Hemodynamic and Endocrine Changes Associated with Potassium Supplementation in Sodium-Loaded Hypertensives

TOSHIRO FUJITA, M.D., AND KATSUYUKI ANDO, M.D.

SUMMARY To clarify the mechanism by which potassium (KCl) protects against the blood pressure rising action of sodium (NaCl), we studied the effects of KCl loading in patients with idiopathic hypertension who, after a period of NaCl restriction, partook of a high NaCl diet. Eleven patients who had taken the KCl supplement (96 mEq/day) during the high NaCl period showed lesser mean blood pressure (MAP) rise with changes in NaCl intake from 25 to 250 mEq/day than 12 patients who had not taken the KCl supplement (p < 0.001). With a high NaCl diet, the KCl-supplemented patients retained less NaCl, gained less weight, and showed a lesser increase in plasma volume and cardiac output than the non-KCl-supplemented ones. Overall, the increase in blood pressure levels during the high Na diet correlated directly either with changes in plasma volume (p < 0.05) or with changes in cardiac output (p < 0.01). The results suggest that KCl may prevent a rise in blood pressure with NaCl loads in hypertensive patients by attenuating the increase in cardiac output, mainly as a result of the natriuresis. Furthermore, plasma norepinephrine was measured to estimate the sympathetic activity, since the sympathetic nervous system is known to control urinary NaCl excretion. From the low NaCl diet to Day 3 of the high NaCl diet, plasma norepinephrine was significantly (p < 0.01) decreased in the KCl-supplemented patients, whereas it remained unchanged in the non-KCl-supplemented ones. Concomitantly, urinary Na excretion was significantly greater in the early period of NaCl loading in the KCl-supplemented group as compared to the other group. Taken together, these results suggest that lower levels of norepinephrine measured in the plasma of the KCl-supplemented patients in the early NaCl-loading phases of the study are indicative of reduced adrenergic neural activity, which might be involved not only in the attenuation of increased cardiac output, but also in the responses of the kidney to shift the pressure-natriuresis relationship toward normal, leading to the natriuresis.

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KEY WORDS • sodium • potassium • norepinephrine • cardiac output

Numerous animal studies have presented evidence that the mechanisms by which excess salt (NaCl) intake increases blood pressure may include augmentation of sympathetic nerve activity and release of norepinephrine from adrenergic nerve endings.1 2 Studies in humans also suggest that an excess of dietary NaCl may augment not only the vascular responsiveness to catecholamines,3 but also the sympathetic nerve activity in hypertensive patients.4 Recently, several investigators found hyperactivity of the sympathetic nervous system in hypertensive patients, who showed a considerable increase in blood pressure with NaCl loads.5 6 Since sympathetic nerve activity is known to influence urinary Na excretion,7 we have demonstrated that hyperactivity of the sympathetic nervous system may be responsible for the relative Na retention, increased cardiac output, and rise in blood pressure with NaCl loads in hypertensive patients.3 Increased sympathetic tone decreases urinary Na excretion, and thus it contributes to the rise in blood pressure with NaCl loads by increasing cardiac output.5

In contrast to the pressor action of NaCl, potassium (KCl) has been known to have antihypertensive properties.6-11 Although the precise mechanism of the antihypertensive action of KCl remains controversial, its natriuretic properties are thought to play an important role.10 12 13 Moreover, recent reports have indicated that dietary KCl supplementation decreased plasma norepinephrine concentration in NaCl-loaded hypertensive rats14 and improved baroreceptor function in hypertensive rats15 and humans.16 Taken together, there is a considerable possibility that KCl may change the sympathetic nerve activity, leading in turn to the natriuresis and resultant attenuation of the rise in blood

From the Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Ibaraki, Japan.
Address for reprints: Toshiro Fujita, M.D., Department of Internal Medicine, Institute of Clinical Medicine, University of Tsukuba, Niiderugun, Ibaraki 305, Japan.
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pressure with NaCl loads in hypertensive patients. Therefore, we undertook hemodynamic and endocrine studies to evaluate how a KCl supplement can moderate the rise in blood pressure with NaCl loads in hypertensive patients and, further, to clarify whether the sympathetic nervous system may be involved in the antihypertensive and natriuretic effects of KCl.

