Renal Function Curve in Patients with Secondary Forms of Hypertension

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SUMMARY The causative mechanisms of hypertension were investigated by studying the renal function (pressure-natriuresis) curve in patients with primary aldosteronism (n = 6) and renovascular hypertension (n = 6). Before and after radical operation (removal of adenoma in primary aldosteronism and percutaneous transluminal angioplasty in renovascular hypertension), dietary NaCl intake was altered from 10 to 13 g/day in Week 1 to 1 to 3 g/day in Week 2. Mean arterial pressure (MAP) and urinary sodium excretion were measured on the last 3 days of each week. By restricting sodium intake before operation, MAP was reduced from 122 ± 7 to 113 ± 7 mm Hg (p<0.025) in primary aldosteronism but not in renovascular hypertension (130 ± 6 to 128 ± 5 mm Hg). The renal function curve was drawn by plotting urinary sodium excretion on the ordinate and MAP on the abscissa before and after operation. The slope of the curve was analyzed between the plotted points, and each curve was extrapolated to zero sodium excretion as an estimate of the degree of shift of the curve along the MAP axis. Before, as compared with after operation, the extrapolated x-intercept of the curve was shifted rightward in both primary aldosteronism (111 ± 7 vs 87 ± 4 mm Hg; p<0.025) and renovascular hypertension (128 ± 5 vs 95 ± 2 mm Hg; p<0.025) and the slope was depressed in primary aldosteronism (16 ± 1 vs 40 ± 17 [mEq/day]/mm Hg; p<0.025) but not in renovascular hypertension (130 ± 75 vs 40 ± 13 [mEq/day]/mm Hg). After operation, the renal function curves in primary aldosteronism and renovascular hypertension were normalized. The rightward shift of the curve in renovascular hypertension probably was due to an increase in renal vascular resistance caused by the stenotic renal vascular lesion as well as to increased resistance caused by stimulation of the renin-angiotensin system. The rightward shift in primary aldosteronism presumably was due to enhancement of renal tubular sodium reabsorption by aldosterone; the depressed slope likely resulted from suppression of the renin-angiotensin feedback mechanism by the excess aldosterone and resultant volume expansion. Thus, an abnormal renal function curve seems to have played a major role in the genesis of each of these forms of secondary hypertension. (Hypertension 10: 11-15, 1987)

Key Words • arterial pressure-natriuresis relationship • pathogenesis • renovascular hypertension • primary aldosteronism

BASED on the hypothesis of Guyton and colleagues,1,2 the renal function curve (pressure-natriuresis relationship) must always be affected in the genesis of hypertension regardless of the factors that initiate the hypertension process (if the sodium intake remains in the normal range). Recently, we developed a water tank model of body fluid volume-blood pressure regulation3 and used this model to predict that an abnormal renal function curve always must occur in the genesis of hypertension. The renal function curve in animal models of hypertension, including deoxycorticosterone acetate–salt hypertension4 and Goldblatt hypertension,5 has been analyzed. However, the renal function curve has not been tested in secondary forms of human hypertension. Therefore, we plotted the renal function curve before and after radical operations for primary aldosteronism (PA) and unilateral renovascular hypertension (RVH) to see whether changes similar to those in animal models could be seen in humans.
Patients and Methods

Six patients with PA caused by an adenoma and six patients with unilateral RVH were studied in the Hypertension Unit of the National Cardiovascular Center Hospital. The PA patients included four women and two men whose mean age was 44 ± 5 years (range, 32–61 years). The diagnosis for PA due to unilateral adenoma (Conn’s syndrome) was based on adrenal venography, scintillation scanning, and computed tomography and was confirmed by histological analysis of the removed adrenal mass after unilateral adrenalectomy. The RVH patients included four men and two women whose mean age was 40 ± 5 years (range, 22–52 years). The diagnosis of unilateral RVH (two-kidney, one clip) was made by 131I-labeled Hippuran (o-iodohippurate sodium) renography, renal angiography (usually digital video subtraction angiography), and renal vein renin sampling. During percutaneous transluminal angioplasty⁶ of the diseased renal artery, the pressure gradient across the stenotic portion was monitored in addition to selective renal arteriography. Finally, in most patients digital subtraction renal angiography was performed approximately 1 week after angioplasty to confirm the patency of the renal artery. The administration of antihypertensive drugs was discontinued at least 2 weeks before the study began.

Study Protocol

The patients, whose diagnosis was established as PA or RVH, were studied in the following four stages. They were placed on a regular sodium diet containing 10 to 13 g of NaCl/day for 1 week (Stage 1) and then on a low sodium diet containing 1 to 3 g of NaCl/day for the following week (Stage 2). After radical operation (adrenalectomy for PA and percutaneous transluminal angioplasty⁶ for RVH), they were placed on regular (Stage 3) and low (Stage 4) sodium diets again for 1 week each.

