significance of differences between values during the 2 diets in urinary excretion of urea nitrogen, systemic blood pressure, and renal function was evaluated by Student’s t test for paired samples. The significance of differences among the groups in urinary excretion of urea nitrogen, systemic blood pressure, and renal function was examined by ANOVA. The significance of differences among the groups in urinary excretion of protein, scores for histological damage, and SSI was evaluated by the Kruskal-Wallis test. The significance of differences in urinary excretion of protein during the 2 diets was examined by the Wilcoxon test. The correlation between SSI, MAP, and the glomerulosclerosis score was evaluated by Pearson’s correlation. The correlation between SSI, MAP, and the score for tubulointerstitial damage was obtained by Spearman’s rank correlation. Statistical analysis was done with Stat-View J, version 4.5 (Abacus Concepts Inc). Differences of P < 0.05 were considered statistically significant.

**Results**

Urinary excretion of protein and urea nitrogen, systemic blood pressure, and renal function in the 3 groups on the 2 diets are shown in Table 2. Urinary excretion of protein was different among the groups and was higher on the diet with an ordinary sodium level than on that with a low sodium level. Urinary excretion of urea nitrogen was not different among the groups or between the diets. Systemic blood pressure on the diet with a low sodium level was significantly lower in the optimal group than in the other groups. Systemic blood pressure on the diet with an ordinary sodium level was higher than on that with a low sodium level. Creatinine clearance on the diet with an ordinary sodium level was higher than on that with a low sodium level. Effective renal plasma flow was not different among the groups or between the diets.

The mean pressure-natriuresis curve was steeper in the optimal group than that in the normal to high-normal or hypertensive groups (Figure 1). SSI was different among the groups. The median glomerulosclerosis score was different in the groups (optimal group, 33 [25th to 75th percentile, 3, 82]; normal to high-normal group, 125 [25, 185]; and hypertensive group, 160 [106, 176] Figure 2a). The median score for tubulointerstitial damage was different among the groups (optimal group, 5 [0, 9]; normal to high-normal group, 10 [10, 30]; and hypertensive group, 30 [20, 40]; Figure 2b).

SSI was correlated significantly with the glomerulosclerosis score (Figure 3a) and with the score for tubulointerstitial damage (Figure 3b). MAP on the diet with an ordinary sodium level was lower in the optimal group than in the other groups. Systemic blood pressure on the diet with an ordinary sodium level was higher than on that with a low sodium level. Creatinine clearance on the diet with an ordinary sodium level was higher than on that with a low sodium level. Effective renal plasma flow was not different among the groups or between the diets.

### Table 2

<table>
<thead>
<tr>
<th>Group</th>
<th>Urinary Excretion of Protein (mg/d)</th>
<th>Urinary Excretion of Urea Nitrogen (mg/d)</th>
<th>Systemic Blood Pressure (mmHg)</th>
<th>Renal Function (ml/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>250 [200, 300]</td>
<td>100 [80, 120]</td>
<td>120 [100, 140]</td>
<td>120 [100, 140]</td>
</tr>
<tr>
<td>Normal to high-normal</td>
<td>300 [250, 350]</td>
<td>120 [100, 140]</td>
<td>140 [120, 160]</td>
<td>140 [120, 160]</td>
</tr>
</tbody>
</table>

**Figure 1.** Pressure-natriuresis curves and SSI in 3 groups: optimal group (circles), normal to high-normal group (squares), and hypertensive group (triangles).

**Figure 2.** Scores for histological damage in the 3 groups. a, Glomerulosclerosis score in the 3 groups. Bars are medians. b, Score for tubulointerstitial damage in the 3 groups. Bars are medians.
sodium level was not correlated significantly with the glomerulosclerosis score (Figure 4a), nor was that on the diet with a low sodium level (Figure 4b). MAP on the diet with an ordinary sodium level was correlated significantly with the score for tubulointerstitial damage (Figure 4c), and MAP on the diet with a low sodium level was slightly correlated with the score for tubulointerstitial damage (Figure 4d).

**Discussion**

We found increased sodium sensitivity of blood pressure in patients with IgA nephropathy but without hypertension (that is, patients with values of 120 to 139/80 to 89 mm Hg); the sensitivity was related to glomerulosclerosis and tubulointerstitial damage.

The pressure-natriuresis curve within the experimental range of sodium intake is linear for experimental animals and humans with normotension or hypertension. The pressure-natriuresis curve is linear for individual patients with a sodium intake of 1 to 18 g/d NaCl. Within this range of sodium intake, the SSI shows the actual sodium sensitivity, independent of the magnitude of the change in sodium intake. We chose to use 5 g/d NaCl for the low level and 12 g/d NaCl for the ordinary level of intake. By the classic method for classification of subjects as sodium sensitive or not, 10 and 250 mmol/d NaCl (0.5 and 15 g/d NaCl, respectively) should be used. This lower level of sodium intake is somewhat extreme for actual use, however, and our purpose was not such classification. SSI can be used to assess the sodium sensitivity of blood pressure without need for the definition of non–sodium-sensitive and sodium-sensitive groups. We used a more practical level, 5 g NaCl, for the low sodium level; this level is close to that recommended by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI), and we advise patients to aim for that level of intake after discharge.

In IgA nephropathy, the mechanism of the initial glomerular damage may involve immunologic abnormalities. Glomerular capillary hypertension is important, however, in the progress of glomerular damage, according to the results of animal studies done by the micropuncture method. In human glomerular disease, glomerular hypertension may cause progression of the disease, but glomerular pressure cannot be measured directly. In our previous study we estimated the glomerular pressure from the pressure-natriuresis curve. The method has a weak point, however, in that it underestimates the glomerular pressure when the pressure-natriuresis curve is extremely steep or has a negative slope. For these reasons, we investigated the sodium sensitivity of blood pressure in patients with IgA nephropathy in terms of the glomerular pressure.

In hypertensive patients with chronic glomerulonephritis or renal failure, sodium sensitivity of blood pressure appears and increases further together with renal insufficiency. The results in our previous study were consistent with results in the previous reports. A new finding in our study is an increase in the sodium sensitivity of blood pressure, which is related to glomerulosclerosis and tubulointerstitial damage, in normotensive (normal to high-normal; 120 to 139/80 to 89 mm Hg) patients with IgA nephropathy. In rats with experimental nephritis or 1-sided nephrectomy, glomerular hypertension appears without hypertension. The glomerular pressure in our patients with normal to high-normal pressure may be higher than that in our patients with optimal pressure. We calculated the glomerular pressure in the patients of this study by the method used in our previous study. Although, as mentioned above, some values of the calculated glomerular pressure might be underestimated, especially in patients with optimal pressure, the pressure in patients with normal to high-normal pressure was higher than that in patients with optimal pressure (data not shown). When renal structural injury increases and the number of healthy nephrons decreases, glomerular capillary hypertension accompanied by an increase in the sodium sensitivity of blood pressure occurs; glomerular capillary pressure rises to compensate for the impairment in sodium excretion by the kidneys in such a sodium-sensitive state. When the number of functioning nephrons further decreases as renal disease progresses, systemic blood pressure may increase from the normal range to the hypertensive range, elevating the glomerular pressure further. Our findings about the relationship between...
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