**Methods**

Twenty-three patients with idiopathic hypertension (17 men, six women) were studied in the Clinical Center, University of Tsukuba. These patients had mild to moderate hypertension, with casual (morning) clinic blood pressures ranging from 150 to 180 mm Hg systolic and 90 to 115 mm Hg diastolic. The patients underwent the usual evaluation for hypertension, including serum electrolytes, urinalysis, intravenous pyelography, and, in two cases, angiography to exclude primary causes of hypertension. Twenty-three unselected hypertensive patients were entered into the study, to be described. All subjects read and signed an informed consent form outlining the details of the tests to be performed.

All antihypertensive medications were discontinued for at least 2 weeks before admission. All subjects were maintained on a constant activity regimen and daily diet containing 25 mEq of sodium and 50 mEq of potassium ("low sodium diet"). Patients were studied for 3 days with this diet to which 140 mEq of NaCl was added each day ("normal sodium diet"). Then, the low sodium diet was given for 3 days, followed by 6 days of the low sodium diet to which 225 mEq of NaCl was added each day ("high sodium diet"). Moreover, during the high sodium diet, 96 mEq of KCl was added each day in 11 ("Group B") of 23 patients, but not in 12 patients ("Group A") (Figure 1). On the first day of the low sodium diet (Day 4), 40 mg of furosemide was injected intravenously.

At 0700 each morning, body weight was measured after the patients had voided. Throughout the study blood pressure was measured by sphygmomanometer every 4 hours, after the patients had been supine for 5 minutes or longer. For statistical comparison of the effects of dietary NaCl and KCl on blood pressure, mean blood pressure (MAP) was calculated for every 4-hour reading (day and night) as diastolic pressure plus one-third of the pulse pressure, for the 3rd day of the first and second regimens and the 6th day of the high sodium diet.

**Plasma Volume**

On the last day of the three experimental diet periods, plasma volume was measured by the Evans blue method. All determinations were done in the early morning on the fasting subjects who were recumbent for 30 minutes prior to dye injection. Heparinized blood samples were drawn at 10, 20, and 30 minutes through an indwelling needle without stasis, and plasma dye concentrations were extrapolated to a given concentration at zero time. With this method in eight other ambulatory subjects, the experimental error estimated from duplicate determinations of plasma volume was 40 ml/m².

**Hemodynamic Studies**

Systemic blood pressure was measured by sphygmomanometer. Cardiac output was determined by dye dilution (indocyanine green), on the 3rd day of the normal sodium and low sodium diets and on the 6th day of the high sodium diet, in 11 KCl-supplemented and 11 non-KCl-supplemented patients. These measurements were made in the morning after the patient had rested supine for at least 30 minutes. Total peripheral resistance was calculated as the ratio of MAP to cardiac output, expressed in dynes-sec-cm⁻²-m⁻².

**Plasma Renin Activity and Urinary Aldosterone**

At 0700 with the patient supine on the last day of the three experimental periods, blood was drawn for determination of plasma renin activity (PRA) by radioimmunoassay of angiotensin I generated during the incubation of plasma at pH 6.5 and 37°C with a modification of the method of Haber et al. To measure 24-hour urinary aldosterone, radioimmunoassay with a commercial kit (CEA-IRE-SORIN, France) was used.

**Plasma Norepinephrine**

For each test procedure, the subject was supine and had an indwelling catheter inserted in an arm vein. At least 30 minutes after insertion of the indwelling catheter but not before the patients were subjectively relaxed and had a stable pulse rate, a 5 ml sample of blood was withdrawn into the tube with 100 μl of the solution containing 9.5 mg of EGTA and 6.0 mg of reduced glutathione at a pH of 6 to 7. This procedure was repeated with each subject on the 3rd day of the low sodium diet, and on the 3rd and the 6th days of the high sodium diet. In the present study, urinary Na excretion in the KCl-supplemented patients was usually equal to the NaCl intake by the 2nd day of NaCl loading, whereas this did not occur in the non-KCl-supplemented patients until the 3rd or 4th day. Therefore, we examined plasma norepinephrine on both Days 3 and 6, so as not to miss immediate changes occurring at the same time as changes in body Na. Plasma norepinephrine was measured by the radioenzymatic methods of Peuler and Johnson.\(^{21}\)
Numerical results are expressed as means ± 1 SEM. Statistical analysis of the data was performed using Student’s paired- and unpaired-t tests and regression analysis according to standard procedures. Changes are reported as significant if the p value was less than 0.05.

