Influence of Digitalis on Intracellular Electrolytes in Patients with Congestive Heart Failure

Investigations on Erythrocytes

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Since Harrison, Pilcher and Ewing\(^1\) described the decrease in potassium content in cardiac muscle in patients who died of congestive heart failure (1930), and Calhoun and Harrison\(^2\) suggested that the potassium content of the cardiac muscle was markedly decreased in dogs receiving toxic doses of digitalis (1931), many investigators reported intracellular electrolyte metabolism in patients with congestive heart failure.

For the purpose of determination on intracellular electrolyte content in patients with congestive heart failure, following four methods are generally used.

1. Total electrolyte balance—Extracellular electrolyte content.
2. To calculate electrolyte content in biopsied skeletal muscle.
3. To substitute erythrocytes for representative cells in human body.
4. To calculate exchangeable electrolyte by a radioactive isotope.

Among these methods, the third one is relatively simple method to infer the change in intracellular electrolyte content in patients with congestive heart failure.

In this study, sodium and potassium concentrations in erythrocytes in patients with congestive heart failure are estimated and then digitalis effects on them are studied.

**Materials and Methods**

Twenty one patients who were admitted in the Third Medical Clinic of Kyoto University Hospital were divided into two groups. The control group consisted of 6 patients who had neither clinical nor laboratory evidence of congestive heart failure. The other group consisted of 15 patients who had mild to severe congestive heart failure (grade II—IV according to New York Heart Association's classification). Thirteen patients of these two groups (4 patients of the former group and 9 patients of the latter group) were administered digitalis (0.2—0.8 mg of lanatoside C intravenously or 0.5—1.0 mg of digoxin orally per day) for one to nine weeks, and in each case 2 to 23 determinations of Na, K concentrations in red cells were carried out under the condition of bed rest without administration of any kind of drug for congestive heart failure. At the same time, Na, K excretion in urine, venous pressure, vital capacity, urine volume, body weight and aldosterone excretion in urine were examined.

Ages, sex, clinical diagnoses, grades of decompensation, kinds of digitalis and their methods of administration are shown in Table I. On the other hand, 9 normal blood samples were obtained from healthy physicians and nurses for determination of normal ranges of red cell Na, K concentrations by the method applied in the present study.

For determination of Na, K concentrations in red cells, heparinized blood is usually used, but in the present study, heparin was not used.

Following an overnight fast, 8 ml of blood was withdrawn from V. mediana cubiti into a dry syringe. Of this blood,

1. 0.5 ml was immediately diluted to 50 ml so as to contain 50 p.p.m. of lithium chloride,
2. 3.5 ml was oxalated for hematocrit,
3. the rest was centrifuged at 2,000 r.p.m. for 5 min. after coagulation, and 0.5 ml of this serum was diluted to 50 ml in the same way mentioned above, within 60 min. after withdrawal from patients.

From these diluted samples, whole blood and serum Na, K were determined by Baird DB-4 flame photometer using internal standard method. Na, K con-

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Table I

<table>
<thead>
<tr>
<th>Case</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical Diagnosis</th>
<th>Grade</th>
<th>Digitalis</th>
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<tbody>
<tr>
<td>1</td>
<td>T. Y.</td>
<td>60</td>
<td>m.</td>
<td>Coronary heart disease</td>
<td>IV</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>2</td>
<td>T. S.</td>
<td>42</td>
<td>m.</td>
<td>Mitral valvular disease, Secondary pulmonary hypertension</td>
<td>III</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>3</td>
<td>H. M.</td>
<td>36</td>
<td>m.</td>
<td>Mitral stenosis</td>
<td>II</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>4</td>
<td>M. Y.</td>
<td>23</td>
<td>f.</td>
<td>Mitral stenosis</td>
<td>II</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>5</td>
<td>T. U.</td>
<td>45</td>
<td>f.</td>
<td>Aortic insufficiency</td>
<td>III</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>6</td>
<td>V. S.</td>
<td>24</td>
<td>m.</td>
<td>Mediastinal tumor</td>
<td>III</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>7</td>
<td>T. S.</td>
<td>60</td>
<td>m.</td>
<td>Hypertensive heart disease</td>
<td>III</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>8</td>
<td>F. L.</td>
<td>19</td>
<td>f.</td>
<td>Mitral valvular disease</td>
<td>III</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>9</td>
<td>R. U.</td>
<td>62</td>
<td>m.</td>
<td>Cor pulmonale</td>
<td>IV</td>
<td>Digoxin</td>
</tr>
<tr>
<td>10</td>
<td>K. O.</td>
<td>32</td>
<td>f.</td>
<td>Friedreich ataxia</td>
<td>I</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>11</td>
<td>T. S.</td>
<td>41</td>
<td>m.</td>
<td>Myocard infarction</td>
<td>C</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>12</td>
<td>S. N.</td>
<td>54</td>
<td>m.</td>
<td>Angina pectoris (after myocardial infarction)</td>
<td>I</td>
<td>Lanatoside C</td>
</tr>
<tr>
<td>13</td>
<td>S. N.</td>
<td>28</td>
<td>m.</td>
<td>Hypertrophic subaortic stenosis</td>
<td>II</td>
<td>Lanatoside C</td>
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<tr>
<td>14</td>
<td>O. S.</td>
<td>65</td>
<td>m.</td>
<td>Hypertensive heart disease</td>
<td>IV</td>
<td>Lanatoside C</td>
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<tr>
<td>15</td>
<td>H. