Sodium Transport Parameters in Erythrocytes of Patients with Primary Aldosteronism

JEAN B. SMITH, MARY B. WADE, NAOMI S. FINEBERG, AND MYRON H. WEINBERGER

SUMMARY Primary aldosteronism is an uncommon cause of hypertension but one of particular interest because of its distinctive pathophysiological mechanism of blood pressure elevation. Aldosterone has been associated with increased Na⁺,K⁺-adenosine triphosphatase (ATPase) activity, but there is controversy over which sodium transport parameters are responsible for this increase. We measured intracellular sodium, ouabain-sensitive and ouabain-insensitive sodium efflux, and the number of Na⁺,K⁺-ATPase sites of washed erythrocytes, as well as Na⁺-Li⁺ countertransport and the Li⁺-K⁺ cotransport rate constant of lithium-loaded red blood cells (RBCs) in six patients with primary aldosteronism and in 50 normal subjects. Ouabain-sensitive sodium efflux was significantly (p<0.001) higher for the primary aldosteronism patients than for normal subjects (1.85 ± 0.29 vs 1.51 ± 0.21 mmol/L RBC/hr) even though the intracellular sodium concentration (7.2 ± 1.5 vs 6.7 ± 1.9 mM) and the number of the Na⁺,K⁺-ATPase sites per RBC (331 ± 52 vs 385 ± 97) were not increased. The elevated sodium efflux appeared to be due to a significant (p<0.001) increase in the rate constant (1.60 ± 0.12 x 10⁻⁹ vs 1.28 ± 0.15 x 10⁻⁹ mmol/site/hr) of the ouabain-sensitive sodium efflux. The rate constant decreased significantly (p<0.01) after treatment.

(Hypertension 11: 141-146, 1988)

KEY WORDS • Na⁺-K⁺ pump • red blood cells • intracellular sodium • Na⁺-K⁺-ATPase

Essential human hypertension may result from a variety of pathophysiological mechanisms. Some studies have suggested that abnormalities of cellular electrolyte transport may be involved. Some hypertensive subjects appear to have an expanded extracellular fluid volume and increased body sodium content, while vasoconstriction and increased vascular resistance predominate in others. Primary aldosteronism is an uncommon cause of hypertension but one of particular interest because of its distinctive pathophysiological mechanism of blood pressure elevation. Excessive mineralocorticoid activity produces increased sodium and water absorption at the distal tubule and results in an expansion of extracellular fluid volume. Although the renal effects of mineralocorticoids are well understood, few studies of their effects on other cells have been reported.

Aldosterone has been linked to increased activity of the Na⁺,K⁺-adenosine triphosphatase (ATPase)-mediated pump in red blood cells (RBCs) of patients with hyperaldosteronism, in tissue preparations exposed to aldosterone in vitro, and in tissues from animals with the deoxycorticosterone acetate-salt form of hypertension due to mineralocorticoid excess. These preliminary studies have engendered controversy about whether the increased Na⁺-K⁺ pump activity is due to an increase in the reactivity of Na⁺,K⁺-ATPase or to an increase in the amount of Na⁺,K⁺-ATPase. Edelman and Marver demonstrated that aldosterone increased protein synthesis in toad bladder but had no effect on the maximum velocity (V₉) or Kₘ for activation of ATPase by adenosine 5'-triphosphate (ATP). In addition to increases caused by an increase in the number of ATPase sites, Jorgensen observed increases in Na⁺,K⁺-ATPase activity that appeared to be too rapid to be attributable to ATPase synthesis. Songu-Mize et al. conducted studies suggesting that the ATPase response to mineralocorticoids may be dependent on the duration of exposure to the steroid.

We measured intracellular sodium, ouabain-sensitive and ouabain-insensitive sodium efflux, and the number of Na⁺,K⁺-ATPase sites of washed erythrocytes, as well as Na⁺-Li⁺ countertransport and the
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Li⁺-K⁺ cotransport rate constant of lithium-loaded RBCs in patients with primary aldosteronism in an attempt to clarify the role of aldosterone on RBC electrolyte transport. These studies were conducted before and after intervention in three patients with the dexamethasone-suppressible form of hyperaldosteronism and in three with adrenal adenomas producing aldosteronism.