Results

There were no significant differences in age, sex distribution, or known duration of hypertension between the patients of Group A and Group B (Table 1). Also, there were no significant differences in systolic and diastolic blood pressure, or in secondary effects of the hypertension, as revealed by serum K or creatinine clearance, or in the incidence of left ventricular hypertrophy, or in supine PRA on the morning after admission. One Group A patient and two Group B patients had “low renin” hypertension as defined in this clinic, and others had “normal renin” hypertension.

Figure 2 shows the course of the average systolic and diastolic blood pressure levels during the high sodium diet for 6 days after the low sodium diet for 3 days, in the 12 Group A and the 11 Group B patients.

The average MAP values for the Group A patients taking the normal sodium diet, the low sodium diet, and the high sodium diet were 108.2 ± 3.6, 100.4 ± 3.2, and 109.6 ± 2.4 mm Hg, respectively (Table 2). Corresponding averages of MAP values for the Group B patients were 106.5 ± 2.5, 100.0 ± 1.8, and 97.0 ± 2.6 mm Hg, respectively. The MAP value of the Group B patients taking the high sodium diet (97.0 ± 2.6 mm Hg) differed significantly (p < 0.01) from the corresponding MAP for the Group A patients (109.6 ± 2.4 mm Hg), although the average MAP values during both the normal sodium and low sodium diets did not differ significantly between the two groups.

The mean decrease in MAP between the normal sodium and low sodium diets is not significantly different between the two groups: −7.1% ± 1.6% in the Group A patients and −5.8% ± 1.4% in Group B (NS).

Table 3 shows the blood pressure data as a series of points for each individual patient for each day of the high NaCl loading in the case of Group A, and for the high-NaCl high-KCl loading in the case of Group B. In the Group A patients, the MAP was gradually but definitely increased with NaCl loads, whereas the Group B patients had no significant increase in blood pressure throughout the NaCl-loading period. Not until the 3rd day of NaCl loading did the MAP differ between the two groups. Finally, the mean MAP increase from the 3rd day of the low sodium diet to the 6th day of the high sodium diet, as analyzed by Student’s t test, differed significantly (p < 0.001) between the groups: 10.0% ± 2.0% (p < 0.001) in Group A patients and −3.5% ± 1.6% (0.05 < p < 0.1) in Group B.

Urinary Na levels on Days 1 and 2 of the high sodium diet were significantly greater in the KCl-supplemented (Group B) patients than in the non-KCl-supplemented (Group A) patients, while the patients of the two groups were in sodium balance during the normal- and low-sodium dietary phases (Figure 3). In addition, the KCl-supplemented (Group B) patients retained significantly (p < 0.05) less Na during the 6 days of the high sodium diet than did the non-KCl-supplemented (Group A) patients and gained significantly less weight than the Group A patients (1.6% ± 0.4% vs 0.6% ± 0.2%, p < 0.05). An estimate of the mean cumulative Na retention (NaCl intake minus urinary Na) over the 6 days of the high sodium diet was 209 ± 35 mEq for the KCl-supplemented (Group B) patients and 311 ± 32 mEq for the non-KCl-supple-
### Table 2. Clinical and Laboratory Findings in Non-KCl-Supplemented and KCl-Supplemented Patients during Three Experimental Periods

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal sodium</td>
<td>Low sodium</td>
</tr>
<tr>
<td>Mean blood pressure (mm Hg)</td>
<td>108.2±3.6</td>
<td>100.4±3.2</td>
</tr>
<tr>
<td>Difference (%)*</td>
<td>-7.1±1.6</td>
<td>10.0±2.0</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>64.5±3.0</td>
<td>63.1±2.9</td>
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<tr>
<td>Difference (%)*</td>
<td>-2.1±0.3</td>
<td>1.6±0.4</td>
</tr>
<tr>
<td>Plasma volume (ml/m²)</td>
<td>1321±94</td>
<td>1079±40</td>
</tr>
<tr>
<td>Differences (%)*</td>
<td>-16.2±2.9</td>
<td>13.7±3.7</td>
</tr>
<tr>
<td>Cardiac index (liter/min/m²)</td>
<td>3.24±0.21</td>
<td>2.90±0.17</td>
</tr>
<tr>
<td>Differences (%)*</td>
<td>-9.78±2.32</td>
<td>17.39±4.40</td>
</tr>
<tr>
<td>Total peripheral resistance (dynes·sec·cm⁻⁵·m²)</td>
<td>2847±168</td>
<td>2963±176</td>
</tr>
<tr>
<td>Difference (%)*</td>
<td>4.41±2.91</td>
<td>-3.49±3.07</td>
</tr>
<tr>
<td>Plasma sodium (mEq/liter)</td>
<td>138.4±0.5</td>
<td>136.2±1.5</td>
</tr>
<tr>
<td>Plasma potassium (mEq/liter)</td>
<td>4.0±0.1</td>
<td>4.1±0.2</td>
</tr>
<tr>
<td>Plasma renin activity (ng/ml/hr)</td>
<td>1.36±0.31</td>
<td>4.04±0.86</td>
</tr>
<tr>
<td>Urinary aldosterone (µg/day)</td>
<td>10.8±1.3</td>
<td>21.2±1.9</td>
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</tbody>
</table>

