Relationship of Cardiorenal Function to Renin-Aldosterone System in Patients with Valvular Heart Disease

By WALTER E. JUDSON, M.D., AND OSCAR M. HELMER, PH.D.

SUMMARY
Metabolic data obtained during sodium (Na) loading, restriction, and depletion with thiazide were compared in 23 patients with valvular heart disease who had cardiac indices (CI) > and < 2.5 liters/min/m². During Na loading (80 mEq Na for 4 days, followed by 150 mEq for 4 days) patients with CI > 2.5 excreted -3.4% Na load than those with the lowest normal values, whereas those with CI < 2.5 excreted -20.8% (P < 0.02). All 12 patients with CI > 2.5 responded to Na loss with elevation of plasma renin activity (PRA). In contrast, of the ill patients with CI < 2.5, none of the six on the 10 mEq diet, and only two of five on thiazide, responded with an increase in PRA; the urinary aldosterone values paralleled the PRA responses. The renin-angiotensin-aldosterone system responded to changes in Na balance. The magnitude and direction of the responses were influenced by cardiohemodynamic abnormalities. Aldosterone plays an important role in the Na retention in patients with valvular heart disease by stimulating Na-K exchange in the distal tubules of the kidney.

Additional Indexing Words:
Aldosterone excretion  Sodium depletion  Spironolactone

BRAUNWALD and his associates have devised an excellent oral sodium (Na) tolerance test that clearly demonstrates the inability of patients with congestive heart failure to excrete a Na load. Also, they found no correlation between creatinine clearance and the load of Na excreted, which confirmed earlier work that showed that abnormalities of the glomerular filtration rate are not primarily responsible for the impaired Na excretion. Evidence is accumulating to prove that the renin-angiotensin-aldosterone system influences the level of Na excretion in patients with congestive heart failure. Brown and others have observed two distinct patterns of renin secretion in untreated patients. More commonly, plasma renin activity (PRA) was normal or low, rising with therapeutic diuresis. In other instances, renin activity was initially high and fell with treatment. We have observed these two distinct patterns with Na restriction and after administration of thiazide diuretics. We have also reported this paradoxical fall in PRA in patients with hypertensive cardiovascular disease treated with thiazide. The purpose of this paper is to correlate cardiohemodynamic data with variations in PRA, urinary aldosterone excretion, and Na and K (potassium) balance during Na depletion and Na loading.

Patients and Methods
Patients with valvular heart disease were used for the study. Before they were transferred to the research ward for metabolic balance studies, the cardiovascular status was determined by methods previously described by Judson and his coworkers. The Na loading studies were patterned after

From the Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana 46202.

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those used by Braunwald and his associates for their oral Na tolerance test. After a 4-day diet of 10 mEq of Na and 90 mEq of K the patients were placed on a Na diet of 80 mEq for 4 days, followed by a Na diet of 150 mEq for the last 4 days. The basic diet was assayed for small variations in the Na and K content. Because of surgery schedules that interfered, the Na loading period had to be reduced to 6 or 7 days in a few patients. Consequently the Na intake varied from 686 to 948 mEq over the duration of the study. In order to relate the effect of changes in the renin-angiotensin-aldosterone system to hemodynamic variables, advantage was taken of the data on Na excretion in normal subjects in the paper of Braunwald and associates. By plotting their data on Na excretion by patients on Na intakes of 320 and 920 mEq, we were able to estimate the expected normal Na excretion.

In the Na depletion studies, after 3 days on a control diet of 150 mEq of Na daily, the patients were placed for 5 days on an intake of 10 mEq of Na and 90 mEq of K. Cyclothiazide (Anhydron K), 2 mg, was given orally every morning during the experimental period.

PRA was assayed by the method of Helmer and Judson. Values were expressed in nanograms (ng) of angiotensin/ml/hr. Blood samples were collected between 11:00 and 11:30 AM after 2 or 3 hr of ambulation; normal values ranged from 0.35 to 2.8 ng/ml/hr (mean = 1.6 ng). Urinary aldosterone excretion was determined by Bio-Science Laboratories; the normal range was 2 to 26 µg/24 hr. The urinary and serum electrolytes were analyzed with the Technicon Auto-Analyzer, as were serum uric acid, blood sugar, and urinary creatinine.

