A POSSIBLE ROLE OF HYPOKALEMIA IN THE MANIFESTATION OF HIGH QRS VOLTAGE AND SINUS BRADYCARDIA IN PATIENTS WITH PRIMARY ALDOSTERONISM

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We analyzed electrocardiograms obtained from 29 Japanese patients with primary aldosteronism (PA) and in 106 patients with essential hypertension (EHT). QRS voltage was higher (p < 0.05) and heart rate was slower (p < 0.01) in cases of PA. A significant reduction in QRS voltage and a significant increase in heart rate were observed after short-term potassium replacement or after short-term administration of spironolactone, preoperatively, and within 2 to 4 weeks after the removal of aldosteronoma. These significant changes in QRS voltage and heart rate were always accompanied by significant increases in the serum potassium concentration but not always by a reduction in blood pressure. The long-term follow-up of EHT-patients showed a slower reduction in their high QRS voltage, despite effective antihypertensive therapy. Thus, hypokalemia, in addition to hypertension, may be relevant to the high QRS voltage in PA. There also appeared to be a relationship between hypokalemia and bradycardia.

High QRS voltage or sinus bradycardia has not been reported to be a characteristic feature on the electrocardiogram (ECG), in patients with hypokalemia. High QRS voltage has usually been attributed to myocardial hypertrophy or to an enlarged heart, and is frequently observed in cases of hypertension. However, it has been reported that the amplitude of the QRS complex increases in hypokalemic animals and that a low extracellular potassium concentration might induce bradycardia by increasing the maximal diastolic potential of the cardiac pacemaker cells.

Although primary aldosteronism (PA) is associated with hypertension and hypokalemia, there has apparently been no report on the high QRS voltage or on the heart rate in relation to the serum potassium concentration in patients with PA. We analyzed ECGs from patients with PA and found that hypokalemia may play a role in the manifestation of high QRS voltage and sinus bradycardia.

SUBJECTS AND METHODS

Study I. Twenty-nine patients with PA and 106 with EHT, as the controls, were investigated. Antihypertensive drugs including diuretics were discontinued for at least 4 weeks prior to the study. The diagnosis of PA was made by Conn’s criteria and was confirmed by adrenal exploration. All patients were Japanese and had been

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TABLE I  CLINICAL PROFILES AND LABORATORY DATA OF PATIENTS WITH PRIMARY ALDOSTERONISM (PA) AND PATIENTS WITH ESSENTIAL HYPERTENSION (EHT)

<table>
<thead>
<tr>
<th></th>
<th>PA</th>
<th>EHT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>preop</td>
<td>postop</td>
</tr>
<tr>
<td>No.</td>
<td>29</td>
<td>106</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.9 ± 10.2</td>
<td>41.5 ± 11.5</td>
</tr>
<tr>
<td>Sex (m:f)</td>
<td>6:23</td>
<td>74:32</td>
</tr>
<tr>
<td>Weight (kgw)</td>
<td>49.0 ± 7.7</td>
<td>46.9 ± 6.9**</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>186.2 ± 23.7</td>
<td>131.3 ± 22.3**</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>105.0 ± 13.5</td>
<td>84.8 ± 13.2**</td>
</tr>
<tr>
<td>S-Na (mEq/L)</td>
<td>146.1 ± 4.3</td>
<td>140.3 ± 3.5**</td>
</tr>
<tr>
<td>S-K (mEq/L)</td>
<td>2.67 ± 0.51</td>
<td>4.80 ± 0.59**</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>0.12 ± 0.17</td>
<td>2.31 ± 1.72*</td>
</tr>
<tr>
<td>PAC (ng/dl)</td>
<td>64.4 ± 37.6</td>
<td>5.7 ± 3.5**</td>
</tr>
<tr>
<td>CTR (%)</td>
<td>52.2 ± 4.4</td>
<td>46.5 ± 5.4**</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>38.0 ± 4.2</td>
<td>37.2 ± 3.4</td>
</tr>
<tr>
<td>Frequency of High QRS volt.</td>
<td>22/29 (75.9%)</td>
<td>10/29 (34.5%$)</td>
</tr>
<tr>
<td>ΣLVP (mm)</td>
<td>53.6 ± 15.9</td>
<td>44.5 ± 11.7**</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>60.3 ± 11.0</td>
<td>71.3 ± 11.6**</td>
</tr>
</tbody>
</table>

*: p < 0.05, **: p < 0.01 (vs preop PA, by paired t-test)
#: p < 0.05, ###: p < 0.01 (vs preop PA, by unpaired t-test)
$: p < 0.05, $$: p < 0.01 (vs preop PA, by x-square test)
SPB = systolic blood pressure; DBP = diastolic blood pressure; S-Na = serum sodium concentration; S-K = serum potassium concentration; PRA = plasma renin activity; PAC = plasma aldosterone concentration; CTR = cardiothoracic ratio; Hct = hematocrit; ΣLVP = SaVF + SV2 + RV5; HR = heart rate

admitted to Kyushu University Hospital.

In patients with PA, the serum potassium concentration, blood pressure and ECG were checked under the following conditions:
1) at the time of admission, no special diet, in all patients,
2) 5th to 8th day of potassium intake with mild salt restriction (34–100 mEq/day of sodium and 100–200 mEq/day of potassium) in 6,
3) 3rd or 4th day of low-salt diet (34 mEq/day of sodium and 50–70 mEq/day of potassium) with 120 mg of furosemide orally on the first day of this period in 14,
4) 7th to 13th day of 300 mg/day of spironolactone administration in 15, and
5) 2 to 4 weeks after the removal of aldosteronoma while on the ordinary hospital diet (220–250 mEq/day of sodium and 50–70 mEq/day of potassium) or on the control diet (170 mEq/day of sodium and 50–70 mEq/day of potassium) in all patients.

In patients with EHT, the ECGs were checked at the time of admission.

**Study 2.** To clarify the rapidity of reduction of high QRS voltage in PA, the ECG and serum K concentration were checked again in patients with EHT, several (6.1 in average) months after the antihypertensive therapy. Only the 7 EHT-patients, among those with a high QRS voltage at the time of admission, responded well to the antihypertensive therapy with a rapid (within 2 weeks) reduction of blood pressure to 110 mmHg of mean blood pressure or less, and this level was maintained throughout the follow-up period. These 7 patients were the subjects in Study 2. Blood pressure was measured by a Riva-Rocci type sphygmomanometer on the right arm after the patient relaxed comfortably, in the supine position, and on the same day ECG and serum electrolytes were checked. A standard 12-lead resting ECG was recorded by one of 2 experts at a paper speed of 25 mm/sec with calibrations of 1.0 mV = 10 mm and 1.0 mV = 5 mm. The same technician recorded all ECGs in each patient.

ECG diagnosis for high QRS voltage was based on the Mori-Nakagawa voltage criteria9 which is considered more apt than the Sokolow-Lyon voltage criteria10 for Japanese; that is when any
TABLE II EFFECTS OF POTASSIUM LOADING, SODIUM-WATER DEPLETION AND SPIRONOLACTONE ADMINISTRATION ON BLOOD PRESSURE AND ELECTROCARDIOGRAM IN PATIENTS WITH PRIMARY ALDOSTERONISM

<table>
<thead>
<tr>
<th>No.</th>
<th>Potassium loading</th>
<th>Sodium-water depletion</th>
<th>Spironolactone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>before</td>
<td>after</td>
<td>before</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>188.0 ± 24.5</td>
<td>183.0 ± 24.7</td>
<td>186.0 ± 24.9</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>97.7 ± 6.5</td>
<td>104.0 ± 9.3</td>
<td>107.6 ± 11.6</td>
</tr>
<tr>
<td>S-K (mEq/L)</td>
<td>2.47 ± 0.45</td>
<td>3.67 ± 0.55**</td>
<td>2.71 ± 0.48</td>
</tr>
<tr>
<td>ΣLVP (mm)</td>
<td>49.6 ± 18.5</td>
<td>45.8 ± 14.2*</td>
<td>54.5 ± 19.8</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>55.7 ± 8.5</td>
<td>67.5 ± 12.3**</td>
<td>60.7 ± 13.9</td>
</tr>
</tbody>
</table>

*: p < 0.05, **: p < 0.01 (vs before each maneuver, by paired t-test)
SBP = systolic blood pressure; DBP = diastolic blood pressure; S-K = serum potassium concentration;
ΣLVP = ΣaVF + ΣV2 + ΣV6 ≥ 35 mm.
HR = heart rate

TABLE III EFFECTS OF LONG-TERM ANTIHYPERTENSIVE THERAPY ON THE BLOOD PRESSURE AND THE ELECTROCARDIOGRAM OF PATIENTS WITH ESSENTIAL HYPERTENSION

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Sex</th>
<th>Follow-up period (months)</th>
<th>At the beginning of the antihypertensive therapy</th>
<th>At the end of the follow-up period</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BP (mmHg)</td>
<td>ΣLVP (mm)</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>M</td>
<td>5.1</td>
<td>164/102</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>28</td>
<td>M</td>
<td>4.8</td>
<td>164/120</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>M</td>
<td>7.0</td>
<td>156/106</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>M</td>
<td>10.1</td>
<td>224/134</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>F</td>
<td>5.8</td>
<td>180/104</td>
<td>54</td>
</tr>
<tr>
<td>6</td>
<td>49</td>
<td>F</td>
<td>6.3</td>
<td>190/128</td>
<td>54</td>
</tr>
<tr>
<td>7</td>
<td>65</td>
<td>F</td>
<td>3.7</td>
<td>164/102</td>
<td>69</td>
</tr>
</tbody>
</table>

mean 39.7    6.1  177/113    61.0  4.2  133**189***  58.1  3.9

**: p < 0.01 (vs BP at the beginning of the antihypertensive therapy, by paired t-test)
BP = blood pressure; ΣLVP = ΣaVF + ΣV2 + ΣV5; S-K = serum potassium concentration

of the following three inequalities was satisfied, a high QRS voltage was assumed.
1) SaVF + SV1 + RV6 ≥ 35 mm.
2) SaVF + SV2 + RV6 ≥ 40 mm.
3) SaVF + SV5 + RV6 ≥ 45 mm.

(with the calibration of 1.0 mV = 10 mm).
And the sum of S in aVF and in V2 and R in V5 (expressed as left ventricular potential, ΣLVP) was adopted for the quantitative analysis of QRS voltage. We did not analyze horizontal or downward ST segment depression, flattened T wave, or prominent U wave, as these findings are established characteristic features of ECG in patients with PA11 All ECG tracings were reviewed by 2 examiners (H.M. and T.K.). In the case of a discrepant assessment, a third examiner provided assistance.

The serum sodium and potassium concentrations were measured by a flame photometer. The plasma renin activity (PRA), the plasma aldosterone concentration (PAC), and the aldosterone excretion rate were measured by radioimmunoassay.

All values were expressed as mean ± standard deviation, and paired or unpaired t-test or X-square test was used for statistical analysis. Differences were considered to be significant when the p-value was less than 0.05.

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RESULTS

Study 1. Clinical profiles and laboratory data of the patients studied at the time of admission are shown in Table I.

1) ECG findings at the time of admission in PA (Table I)

Sinus rhythm revealed a slower (p < 0.01) heart rate (60.3 ± 11.0 beats/min) than in the cases of EHT. PQ-time, axis and duration of QRS complex showed no marked abnormalities. The ΣLVP ranged from 34 to 91 mm with an average of 53.6 mm, such being a significantly higher value (p < 0.05) than in EHT, that is 45.5 mm. According to the Mori-Nakagawa criteria, the ECG was diagnosed as high QRS voltage in 22 out of 29 cases (75.9%), and significantly more frequent (p < 0.01) than in EHT (38.7%).

2) Effect of potassium loading (Table II)

No significant change was observed in blood pressure 5 to 8 days after potassium loading in 6 cases, whereas the serum potassium concentration significantly increased from 2.47 ± 0.45 to 3.67 ± 0.55 mEq/l (p < 0.01) and the ΣLVP decreased from 49.6 ± 18.5 to 45.8 ± 14.2 mm (p < 0.05). Heart rate increased from 55.7 ± 8.5 to 67.5 ± 12.3 beats/min (p < 0.01).

3) Effect of sodium-water depletion induced by a low-salt diet and oral furosemide administration (Table II)

Although systolic (SBP) and diastolic (DBP) blood pressures significantly decreased, there were no changes in the serum potassium concentration, ΣLVP, or heart rate. The hematocrit measured in 5 patients increased significantly; from 36.7 ± 2.2 to 40.8 ± 3.9% (p < 0.01).

4) Effect of spironolactone administration (Table II)

A decrease in blood pressure was observed with an average of 32.4 mmHg in SBP (p < 0.01) and 5.7 mmHg in DBP (not significant) 7 to 13 days after spironolactone administration. The serum potassium concentration reverted to the normal range, from 2.72 ± 0.51 to 3.90 ± 1.02 mEq/l (p < 0.01). ECG findings revealed a diminution in ΣLVP from 53.8 ± 18.5 to 48.3 ± 15.3 mm (p < 0.05). Heart rate increased from 56.5 ± 12.4 to 65.4 ± 6.4 beats/min (p < 0.05).

5) Effect of the surgical treatment (Table I)

Replacement therapy was not given to any patient after unilateral adrenalectomy. Blood pressure decreased from 186.2 ± 23.7 / 105.0 ± 13.5 to 131.3 ± 22.3 / 84.8 ± 13.2 mmHg (p < 0.01 for both SBP and DBP) 2 to 4 weeks after the surgery. Similarly, the cardiothoracic ratio (CTR) also significantly decreased from 52.2 ± 4.4 to 46.5 ± 5.4% (p < 0.01), and the serum potassium concentration increased from 2.67 ± 0.51 to 4.80 ± 0.59 mEq/l (p < 0.01). The high QRS voltage disappeared in 12 out of 22 diagnosed at the time of admission. The reduction in ΣLVP from 53.6 ± 15.9 to 44.5 ± 11.7 mm was statistically significant (p < 0.01). Heart rate increased from 60.3 ± 11.0 to 71.3 ± 11.6 beats/min (p < 0.01).

Study 2. In the followed-up EHT-patients, the average value of the ΣLVP was 61.0 mm, the average blood pressure was 177.4/113.7 mmHg, and the average value of the serum potassium concentration was 4.2 mEq/l at the beginning of the antihypertensive therapy. The values were 58.1 mm, 133.1/89.4 mmHg, and 3.9 mEq/l at the end of the period observed, respectively (Table III). Although the blood pressure decreased significantly, the change in the ΣLVP was not statistically significant. In addition, the QRS voltage remained high in 6 out of the 7 patients.

DISCUSSION

Out study revealed that in patients with PA, QRS voltage on precordial leads was higher (p < 0.05) and heart rate was slower (p < 0.01) than in patients with EHT. The incidence of high QRS voltage in PA was more frequent than the previously reported value in cases of clinical hypertension. Moreover, in our present study, PA-patients showed a marked reduction in QRS voltage within 2 to 4 weeks after the removal of the aldosteronoma, whereas in only 2 out of 7 with EHT was there a considerable reduction in QRS voltage after 6 months of effective antihypertensive therapy.

The high QRS voltage seen in hypertension has previously attributed to left ventricular hypertrophy or to an enlarged heart. A reduction in QRS voltage was apparent after long-term antihypertensive therapy, probably due to decrease in the left ventricular mass. However, it has also been reported that left ventricular hypertrophy did not decrease within...
several weeks following surgical relief of chronic pressure- or volume-overload, but did decrease after 3 to 6 months or more in patients with aortic regurgitation\textsuperscript{13-15} or with aortic stenosis\textsuperscript{15} Therefore, it is questionable whether a high QRS voltage in PA-patients reflects only an increase in the left ventricular mass, or whether the rapid reduction in the QRS voltage is actually due to the reduction in the left ventricular mass.

In pre-operative PA-patients, a significant reduction in the QRS voltage was observed in response to potassium loading and/or spironolactone administration, during which time the serum potassium concentration was significantly elevated. However, the blood pressure level remained unchanged during the potassium loading. The QRS voltage did not decrease in response to sodium-water depletion, following which the blood pressure but not the serum potassium concentration was significantly reduced. Surawicz\textsuperscript{5} reported that the amplitude of the QRS complex increased, in a typical pattern, in animals with an advanced hypokalemia. All these findings suggest the possibility that the high QRS voltage seen in PA-patients is at least partly attributed to hypokalemia. Also the mechanism by which the hypokalemia induced the high voltage may be as following: the resting membrane potential of the cardiac muscle is mainly attributable to the ratio of potassium concentration on the two sides of the cell membrane.\textsuperscript{16} Therefore, in the presence of hypokalemia, the ratio would be greater, and the resting potential would also increase. Then the increased resting potential would make the amplitude of the action potential greater, and as the QRS voltage reflects the summation of action potentials from the ventricular muscle fibers, the QRS voltage would become high in the presence of hypokalemia.

Ditchey et al\textsuperscript{17} reported that left ventricular hypertrophy in ECG diagnosed from voltage criteria does not necessarily mean an increase of the left ventricular mass, especially in patients with volume-overload. It is well known that PA is accompanied by sodium and water retention.\textsuperscript{17} In the present study, high PAC, high serum sodium concentration, suppressed PRA and an increased CTR were all present before the surgery, and the values became normal after the surgery (Table I). Therefore, the combination of hypokalemia, increased left ventricular mass, if any, and volume-overload may be relevant to the high QRS voltage in PA-patients. The contribution of volume overload, however, may be minor, because no significant change in the QRS voltage was observed during the short-term depletion of sodium and water induced by furosemide administration and a low-salt diet, while a significant increase in the hematocrit was observed.

In addition to the high QRS voltage, relative bradycardia seemed to be at least partly due to hypokalemia. As the blood pressure level in EHT-and preop PA-patients was similar, and as the heart rate did not increase during sodium-water depletion, despite a significant reduction in SBP and DBP, the bradycardia seen in PA-patients could not be attributed to a barofunction mechanism\textsuperscript{18} of sustained hypertension. The bradycardia disappeared after the surgery, concomitant with the normalization of serum potassium concentration. The heart rate also significantly increased after potassium loading, and after spironolactone administration, and the increase in the heart rate was accompanied by a slight but significant increase in the serum potassium concentration. These findings strongly suggest the contribution of hypokalemia to bradycardia in PA-patients. The bradycardia in hypokalemic PA-patients may be attributable to the increased maximal diastolic potential of the cardiac pacemaker cells\textsuperscript{6}

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