Values are given as means ± SEM. Normal sodium = the 3rd day of the normal sodium diet. Low sodium = the 3rd day of the low sodium diet. High sodium = the 6th day of the high sodium diet.

*Percent changes from low sodium to normal sodium diets and from high sodium to low sodium diets.

†p < 0.05, vs non-KCl-supplemented patients.

‡p < 0.01.

§p < 0.001

### Table 3. Mean Blood Pressure (mm Hg) for Each Patient during the High Sodium Diet

<table>
<thead>
<tr>
<th>Patients</th>
<th>Low-3</th>
<th>High-1</th>
<th>High-2</th>
<th>High-3</th>
<th>High-4</th>
<th>High-5</th>
<th>High-6</th>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
<td>91.4</td>
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<td>109.2</td>
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<td>5</td>
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<td>93.9</td>
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<td>103.6</td>
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<td>106.6</td>
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<td>6</td>
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<td>93.4</td>
<td>103.0</td>
<td>106.8</td>
<td>102.2</td>
<td>105.0</td>
<td>110.8</td>
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<td>7</td>
<td>122.3</td>
<td>125.2</td>
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<td>132.0</td>
<td>128.3</td>
<td>133.2</td>
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<td>95.9</td>
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<td>94.0</td>
<td>99.2</td>
<td>99.3</td>
<td>98.2</td>
<td>99.4</td>
<td>104.6</td>
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<tr>
<td>10</td>
<td>93.8</td>
<td>90.2</td>
<td>97.8</td>
<td>102.5</td>
<td>107.4</td>
<td>106.7</td>
<td>111.4</td>
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<tr>
<td>11</td>
<td>102.8</td>
<td>105.2</td>
<td>109.8</td>
<td>111.6</td>
<td>106.7</td>
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<td>118.1</td>
<td>122.6</td>
<td>125.7</td>
<td>117.4</td>
<td>117.4</td>
</tr>
</tbody>
</table>
<| mean ± SEM | 100.4±3.2 | 101.5±2.6 | 105.3±2.2 | 108.3±3.0 | 107.2±3.0 | 108.0±2.3 | 109.6±2.4 |
| Group B  |       |        |        |        |        |        |        |
| 1        | 93.5  | 89.5   | 84.3   | 88.6   | 87.2   | 87.1   | 84.4   |
| 2        | 104.9 | 105.1  | 99.2   | 101.6  | 99.3   | 99.3   | 104.5  |
| 3        | 112.7 | 112.1  | 111.5  | 112.0  | 112.0  | 115.0  | 114.4  |
| 4        | 107.9 | 101.6  | 110.8  | 102.5  | 97.9   | 101.7  | 101.4  |
| 5        | 93.6  | 106.0  | 102.5  | 102.4  | 98.7   | 99.5   | 102.2  |
| 6        | 96.1  | 93.7   | 98.5   | 96.8   | 95.6   | 92.8   | 88.1   |
| 7        | 96.8  | 91.5   | 98.9   | 98.0   | 99.2   | 98.8   | 97.3   |
| 8        | 98.7  | 92.1   | 84.3   | 86.7   | 89.3   | 83.7   | 88.4   |
| 9        | 97.7  | 105.5  | 100.7  | 103.0  | 105.4  | 99.2   | 103.3  |
| 10       | 93.2  | 90.9   | 86.6   | 86.5   | 85.9   | 85.5   | 83.2   |
| 11       | 105.0 | 106.1  | 107.6  | 102.8  | 100.3  | 98.4   | 99.7   |
<| mean ± SEM | 100.0±1.8 | 99.5±2.3 | 98.6±2.8 | 98.3±2.3 | 97.3±2.2 | 96.5±2.6 | 97.0±2.6 |

| Group A vs Group B | NS | NS | NS | <0.05 | <0.05 | <0.01 | <0.01 |

Low-3 = Day 3 of low sodium diet. High-1 and High-6 = Day 1 and Day 6 of high sodium diet, respectively.
Normal Na
Low Na
KCI Supplement
Na