Subjects and Methods

Three of the patients were members of the same family, a father (Patient D-1; age, 42 years) and two sons (Patient D-2; age, 17 years; Patient D-3; age, 20 years) who had been diagnosed as having dexamethasone-suppressible hyperaldosteronism and had been previously described. Erythrocytes from all three were studied after medication had been withdrawn for at least 14 days. Two of these patients (D-1 and D-2) were also studied after 3 months on a regimen of 0.25 mg of dexamethasone twice daily. The other three patients had been diagnosed by established techniques as having hyperaldosteronism caused by an adrenal adenoma. One woman (Patient P-1; age, 38 years) had been without medication for 1 month when studied, the other woman (Patient P-2; age, 61 years) had been without medication for 10 days; the male patient (P-3; age, 35 years) had been taking spironolactone (50 mg/day) until 7 days before the study began. All three were studied before and at least 4 months after surgical removal of a solitary adrenal adenoma.

The normotensive subjects included for comparison were 27 men and 23 women. Their age range was 20 to 47 years.

RBC Preparation

Venous blood (40 ml) was drawn into heparinized Vacutainer tubes and processed within 1 hour. The RBCs were separated from the plasma and buffy coat after centrifugation for 10 minutes at 1000 g and washed three times in a washing solution (150 mM choline chloride); preparations were centrifuged after each wash for 10 minutes at 1000 g. Packed cells (2 ml) were separated and suspended in a buffer solution (140 mM NaCl, 30 mM HEPES, 10 mM dextrose) for determination of the number of ouabain binding sites; the remaining cells were washed three more times, and a suspension of approximately 50% was prepared in the washing solution to be used for intracellular sodium determination and sodium efflux measurements. The hematocrit of the suspension was determined.

[³H]Ouabain Binding Assay

Details of the ouabain binding assay procedure, a modification of the method of DeLuise et al., have been previously published. Aliquots (0.8 ml) of the cell suspension in HEPES buffer were added to solutions containing 100 μl of [³H]ouabain (0.12 pmol; 20.9 Ci/mmol; New England Nuclear, Boston, MA, USA) and 100 μl of an unlabeled ouabain solution. The unlabeled ouabain concentration in the final dilution was 0.5, 5.0, or 10.0 nM. Each concentration was assayed in duplicate. Samples were incubated in a shaking water bath at 37°C for 3 hours. The cells were then washed three times in 150 mM choline chloride (3 ml) to remove unbound ouabain; the supernatant was removed by aspiration after each wash. A 5% solution of trichloroacetic acid (1.2 ml) was added to release the bound ouabain from the cells, the sample was centrifuged at 800 g for 5 minutes, and 1 ml of the supernatant was added to 10 ml of scintillation fluid (New England Nuclear.) The bound [³H]ouabain was assessed using a Nuclear Chicago Mark II liquid scintillation counter (TM Analytic, Elk Grove, IL, USA). Scatchard plots (bound/free vs total bound ouabain) were constructed to determine the concentration of [³H]ouabain binding sites (x-intercept) in the incubated cell suspension. A representative plot is given in Figure 1, and a sample calculation is given in the legend.

Intracellular Sodium Concentration

Further dilution (1:51) of the 50% suspension of cells washed six times was prepared in 0.02% aca- tionox (Scientific Products, McGaw Park, IL, USA), and the sodium concentration was measured by atomic absorption spectroscopy (Instrumentation Laboratories, Andover, MA, USA). Intracellular sodium concentration [Na⁺], was calculated from the following equation:

\[
[Na⁺] = \frac{Na⁺ concentration of 1:51 dilution \times 51}{Hematocrit of suspension}
\]