Blood volume was determined by the RISA-131 technique by the staff of the radioisotope laboratory. Five microcuries of 131I human serum albumin were injected. Total blood radioactivity was measured with the use of a 10-min

![Graphs](image)

**Figure 1**

Cardiohemodynamic data. Group A, patients studied with Na tolerance test with CI > 2.5, Group B with CI < 2.5; Group C, patients who were Na depleted with CI > 2.5, group D with CI < 2.5. Abbreviations: CI = cardiac index (liters/min/m²); LVED = left ventricular end-diastolic pressure; RVED = right ventricular end-diastolic pressure; PA = mean pulmonary arterial pressure; PC = pulmonary capillary pressure; LA = left atrial pressure. All pressures are expressed in mm Hg.
equilibrium sample and plasma volume calculated from the diluent volume and venous hematocrit. Results were expressed as a percentage of the normal expected value, by means of Hidalgo and associates’ modification of Allen’s height-body mass prediction formula. The values found in 15 normal subjects, ranging in age from 19 to 47 years, were $+3.5 \pm 4.14\%$ (SE), with a range of $-15.5$ to $+23.1\%$.

In addition, the following analyses were performed: urinary catecholamines, 17-ketosteroids, 17-hydroxycorticosteroids, urinary pH, total serum proteins, albumin-globulin ratio, blood urea nitrogen, 15-min PSP excretion, and creatinine clearance. Complete blood counts, concentrations of hemoglobin, hematocrit values, and X-ray films of the chest were obtained.

The patients were weighed daily, and blood pressure was recorded four times daily with the patients lying and standing.

**Results**

**Cardiohemodynamic Data**

The patients studied were arbitrarily grouped according to cardiac indices (CI). Group A includes patients studied with Na tolerance test with CI $>2.5$ liters/min/m²; group B, patients with CI $<2.5$; group C, patients who were Na-depleted with CI $>2.5$; and group D, patients who were Na-depleted with CI $<2.5$. The data are presented in figure 1.

**Effect of Na Restriction and Na Depletion on PRA**

The effect of Na restriction and Na depletion on the pattern of PRA is shown in figure 2. The data on patients with CI $>2.5$ liters/min/m² are compared with those with lower indices. All 12 patients in the groups with higher CI responded to Na loss with elevation of PRA. In contrast, none of the six patients with CI $<2.5$ liters/min/m² on the 10-mEq Na diet and only two of five patients on thiazides responded with an increase in PRA. The modifying effect of cardiohemodynamic factors on PRA as well as on aldosterone excretion will be presented later.

**PRA and Urinary Aldosterone Excretion During Oral Na Tolerance Test**

Figures 3 and 4 present contrasting patterns of renin release from the kidneys as a result of
Na restriction and Na loading in two patients. On a low Na diet patient 3 (fig. 3), with a CI of 2.74 liters/min/m², responded with a prompt rise in PRA that was sustained through 3 days of the 80-mEq Na period. With the increase of Na load to 150 mEq, PRA fell toward the control level. Aldosterone excretion followed the same pattern. In this patient 80% of the Na was excreted in the last 4 days, accompanying the fall in PRA. Only 20% was excreted during the first 4 days of Na loading when the PRA and aldosterone production were elevated.

In contrast, figure 4 shows that during Na restriction the PRA in patient 9 (CI = 1.96 liters/min/m²) fell from 9.5 to 3.4 ng/ml/hr. With the fall in PRA and aldosterone excretion there was only a gradual decrease in urinary Na output. With Na loading the PRA rose to the original control level and did not fall until the last 2 days of the Na tolerance test. Even though patient 3 (fig. 3) had a CI of 2.74 liters/min/m² compared to 1.96 for patient 9 (fig. 4), there was only a small difference in Na load excreted, expressed in percent of lowest normal Na excretion, -12.5% for patient 3 and -15.1% for patient 9.

In table 1 data are presented demonstrating changes in PRA and aldosterone excretion in the individual subjects during different stages of the Na tolerance test. The effect of acute stress on PRA and urinary Na excretion is illustrated in patients 2 and 10. Patient 2, on the first day of the 150-mEq Na diet, had a cardiogenic arterial embolus secondary to rapid atrial fibrillation. PRA rose to 13.9 ng/ml/hr. The usual reduction in urinary aldosterone with Na loading did not occur. The excretion of Na load was -70% of the lowest normal value. Patient 10 developed pneumonia with a temperature of 102° F on the second day of the 150-mEq Na loading period. PRA rose to 12.3 ng/ml/hr, and aldosterone excretion increased during the 80-mEq diet from 15 to 21 μg/day. The Na excretion was -42.5% below normal. In both patients the insertion of prosthetic valves resulted in a marked improvement in symptoms with an increase in effort tolerance, which has been maintained for more than 2 years.

Figure 5 presents the relation between cardiac indices and excretion of Na load. As a group the patients with CI > 2.5 liters/min/m² excreted 3.24% less Na than the lowest normal value, compared to 20.2% for the group with CI < 2.5 (P < 0.02).