FIGURE 3. Daily urinary sodium excretion (upper panel) and urinary potassium excretion (lower panel) during the three experimental periods, in Group A (shaded column) and Group B patients (open column). Note that urinary sodium excretions on the 1st and the 2nd days of the high sodium diet were significantly greater in KCI-supplemented (Group B) patients compared to those in non-KCI-supplemented (Group A) patients. Note that urinary sodium excretion in the KCI-supplemented (Group B) patients was equal to the sodium intake by the 2nd day of the high sodium diet, whereas this did not occur in the non-KCI-supplemented (Group A) patients until the 3rd day.

demted (Group A) patients (p < 0.05). Furthermore, urinary Na excretion was equal to the NaCl intake on Day 2 in the KCI-supplemented patients as opposed to Day 3 in the non-KCI-supplemented patients, and thus the KCI-supplemented group achieved NaCl balance sooner than the other group.

During the normal sodium and low sodium diets, patients of the two groups were in K balance. Urinary K was greater during the high sodium diet than during the low sodium diet in the Group A patients (p < 0.01), although the KCI intake was the same during the two periods (Figure 3). In the KCI-supplemented (Group B) patients, however, the amount of urinary K excreted on Day 1 of the high sodium diet was 102 ± 7 mEq/day, while the total KCI intake was 146 mEq/day; this shows a positive K balance. An estimate of the mean cumulative K retention (KCI intake minus urinary K) over the 6 days of the high sodium diet is −10 ± 14 mEq for the non-KCI-supplemented (Group A) patients and 103 ± 15 mEq for the KCI-supplemented (Group B) ones (p < 0.001). Accordingly, plasma K was significantly (p < 0.01) decreased from 4.1 ± 0.2 mEq/liter on the low sodium diet to 3.8 ± 0.1 mEq/liter on the high sodium diet, in the Group A patients. In the KCI-supplemented (Group B) patients, however, plasma K concentration remained unchanged (4.1 ± 0.2 mEq/liter on the low sodium diet and 4.2 ± 0.1 mEq/liter on the high sodium diet (NS)). There was no difference in plasma Na values between the Group A and the Group B patients on the low sodium diet or high sodium diet.

**Plasma Volume**

Mean plasma volume on the 3rd day of the normal sodium diet did not differ between the Group A and Group B patients (Table 2). The mean decrement in plasma volume with the low sodium diet did not differ between the two groups: −16.2% ± 2.9% in the Group A patients and −17.4% ± 2.6% in the Group B ones. However, plasma volume was significantly increased during changes in NaCl intake from 25 to 250 mEq/day in the Group A patients; the mean plasma volume increment was 13.7% ± 3.7% (p < 0.01). In contrast, there were no significant changes in plasma volume with the high sodium diet, as analyzed by paired t test, in the KCI-supplemented (Group B) patients (−0.1% ± 4.4%, NS); thus, the plasma volume was significantly less compared to that in the Group A patients (p < 0.02). Moreover, the increments of blood pressure with the high sodium diet directly correlated to the changes in plasma volume (r = 0.439, p < 0.05).

**Hemodynamics**

The average cardiac output on the 3rd day of the normal sodium diet did not significantly differ between the Group A and B patients (Table 2). The mean decrease in cardiac output between the normal sodium and low sodium diets, calculated for each patient, did not differ significantly between the two groups: −9.78% ± 2.32% in the Group A patients and −9.80% ± 4.17% in the Group B ones. However, the average cardiac output was significantly increased during changes in NaCl intake from 25 to 250 mEq/day in the Group A patients; the mean increase was 17.39% ± 4.40% (p < 0.01) (Figure 4). In contrast, there were no significant changes in cardiac output with the high sodium diet in the KCI-supplemented (Group B) patients (3.24% ± 3.70%); thus, changes in cardiac output were significantly less as compared to those in the non-KCI-supplemented (Group A) subjects (p < 0.05) (Figure 4). When data from both groups were considered together, there were significant positive correlations between the increase in MAP and the increase in cardiac output (r = 0.617, p < 0.01) (Figure 5) and between the increase in cardiac output and the increase in plasma volume (r = 0.435, p < 0.05) with NaCl loads. There was no significant change of total peripheral resistance (TPR) with NaCl loads, in either group (Table 2 and Figure 4).
ANTIHYPERTENSIVE EFFECT OF POTASSIUM/Fu/Vto