Sodium Efflux Rate Determinations

Further dilutions of 4 ml of the 50% suspension were prepared for sodium efflux rate measurements in 10 ml of a MgCl₂ solution without ouabain (70 mM MgCl₂, 85 mM sucrose, 10 mM KCl, 1 mM glucose, 10 mM Tris-morpholinoepanesulfonic acid [MOPS], pH 7.4 at 37°C) and 10 ml of a MgCl₂ solution with ouabain (70 mM MgCl₂, 85 mM sucrose, 10 mM KCl, 1 mM glucose, 0.1 mM ouabain, 10 mM Tris-MOPS, pH 7.4 at 37°C). The suspensions were incubated at 37°C in a shaking water bath, and duplicate samples were removed at 0, 5, and 13 minutes. The suspension was centrifuged, and the supernatant was removed for sodium analysis by atomic absorption spectroscopy. Graphs of the sodium concentration in the supernatant versus the incubation period yielded the rate of sodium efflux into the solutions with and without ouabain. The difference was calculated to be the ouabain-inhibitable sodium efflux rate. This method of deriving a rate constant for the efflux per RBC yields the same value as a graph of \( -\ln[Na⁺] \) versus time for conditions in which less than 5% of the [Na⁺] has effuxed.

Sodium efflux has been related to [Na⁺], by the following equation:

\[
Na⁺ efflux = \frac{V_{max}}{K_n + [Na⁺]^3}
\]

where \( K_n \) is the apparent dissociation constant for sodium (approximately 3.2 mM) and \( V_{max} \) is the maximum efflux, which is proportional to the number of
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ATPase sites. Substituting $k \times$ sites for $V_{\text{max}}$ and rearranging yields:

$$\text{Na efflux} = \frac{k \times \text{sites}}{(\text{Na}^+, + K\text{Na})^3} \quad (3)$$

Independent determinations of sodium efflux, $[\text{Na}]$, and sites per erythrocyte permitted calculation of a rate constant ($k$) for all subjects.

**Na$^+$-Li$^+$ Countertransport and Li$^+$-K$^+$ Cotransport**

These transports were determined according to a previously published method. In both transport systems lithium replaces sodium to reflect Na$^+$-Na$^+$ countertransport and Na$^+$-K$^+$ cotransport, respectively. A 5-ml aliquot of packed RBCs was added to 20 ml of 150 mM LiCl and incubated at 37°C for 3 hours in a shaking water bath. The cells were washed five times in the choline chloride washing solution to remove extracellular lithium, and a suspension (~50%) of the cells in the choline chloride solution was prepared. The hematocrit of the suspension was determined, a dilution was prepared for intracellular determination, and 2.0 ml was added to 10 ml of each of the following solutions: 1) 150 mM NaCl, 0.10 mM ouabain, 10 mM glucose, 10 mM Tris-MOPS, pH 7.4 at 37°C; 2) 150 mM choline chloride, 0.10 mM ouabain, 10 mM glucose, 10 mM Tris-MOPS, pH 7.4 at 37°C; and 3) 150 mM choline chloride, 0.10 mM ouabain, 10 mM glucose, 1 mM furosemide, 10 mM Tris-MOPS, pH 7.4 at 37°C.

These suspensions were incubated at 37°C in a shaking water bath with samples removed at 45 and 90 minutes. The samples were centrifuged for 5 minutes at 1000 g, and the supernatant was removed to be analyzed for lithium by atomic absorption spectroscopy. The lithium efflux into each of the solutions was calculated from graphs of lithium concentration versus time. The Na$^+$-Li$^+$ countertransport is the difference between the efflux into Solutions 1 and 2; the Li$^+$-K$^+$ cotransport rate constant is the difference between Solutions 2 and 3 divided by the intracellular lithium concentration.

The coefficient of variation for the assays established by repeated (2–8) measurements for the same normotensive subjects ($n = 21$) over a 14-month period was 6.3% for $[\text{Na}]$, 6.1% for sodium efflux, 5.1% for the number of sites per RBC, 10.0% for Na$^+$-Li$^+$ countertransport, and 23.2% for Li$^+$-K$^+$ cotransport.

**Statistics**

Data are given as means ± SD. Values of the transport parameters were compared in the two groups of hypertensive patients. If there were no differences, the groups were combined for analysis. As only ouabain-sensitive sodium efflux showed a difference, the groups were examined separately for that parameter.