Blood pressure in the supine position and urinary sodium and creatinine excretion were measured on the last 3 days of each stage. Blood pressure measurements were performed by nurses three times at about 1000 each day, and the lowest value was used. Mean arterial pressure (MAP) was calculated by adding one third of the pulse pressure to the diastolic pressure, which were the average pressures of the last 3 days. Plasma renin activity (PRA), aldosterone concentration, and creatinine concentration were measured on the last day of each stage. Creatinine clearance (Ccr) was calculated from plasma creatinine and the average value of the urinary creatinine excretion rate.

Determination of the Renal Function Curve

The arterial pressure–natriuresis relationship was assumed to be linear, and the renal function curve (line) was drawn by linking two data points obtained under two different amounts of sodium intake, regular and low, in each patient both before and after radical operation, where the MAP and urinary sodium excretion rate (UnV) were plotted on the x- and y-axes, respectively (see Figure 1). To compare the major characteristics of the curve (i.e., shift of the curve along the MAP axis and slope of the curve) before and after radical operation as well as between PA and RVH patients, the extrapolated x-intercept, A, and the slope, B, were calculated as follows:

\[ A = \frac{U_n V(R) \times MAP(L) - U_n V(L) \times MAP(R)}{U_n V(R) - U_n V(L)} \]

\[ B = \frac{U_n V(R) - U_n V(L)}{MAP(R) - MAP(L)} \]

where R and L mean the data obtained during regular (Stage 1 or 3) and low (Stage 2 or 4) sodium diets, respectively. The reciprocal of the slope of the curve, 1/B, corresponds to the salt sensitivity index.

Statistical Analysis

Results are expressed as the mean ± SEM, and the significances of the differences within the same group as well as between groups (PA and RVH) were evaluated by Wilcoxon’s test for paired and unpaired data, respectively. Since the amount of sodium intake was primarily altered and a secondary change in blood pressure was observed, the statistical comparison of the slopes of the renal function curve was based on the reciprocal of the slopes.

Results

PRA, Aldosterone Concentration, and Creatinine Clearance

PRA, plasma aldosterone concentration, and Ccr were measured in six patients with PA and six patients with RVH in the following four stages: on regular and low sodium diets before and after radical operation (adrenalectomy for PA and percutaneous transluminal angioplasty for RVH). The results are summarized in Table 1. Before radical operation, PRA was suppressed, even on the low sodium diet (Stage 2), in PA patients while it was stimulated, even on the regular sodium diet (Stage 1), in RVH patients. After operation, PRA was normalized in both PA and RVH patients. Plasma aldosterone concentration on the regular sodium diet before operation was significantly higher in PA than in RVH patients but normalized after operations. Ccr was significantly higher before operation in PA patients (p < 0.025 for Stage 1 vs 3; p < 0.025 for Stage 2 vs 4), but it was not altered in RVH patients. Although there was a tendency for a reduction in Ccr by sodium restriction in all patients, a statistically significant difference was seen only in PA patients.

MAP and Urinary Sodium Excretion

MAP and UnV were measured during the regular and low sodium diets before and after radical operation in PA and RVH patients, and results are summarized in Table 1. MAP was significantly reduced and normalized in all patients by radical operation. Before operation, MAP was altered by the change in sodium intake in PA patients, but not in RVH patients. UnV reflected the amount of sodium intake and indicated that a steady state of sodium balance had been achieved.
Renal Function Curve Before and After Operation

The renal function curve (arterial pressure–urinary sodium output relationship) was drawn before and after radical operation by plotting the UrNaV on the ordinate as a function of MAP on the abscissa, as shown in Figure 1. UrNaV and MAP were measured after a steady state of sodium balance had been achieved on two different amounts of sodium intake. Table 2 shows the extrapolated x-intercepts and the slopes of the renal function curves before and after operation. The x-intercepts were significantly reduced in both PA and RVH patients after operation, indicating that the curves were shifted rightward before operation. The slope was significantly increased after operation in PA patients, but it was not altered significantly in RVH patients. The slopes in PA and RVH patients

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FIGURE 1. Renal function curve before and after radical operation in primary aldosteronism (PA) and unilateral renovascular hypertension (RVH). The renal function curve was shifted rightward before operation, with a decrease in the slope in PA patients and without a significant change in the slope in RVH patients (see Table 2).

### TABLE 1. PRA, Aldosterone Concentration, Creatinine Clearance, Urinary Sodium Excretion, and MAP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before operation</th>
<th>After operation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Regular Na diet (Stage 1)</td>
<td>Low Na diet (Stage 2)</td>
</tr>
<tr>
<td>PRA (ng ANG I ml/hr)</td>
<td>0.3 ± 0.06</td>
<td>0.3 ± 0.04</td>
</tr>
<tr>
<td>PA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP (mm Hg)</td>
<td>130 ± 6</td>
<td>128 ± 5</td>
</tr>
<tr>
<td>RVH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

Values are means ± SEM (n = 6/group). See text for explanation of special method used in determining significances of slope differences.