Group A (NaCl Load) Group B (NaCl+KCl Load)

\[ \Delta \text{Cardiac Index} (\%) \]

\[ \Delta \text{Total Peripheral Resistance} (\%) \]

Low Na •High Na Low Na •High Na

\[ P < 0.02 \]

\[ \text{N.S.} \]

**Figure 4.** Effects of KCl supplements on changes in cardiac index (upper panel) and total peripheral resistance (lower panel) from the 3rd day of the low sodium diet to the 6th day of the high sodium diet for Group A (left panel) and Group B (right panel) patients are indicated on the right side of the figure. Note that the increases in cardiac index with the high sodium diet in the Group A patients were significantly (\( p < 0.02 \)) greater than in the Group B patients, whereas there was no significant change in total peripheral resistance with sodium loads in either group.

**Figure 5.** There is a positive correlation between the increases in cardiac index (\%\) and in mean blood pressure (\%\) from the 3rd day of the low sodium diet to the 6th day of the high sodium diet for each patient (\( r = 0.617, \ p < 0.01 \)).

**Plasma Renin Activity and Urinary Aldosterone Excretion**

With the normal sodium or the low sodium diets, there were no significant differences in PRA or urinary aldosterone between the Group A and B patients (Table 2). Also, there was no significant difference in PRA "stimulated" with furosemide: 4.65 ± 0.87 and 5.07 ± 1.16 ng/ml/hr in Group A and Group B patients, respectively. On the 6th day of the high sodium diet, PRA was significantly (\( p < 0.05 \)) higher in the KCl-supplemented (Group B) patients, as was urinary aldosterone excretion (\( p < 0.05 \)).

**Plasma Norepinephrine**

Mean plasma norepinephrine concentration on the 3rd day of the low sodium diet did not differ between the Group A and B patients. From the 3rd day of the low sodium diet to the third day of the high sodium diet, however, plasma norepinephrine decreased significantly in the KCl-supplemented (Group B) patients (from a mean of 335.7 ± 38.7 to one of 211.9 ± 21.6 pg/ml, \( p < 0.01 \), by paired t test), whereas it showed an insignificant decrease in the non-KCl-supplemented (Group A) patients (from a mean of 289.4 ± 35.4 to one of 260.8 ± 49.6 pg/ml, NS) (Figure 6). Plasma norepinephrine did not decrease in the Group A patients until Day 6. Concomitant with the changes in plasma norepinephrine concentration, the heart rate of the KCl-supplemented (Group B) patients was significantly decreased in the early period of NaCl loading, whereas that of the Group A patients was not significantly decreased (Figure 6). Moreover, there was a significant correlation between the decreases in plasma norepinephrine from the end of the low sodium diet to the 3rd day of the high sodium diet and the amount of Na excreted in the urine on Days 1 and 2 of the high sodium diet (\( r = 0.488, \ p < 0.05 \)).

**Discussion**

Several investigators reported that dietary KCl supplementation only lowered blood pressure slightly in hypertensive patients, and the results of these studies did not indicate normalization of blood pressure in the presence of KCl loading. Although the present study showed the remarkable antihypertensive effect of short-term KCl supplementation in NaCl-loaded hypertensive patients, added KCl only prevented the increase in blood pressure associated with increased dietary NaCl intake. MacGregor et al. reported that blood pressure had fallen only by 4% on KCl supplementation (60 mEq/day) for 4 weeks while subjects received a normal NaCl intake (about 150 mEq/day). However, the other controlled study showed a greater fall in blood pressure on KCl supplementation for 10 days and on a high NaCl intake of 260 mEq/day. On the other hand, no significant change in blood pressure with KCl supplementation was observed in hypertensive patients on a low sodium diet.

Taken together, the results of these studies suggest that the fall in blood pressure may be greater the higher...
the NaCl intake, and that the hypotensive action of KCl may be related to the resultant loss of Na. This conclusion is supported by the present balance study, showing that the 11 KCl-supplemented patients retained less Na and had smaller increases in plasma volume, cardiac output, and blood pressure during changes in NaCl intake from 25 to 250 mEq/day than did 12 Group A patients who had not taken the KCl supplement. Overall, the MAP increases directly correlated either to the increases in plasma volume or in cardiac output with the NaCl load. The data suggest that the KCl supplement can promote the natriuresis, leading in turn to attenuation of the increase in cardiac output via the suppression of plasma volume expansion, and thus inhibiting the elevation of blood pressure with the NaCl load.