Pretreatment and posttreatment values in patients with hypertension were analyzed with a paired $t$ test. For comparisons with all normotensive subjects a group $t$ test was used.

**Results**

There were abnormalities in several of the sodium transport parameters in patients with hyperaldosteronism. Although $[\text{Na}]$ was not significantly elevated among the hyperaldosteronism patients, values for two of the patients with primary aldosteronism caused by an adenoma declined considerably postoperatively (Table 1). Ouabain-sensitive sodium efflux was significantly ($p < 0.001$) elevated among all the patients before treatment. The difference between the pretreatment and posttreatment values approached significance ($p = 0.061$, paired $t$); posttreatment values were similar to those of normal subjects (see Table 1). The number of sites per RBC among the patients approached a significant difference ($p = 0.051$) from that of the normotensive subjects, but it was not significantly altered by treatment. Ouabain-insensitive sodium efflux was significantly ($p < 0.025$) higher for the dexamethasone-suppressible hypertensive patients than for the normotensive subjects, but the lack of change after treatment among the dexamethasone-treated patients suggests that this difference may not be due to the aldosterone excess (see Table 1).

The rate constant calculated from Equation 3 was significantly ($p < 0.001$) elevated among all six of the patients and decreased significantly ($p < 0.01$) after treatment (Figure 2). In addition, Na$^+$-Li$^+$ countertransport was significantly ($p < 0.01$) elevated among all six patients.
TABLE 1. Measurements on Washed Erythrocytes

<table>
<thead>
<tr>
<th>Group</th>
<th>[Na] (mmol/L RBC)</th>
<th>Sites/RBC</th>
<th>Ouabain-sensitive Na efflux (mmol/L RBC/hr)</th>
<th>Ouabain-insensitive Na efflux (mmol/L RBC/hr)</th>
<th>Plasma K⁺ (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n = 27)</td>
<td>7.1 ± 2.0</td>
<td>389 ± 111</td>
<td>1.57 ± 0.24</td>
<td>0.43 ± 0.15</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>Women (n = 23)</td>
<td>6.3 ± 1.4</td>
<td>380 ± 82</td>
<td>1.45 ± 0.15</td>
<td>0.34 ± 0.11</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>All (n = 50)</td>
<td>6.7 ± 1.9</td>
<td>385 ± 97</td>
<td>1.51 ± 0.21</td>
<td>0.39 ± 0.14</td>
<td>4.3 ± 0.4</td>
</tr>
<tr>
<td>Dexamethasone-suppressible hyperaldosteronism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-1 PRETREATMENT</td>
<td>9.1</td>
<td>249</td>
<td>1.88</td>
<td>0.59</td>
<td>4.1</td>
</tr>
<tr>
<td>POSTTREATMENT</td>
<td>9.2</td>
<td>264</td>
<td>1.70</td>
<td>0.57</td>
<td>4.2</td>
</tr>
<tr>
<td>D-2 PRETREATMENT</td>
<td>7.2</td>
<td>306</td>
<td>1.89</td>
<td>0.64</td>
<td>3.8</td>
</tr>
<tr>
<td>POSTTREATMENT</td>
<td>7.5</td>
<td>295</td>
<td>1.71</td>
<td>0.57</td>
<td>4.2</td>
</tr>
<tr>
<td>D-3 (untreated)</td>
<td>6.4</td>
<td>314</td>
<td>1.45</td>
<td>0.52</td>
<td>4.7</td>
</tr>
<tr>
<td>Primary hyperaldosteronism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-1 PREOPERATIVE</td>
<td>8.2</td>
<td>356</td>
<td>2.12</td>
<td>0.29</td>
<td>2.8</td>
</tr>
<tr>
<td>POSTOPERATIVE</td>
<td>6.1</td>
<td>327</td>
<td>1.37</td>
<td>0.16</td>
<td>4.0</td>
</tr>
<tr>
<td>P-2 PREOPERATIVE</td>
<td>7.7</td>
<td>366</td>
<td>2.18</td>
<td>0.33</td>
<td>3.2</td>
</tr>
<tr>
<td>POSTOPERATIVE</td>
<td>4.9</td>
<td>452</td>
<td>1.41</td>
<td>0.21</td>
<td>3.7</td>
</tr>
<tr>
<td>P-3 PREOPERATIVE</td>
<td>4.9</td>
<td>396</td>
<td>1.58</td>
<td>0.30</td>
<td>3.7</td>
</tr>
<tr>
<td>POSTOPERATIVE</td>
<td>5.2</td>
<td>372</td>
<td>1.50</td>
<td>0.25</td>
<td>3.9</td>
</tr>
</tbody>
</table>

Normotensive values are means ± SD.