PA = primary aldosteronism; RVH = unilateral renovascular hypertension.

### TABLE 2. Extrapolated x-intercept (mm Hg) and Slope (mEq/day)/mm Hg

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before Operation</th>
<th>After Operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extrapolated x-intercept (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>111 ± 7</td>
<td>87 ± 4*</td>
</tr>
<tr>
<td>RVH</td>
<td>128 ± 5</td>
<td>95 ± 2*</td>
</tr>
<tr>
<td>Slope (mEq/day)/mm Hg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PA</td>
<td>16 ± 1</td>
<td>40 ± 17*</td>
</tr>
<tr>
<td>RVH</td>
<td>130 ± 75†</td>
<td>40 ± 13</td>
</tr>
</tbody>
</table>

Values are means ± SEM (n = 6/group). See text for explanation of special method used in determining significances of slope differences.

PA = primary aldosteronism; RVH = unilateral renovascular hypertension.

*p < 0.025, compared with preoperative values.

†p < 0.01, compared with PA values.
became virtually identical after operation, indicating that the preoperative slope of the renal function curve was depressed in PA patients but not in RVH patients.

Discussion

In our experimental design, the renal function curve (arterial pressure–urinary sodium output relationship) was derived by linking two data points in each patient, where the MAP and U\textsubscript{Na}\textsubscript{V} were plotted on the x- and y-axes, respectively. Although it is ideal to generate data over a larger continuum to assess this curve more precisely, the arterial pressure–natriuresis relationship usually has been found to be reasonably linear within the experimental range of sodium intake used in animals\textsuperscript{1,4,5,8,9} and within the wide range of sodium intake in normal humans.\textsuperscript{10,11} On these bases, Parfrey\textsuperscript{12} analyzed the renal function curve in essential hypertension after assuming its linearity. In fact, our preliminary study showed that this relationship was statistically linear for a daily NaCl intake of 2, 7, and 15 g in individual patients with essential hypertension (F. Saito, G. Kimura, T. Omoe, et al., unpublished observation, 1987). Although sodium intake was kept constant only for a week in this study, on the basis of multiple past studies, 4 to 5 days should be sufficient for sodium balance and arterial pressure to reach a steady state on a fixed sodium intake.\textsuperscript{13} Thus, we believe that the present simple protocol can be used to determine the major characteristics of the renal function curve: shift of the curve along the arterial pressure axis and slope of the curve.

Our results show that the renal function curve was shifted upward, with a decrease in the slope, in patients with PA, and also in patients with RVH but without a significant change in the slope. These changes in the renal function curve are comparable to those reported in animal models of hypertension, such as deoxycorticosterone acetate–salt hypertension\textsuperscript{4} and Goldblatt hypertension.\textsuperscript{5} Although neither the entity of the renal function curve nor factors affecting the curve are fully understood, the degree of shift along the pressure axis has been shown in mathematical models in many instances by the arterial pressure drop from the aorta to the glomerular,\textsuperscript{1} which in turn is equal to the product of renal vascular resistance from the aorta to the glomeruli and renal blood flow rate. Thus, we postulate that the rightward shift in RVH patients probably was due mainly to the increase in renal vascular resistance caused by the stenotic vascular lesion. In addition, the stimulation of the renin-angiotensin system in these patients, which was demonstrated by the elevated PRA, could have increased this resistance still more. The rightward shift of the curve in PA patients likely was due to the increased sodium reabsorption by the renal tubules, which in turn required an elevated pressure and elevated glomerular filtration rate to overcome the excess sodium reabsorption and still excrete the daily intake of sodium. This sequence of events has been demonstrated in dogs by Hall et al.\textsuperscript{14} Also supporting this explanation is the finding that the C\textsubscript{cr}, an index of the glomerular filtration rate, was statistically higher in the PA patients of this study than operation than afterward. With regard to the slope of the renal function curve in PA patients, this slope has been shown by others to be considerably depressed when the negative feedback mechanisms of the renin-angiotensin system are suppressed either by administering captopril\textsuperscript{8} or by blocking the feedback with continuous infusion of excess angiotensin.\textsuperscript{9} In a similar manner, we believe that the decrease in the slope in PA patients likely resulted from the suppression of the renin-angiotensin feedback system found in the PA patients before operation.

These data are consistent with the hypothesis of Guyton and colleagues,\textsuperscript{1,2} that abnormality of the renal function curve, a rightward shift, or a decrease in the steepness of the slope is essential in the genesis of hypertension in a steady state (when the sodium intake is in the normal range). It is clear from this study performed in patients with well-known causes of hypertension that the renal function curve was abnormal, even though the cause of hypertension was from outside the kidney.

Acknowledgment

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References


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