To account for the observation that the KCl-supplemented patients retained less Na during the high sodium diet, one might speculate that they had become more depleted of NaCl and of plasma volume during the preceding low NaCl period and, thus, were able to retain more Na without "overexpansion" than the non-KCl-supplemented subjects. The evidence does not support such a suggestion, since the patients in the two groups were in NaCl balance during the normal and low sodium diets. Second, with the low sodium diet, the decreases in plasma volume were similar in the two groups, and the PRA levels did not differ. Finally, the increases in plasma volume with the high sodium diet were significantly smaller in the KCl-supplemented group as compared to the other group. It appears, then, that the Na retained during the high sodium diet was less in the KCl-supplemented group although at the outset of the NaCl loading there were no significant differences in "volume-status" between the two groups.

Regarding Na sensitivity, it is suggested that the differential responses to NaCl loading could reflect differences in susceptibility to Na rather than the protective effect of KCl against the blood pressure rising action of NaCl. However, the evidence does not support such a suggestion, since there were no significant differences in age, sex distribution, systolic and diastolic blood pressures, or secondary effects of hypertension, as revealed by creatinine clearance and the incidence of left ventricular hypertrophy. Moreover, both the basal and stimulated PRA levels were not significantly different between the two groups, and there were no significant differences in numbers of patients with low renin hypertension included in the two groups. Finally, the depressor response to NaCl restriction with the low sodium diet was not significantly different between the groups. Since our previous report indicated that patients who had a greater increase in blood pressure with NaCl loads showed a greater decrease in blood pressure after NaCl restriction, it seems that there was no significant difference in Na sensitivity between the two groups of patients.

On the 1st and 2nd days of the high sodium diets, urinary Na excretion was significantly greater in the KCl-supplemented patients than the non-KCl-supplemented ones, although blood pressure at the outset and on Days 1 and 2 of NaCl loading did not differ (Table 3). In the KCl-supplemented patients, Na was readily excreted in the urine in response to NaCl loading after NaCl depletion, and thus, Na balance was achieved sooner (Day 2), compared to the patients of the other group. In the non-KCl-supplemented patients, however, Na balance was not achieved until the 3rd day of the high sodium diet, when there was an increase in MAP of 8 mm Hg (Table 3), possibly resulting in a "pressure natriuresis." A recent report demonstrated in
conscious dogs that an increase in renal perfusion pressure of only 5 mm Hg results in a twofold increase in Na excretion. Despite a significant rise in blood pressure with the NaCl load, the non-KCl-supplemented patients retained more Na than the KCl-supplemented ones, whose pressures remained unchanged throughout the high sodium diet. If it is assumed that the blood pressure/Na excretion curve for the kidney of hypertensive animals had shifted to the right, the KCl supplement might have restored this blood pressure/urinary Na excretion relationship near to normal, leading to the natriuresis.

The mechanisms for the natriuresis induced by KCl loading remain unknown. First, the natriuresis induced by KCl might be based upon the finding that the KCl loading prevented decreases in the levels of plasma and/or intracellular K concentration. But, it is still questionable whether the considerable degree of the overall natriuresis observed in our study can only be explained by the 0.4 mEq/liter increase in plasma K concentration (4.2 mEq/liter in Group B patients vs 3.8 mEq/liter in Group A patients). On the other hand, it is well known that sympathetic nerve activity influences renal Na excretion. Norepinephrine infused into the renal artery decreases urinary Na excretion, and renal denervation causes an increase in Na excretion. Then, we studied the effect of KCl loading on the sympathetic nerve activity to clarify the mechanisms governing the natriuresis induced by K. The results showed no differences between the plasma norepinephrine value of the Group A patients and that of the Group B patients at the end of the low sodium diet. From the end of the low sodium diet to the 3rd day of the high sodium diet, plasma norepinephrine decreased significantly in the KCl-supplemented patients, whereas it showed an insignificant decrease in the non-KCl-supplemented patients. In the Group A patients, plasma norepinephrine did not significantly decrease until Day 6. Moreover, such a change in sympathetic nerve activity may be reflected by the present observation that, concomitantly with the change in plasma norepinephrine, the heart rate of Group B patients was significantly decreased in the early period of NaCl loading, whereas that of the Group A patients was not significantly decreased. Thus, the present results lead us to suggest that the lower levels of norepinephrine measured in the plasma early in the NaCl-loading phases of the study indicate reduced adrenergic neural activity, which might be involved in the early natriuresis in the KCl-supplemented patients. This hypothesis was supported by the finding that there was a significant correlation between the degree of the decrease in plasma norepinephrine concentration from the end of the low sodium diet to the 3rd day of the high sodium diet and the amount of urinary sodium excretion in the early period of NaCl loading. It is suggested, therefore, that the KCl loading could shift the pressure/natriuresis relationship toward normal, partly by reduced sympathetic nerve activity, since the sympathetic nervous system is one of the important systems that control the renal function for Na excretion.