FIGURE 2. Rate constant for ouabain-sensitive sodium efflux before and after treatment in patients with dexamethasone-suppressible primary aldosteronism (○) and primary aldosteronism due to an adrenal adenoma (□). Bar represents means ± SD for 50 normal subjects. Single asterisk indicates significant difference (p < 0.01) between pretreatment and posttreatment values (by paired t test). Double dagger indicates significant pretreatment difference (p < 0.001) between patients and normal subjects (by Student's t test).

these subjects, but treatment did not affect this elevation except in the patient taking spironolactone (Patient P-3; Table 2).

Discussion

The observation of an elevated ouabain-sensitive sodium efflux among patients with hyperaldosteronism is in agreement with previous studies showing increases in ²²Na efflux,¹ inorganic phosphate production,²,⁴,⁶ and ⁸⁶Rb uptake.⁷ Gall et al.¹ reported increased sodium efflux per RBC and elevated first-order rate constants for sodium efflux per RBC for subjects with hyperaldosteronism. Since the first-order rate constant reflects the activity of the Na⁺,K⁺-ATPase and is directly proportional to the number of ATPase sites per cell,¹⁵ it was not clear whether the increased rate constants they observed were due to an increase in the number of sites or to an increased activity per site. Our results, which show no increase in the number of ATPase sites measured by [³H]ouabain binding for patients with primary aldosteronism in combination with an elevated rate constant for the sodium efflux per site (k), indicate that the increase in sodium efflux is due to an increase in the reactivity of the Na⁺,K⁺-ATPase.

Jorgensen⁴ has proposed that the rapid increase in sodium efflux in the presence of aldosterone may be due to an initial increase in [Na], followed by a chronic adaptation in which the number of ATPase sites is increased. The results of our study showing normal values for both [Na], and the number of sites do not support this hypothesis. If the rate expression (Equation 3) accurately describes sodium efflux, the increased sodium efflux per cell in patients with primary aldosteronism is due to a change in the rate constant, k. This behavior suggests that the effect of aldosterone on Na⁺,K⁺-ATPase activity may be due to a change in the conformation of ATPase, permitting increased activity. Perhaps the altered conformation allows sodium to bind more readily or to have easier access to the transport channel.
**TABLE 2. Measurements on Lithium-Loaded Cells**