**Effect of Na Depletion with Thiazides on PRA and Cumulative Na and K Balance**

Figure 6 shows that Na depletion by means of thiazide administration caused a prompt and marked elevation of PRA in the patients with CI > 2.5 liters/min/m² (group C). In contrast, the response was delayed until the fourth or fifth day of Na depletion in the two patients in the group with CI < 2.5 liters/min/m² (group D) who responded with an increase in PRA. Although there was good correlation between weight loss and cumulative Na loss (r = 0.914, P < 0.001) in patients with Na restriction or Na depletion, the relation between Na loss and PRA is more complex.

As shown in figure 6, on the first day of Na depletion group D lost slightly less Na than
Table 1

Data on Plasma Renin Activity and Aldosterone Excretion During Different Stages of Sodium Tolerance Test

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Plasma renin activity (ng/ml/hr) control</th>
<th>PRA at end of diet period</th>
<th>Aldosterone excretion (µg/24 hr) at end of diet period</th>
<th>CrCl (ml/min)</th>
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<tr>
<td></td>
<td>control 10 mEq 80 mEq 150 mEq</td>
<td>10 mEq 80 mEq 150 mEq</td>
<td>CrCl 80 mEq 150 mEq</td>
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<td>Group A</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>1</td>
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<tr>
<td>2</td>
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<td>5.3</td>
<td>9.8</td>
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<tr>
<td>3</td>
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<td>1.4</td>
<td>6.9</td>
<td>28</td>
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<td>0.7</td>
<td>19</td>
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<td>0</td>
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<td>2.87</td>
<td>1.8</td>
<td>8.4</td>
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<td>SE</td>
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<td>&lt;0.01</td>
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Abbreviations: PRA = plasma renin activity; CrCl = creatinine clearance.

*Values in parentheses are not included in statistics.

Group C. After 5 days of thiazide administration, the mean of the cumulative Na loss for this group was 186 ± 36.4 (SD) mEq/m² body surface area (BSA) compared with 145 ± 88.7 (SD) mEq/m² BSA for group C. The wide variation in cumulative Na balance in patients in group D was accompanied by diverse patterns of PRA and aldosterone responses. Patients who responded to Na depletion with an increase, even if delayed, in PRA, differed from the other patients in group D in that they both had right ventricular end-diastolic (RVED) and mean pulmonary arterial (PA) pressures in the normal range. Five days of thiazide administration did not elevate PRA in three patients who had elevated mean PA and RVED pressures. In addition, one patient had high blood volumes and peripheral edema. Another patient, with a control PRA value of 4.6 ng/ml/hr, had a negative Na balance of only 56.7 mEq on the first day and a 5-day cumulative Na loss of only 78.6 mEq/m² BSA. Although on the fifth day the PRA of this patient did not reach the control value, PRA was moderately elevated during the whole depletion period, and aldosterone excretion was also slightly above normal. This patient had a urinary aldosterone of 40 µg/day without an increase in PRA. Administration of spironolactone (Aldactone) for 3 days raised...

Figure 5

Relation between cardiac indices and percent excretion of Na load.
the cumulated Na loss from 175 to 262 mEq. With this degree of Na loss, PRA rose to 8.4 ng/ml/hr and aldosterone excretion to 60 µg/day.

It was interesting to note the effect of the 5-day Na depletion regimen on blood volume expressed as a percentage of the expected normal value.12 The mean control value of blood volume for group C was +17.4 ± 4.13% (SE) compared to 31.7 ± 7.45% for group D (P < 0.3). After 5 days of Na depletion the mean value of the former group was −0.03 ± 5.83% (SE) compared to a mean of +19.1 ± 5.09% for the latter group (P < 0.05).

Na and K Exchange in the Kidney

In table 2 are presented data on percentage of filtered Na and K load excreted during different stages of the Na loading and thiazide regimens. K/Na ratios of percent of filtered load were used to express this cation exchange for comparison with urinary Na and aldosterone excretion and PRA. The values for the

![Figure 6](http://circ.ahajournals.org/)

**Figure 6**

The relation of mean PRA values to cumulative Na and K balance in patients with valvular heart disease on a 10-mEq Na diet plus a thiazide diuretic. Horizontal lines mark Na depletion period. In upper panel the vertical bracketed lines show range. In lower panel, they denote standard deviation of the mean.

### Table 2

<table>
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<th>Patient no.</th>
<th>2 days, 10 mEq Na</th>
<th>4 days, 10 mEq Na</th>
<th>2 days, 80 mEq Na</th>
<th>4 days, 80 mEq Na</th>
<th>2 days, 150 mEq Na</th>
<th>4 days, 150 mEq Na</th>
<th>PRA (µg/ml/hr)</th>
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K/Na ratio varied inversely with those of the urinary Na and directly with the 24-hr urinary aldosterone excretion and PRA. The data on patient 17 demonstrate that spironolactone definitely reduced the K-Na exchange.

By using the 24-hr endogenous creatinine clearance to calculate the filtered load, the profound effect of spironolactone on the Na-K exchange in the kidney could be demonstrated in the patients of groups C and D. In all nine of the patients who had received spironolactone, the K/Na ratio of percent of filtered load excreted fell from a mean value of 315 ± 66 to 47 ± 4.3 (P < 0.001). The urinary Na/K ratio increased from 0.164 to 0.979 (P < 0.001).

**Effect of Na Loading and Na Depletion on Mean Blood Pressure**

With Na loading, patients with CI > 2.5 liters/min/m² had an increase of mean blood pressure (MBP) of 4.12 mm Hg standing and 5.46 mm Hg lying. In those with CI < 2.5 liters/min/m², MBP increased 0.48 mm Hg standing and decreased 0.85 mm Hg lying. With Na depletion, MBP of those with CI > 2.5 liters/min/m² increased 0.69 mm Hg standing and decreased 5.38 mm Hg sitting. In those with CI < 2.5 liters/min/m², MBP fell 5.05 mm Hg standing and 6.45 mm Hg sitting.

**Discussion**

The data presented in this paper indicate that the responses of PRA and aldosterone excretion to Na depletion or loading in patients with valvular heart disease are influenced by cardiohemodynamic factors. The patients with CI > 2.5 liters/min/m² (groups A and C) responded to a 10-mEq Na diet or thiazide therapy with a prompt rise in PRA and a corresponding rise in urinary aldosterone excretion. With Na loading, PRA and aldosterone values fell. The renal data on the subjects in this group are compatible with the macula densa theory as presented by Vander and by Reeves and Sommers.

It is more difficult to try to explain the mechanisms responsible for control of renin release in groups B and D (CI < 2.5 liters/min/m²), in which wide variations in hemodynamic abnormalities were found. The techniques of Braunwald's Na tolerance test proved useful in demonstrating that, as a group, patients with lower cardiac indices retained a higher percent of ingested Na; however, the determination of cardiac index does not predict the ability of an individual to excrete a Na load. The paradoxical fall in PRA in this group as a result of Na restriction may be due to improvement in cardiac function. Conversely, the rise in PRA of some of these patients may be caused by reduction in cardiac reserve with a concurrent decrease in renal blood flow. Elevation of mean blood pressure and blood volume blunted the response of PRA to Na loss in all groups, but was particularly noticeable in group D. The findings of Zelis and his colleagues may help to clarify this phenomenon. They reported that in congestive heart failure there is a diminished dilator capacity of the resistance vessels which is related to an excessive Na and water content of the vasculature. The reactive hyperemic blood flow response is also diminished in hypertension in which it is established that arterial Na is elevated. The delayed or suppressed renin release by the kidney in response to thiazide in the patients in group D, where Na retention is due to heart failure, is similar to that which we recently reported in patients with chronic essential hypertension with renin suppression. In both, renin suppression can be overcome. In the individual patient a critical loss of Na may be necessary before the stretch of the baroreceptors, postulated by Tobian, can be reduced to the degree necessary for the release of renin by the juxtaglomerular cells. It is equally possible that an increased intracellular Na and decreased intracellular K concentration in the macula densa cells could inhibit the activity of the macula densa enzymes which Reeves and Sommers have postulated influence renin production by the juxtaglomerular cells. With sufficient Na loss, the activity of these enzymes would be enhanced, thereby increasing renin release.

The increase in urinary aldosterone excretion without an increase in renin activity in a
patient of group D, the only patient in this study with edema, may be due to a decreased rate of metabolism of aldosterone by the liver. The administration of the aldosterone antagonist, spironolactone, to this patient, as well as to eight other patients, caused a marked increase in Na excretion and urinary Na/K ratio as well as in PRA. Braunwald reported that administration of spironolactone markedly improved the response to Na load in three patients with valvular heart disease by blocking aldosterone-induced Na reabsorption. These findings are compatible with the view that increased levels of circulating aldosterone play an important role in Na and water retention, which is characteristic of heart failure.

Davis has concluded from his studies on congestive heart failure that “the basic mechanisms for the continued chronic retention of salt and water appear to be secondary to the prolonged alteration in renal afferent arteriolar function, release of renin, and increased aldosterone production. Sudden acute changes in glomerular filtration rate during the chronic course of heart failure contribute to alterations in Na and water excretion.” Patients 2 and 10 (table 1) are examples of acute changes in Na retention with an elevation in PRA and urinary aldosterone excretion.

The data presented demonstrate the usefulness of the determinations of PRA and urinary aldosterone excretion in evaluating the mechanisms by which the kidney retains Na in patients with valvular heart disease.

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