The present observation of reduced adrenergic neural activity by KCl loading is consistent with the results of previous studies. Improvement of baroreceptor function with high KCl intake has been observed in humans and animals. Also, the increased extracellular K concentration could decrease the nerve-evoked release of norepinephrine from the nerve ending, in vitro. Finally, KCl supplementation could decrease plasma norepinephrine concentration in NaCl-loaded stroke-prone spontaneously hypertensive rats.

The present observation with respect to hemodynamics is in keeping with our previous report, namely, that the increase in blood pressure with NaCl loads in hypertensive patients might be attributed to the increase in cardiac output. Concomitant with the inhibition of blood pressure elevations, KCl loading could attenuate the increase in cardiac output with the NaCl load. The finding of the direct correlation between the changes in cardiac output and changes in MAP suggests that the protective effect of KCl against the blood pressure rising action of NaCl might be attributed to the attenuation of the increase in cardiac output. Two group B patients (B-8 and B-11) whose cardiac output was greatly decreased (−19.0% and −15.2%) showed a marked reduction in blood pressure (−10.4% and −5.0%). Since the two patients markedly affect the overall significance of the changes in cardiac output between Groups A and B, the antihypertensive effect of KCl might not be due only to the disproportionately decreased cardiac output but also to the relatively decreased peripheral resistance. The lesser increments of cardiac output in the high sodium KCl-loaded group could be explained by the lesser increments of venous return, as a result of the suppression of plasma volume expansion. If there is lesser adrenergic activity in the KCl-supplemented (Group B) patients, such activity could also contribute to the attenuation of the increase in cardiac output in these patients, by negative cardiac inotropic and chronotropic drive. In addition, a lesser adrenergic activity at alpha-receptor endplates could, of course, promote a decrease in blood pressure directly. Moreover, the lesser contraction of capacitance vessels could also contribute to the smaller increments in cardiac output, by the lesser increase in central blood volume.

Although several mechanisms have been demonstrated by which KCl may moderate hypertension, there is still no general agreement as to which mechanism is most likely. Both acute and chronic KCl loading has been shown to inhibit renin secretion. In our present study, however, PRA during NaCl loading was relatively higher in the KCl-supplemented patients than in the non-KCl-supplemented ones because of the natriuresis induced by KCl via suppression of Na retention. Also, the relatively higher urinary aldosterone levels may not only be due to the aldosterone-secreting effect of KCl per se, but also to the augmented renin-angiotensin system by KCl-induced natriuresis. KCl has been reported to have both direct and indirect effects on the vascular system. Intravenous infusion of KCl is known to cause arterial vaso-
dilation, the degree of which is reduced by pretreatment with ouabain. This observation led Overbeck and others to speculate that there might be a defect in Na, K-ATPase in vascular smooth muscle in some patients with essential hypertension whose K vasodilation was attenuated, and that an increase in plasma K would stimulate the Na-K pump, leading to a reduction in blood pressure by vasodilation. KCl may also reduce the reactivity of the peripheral arterioles to pressor substances. The increased pressor response to intravenous angiotensin II in rats maintained on a high sodium diet does not occur among rats receiving KCl in addition to NaCl. KCl may influence the pressor responses indirectly by augmenting renal Na excretion and thereby reducing body Na content, since NaCl restriction diminishes the pressor response to angiotensin II and catecholamines.

In the present study, therefore, KCl-induced natriuresis with the resultant decrease in body Na content may change the pressor responses to angiotensin II and catecholamines, which, in turn, promote the reduction of blood pressure. Therefore, it should not be dissociated from the natriuretic effect of KCl administration, although the hypotensive effect of KCl may be multifactorial.

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Hemodynamic and endocrine changes associated with potassium supplementation in sodium-loaded hypertensives.

T Fujita and K Ando

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