<table>
<thead>
<tr>
<th>Group</th>
<th>Na(^+)-Li(^+) countertransport (mmol/L RBC/hr)</th>
<th>Li(^+)-K(^+) cotransport rate constant (hr(^{-1}) x 10(^{-2}))</th>
<th>Li leak rate constant (hr(^{-1}) x 10(^{-2}))</th>
<th>[Li](_i) (mmol/L RBC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n = 17)</td>
<td>0.226 ± 0.066</td>
<td>10.0 ± 5.0</td>
<td>2.2 ± 0.3</td>
<td>7.3 ± 1.0</td>
</tr>
<tr>
<td>Women (n = 13)</td>
<td>0.224 ± 0.080</td>
<td>8.0 ± 3.1</td>
<td>2.1 ± 0.3</td>
<td>6.6 ± 0.8</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men (n = 10)</td>
<td>0.142 ± 0.076</td>
<td>6.2 ± 3.7</td>
<td>2.4 ± 0.4</td>
<td>6.1 ± 0.4</td>
</tr>
<tr>
<td>Women (n = 9)</td>
<td>0.142 ± 0.132</td>
<td>5.1 ± 2.7</td>
<td>2.3 ± 0.6</td>
<td>6.2 ± 1.3</td>
</tr>
<tr>
<td>Dexamethasone-suppressible hyperaldosteronism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-1</td>
<td>Pretreatment 0.438</td>
<td>11.3</td>
<td>2.6</td>
<td>7.5</td>
</tr>
<tr>
<td></td>
<td>Posttreatment 0.519</td>
<td>14.5</td>
<td>3.1</td>
<td>6.2</td>
</tr>
<tr>
<td>D-2</td>
<td>Pretreatment 0.315</td>
<td>13.5</td>
<td>2.7</td>
<td>6.8</td>
</tr>
<tr>
<td></td>
<td>Posttreatment 0.316</td>
<td>19.3</td>
<td>1.9</td>
<td>5.6</td>
</tr>
<tr>
<td>D-3 (untreated)</td>
<td>0.287</td>
<td>17.3</td>
<td>2.7</td>
<td>6.6</td>
</tr>
<tr>
<td>Primary hyperaldosteronism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-1</td>
<td>Preoperative 0.169</td>
<td>4.2</td>
<td>2.0</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>Postoperative 0.176</td>
<td>2.8</td>
<td>1.5</td>
<td>5.3</td>
</tr>
<tr>
<td>P-2</td>
<td>Preoperative 0.287</td>
<td>9.5</td>
<td>2.3</td>
<td>6.4</td>
</tr>
<tr>
<td></td>
<td>Postoperative 0.235</td>
<td>6.2</td>
<td>1.6</td>
<td>5.2</td>
</tr>
<tr>
<td>P-3</td>
<td>Preoperative 0.512</td>
<td>9.6</td>
<td>2.2</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Postoperative 0.325</td>
<td>7.5</td>
<td>1.9</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Normotensive values are means ± SD. [Li]\(_i\) = intracellular Li concentration.

Sodium transport measurements for the patient who had been taking spironolactone (Patient P-3) exhibited several differences from the other two patients with adrenal adenomas. Patient P-3 did not have the elevated sodium efflux evident in the other patients; his postoperative values were similar to preoperative values. These observations are consistent with an antagonistic action of spironolactone on the erythrocytes' response to aldosterone previously reported by Gall et al.\(^1\) in patients with hyperaldosteronism and in normal subjects. However, the finding that the patient taking spironolactone had an elevated rate constant compared with that for normal subjects implies that aldosterone had an effect on Na\(^+\),K\(^+\)-ATPase activity that was not antagonized by spironolactone. Perhaps his pretreatment rate constant value would have been even higher in the absence of spironolactone.

In view of reports indicating possible environmental\(^16\) and genetic\(^17\) influences on erythrocyte sodium transport, we cannot exclude the possibility that the similarities exhibited by two of the three patients with dexamethasone-suppressible hyperaldosteronism (Patients D-1 and D-2) may have been due to such factors. With the exception of the patient who had taken spironolactone, the Na\(^+\)-Li\(^+\) countertransport values were similar before and after treatment for both the dexamethasone-suppressible patients and the patients with primary aldosteronism. This lack of effect of aldosterone on Na\(^+\)-Li\(^+\) countertransport is consistent with animal studies showing the effect of aldosterone to be primarily in the distal regions of the kidney, where Na\(^+\),K\(^+\)-ATPase is the principal sodium transport mechanism.\(^3\)\(^-\)\(^18\) Although the interpretation is somewhat controversial,\(^19\) Na\(^+\)-Li\(^+\) countertransport has been proposed as an indicator of Na\(^+\)-H\(^+\) exchange in the proximal tubules,\(^20\) a region where aldosterone probably exerts little influence. Since the only patient who had different pretreatment and posttreatment values for Na\(^+\)-Li\(^+\) countertransport was the one who had taken spironolactone (preoperation, 0.512 mmol/L RBC/hr; postoperation, 0.325 mmol/L RBC/hr), and Na\(^+\)-Li\(^+\) countertransport may be related to sodium reabsorption in the proximal tubular region, the possibility that spironolactone may affect proximal tubular reabsorption should be investigated.

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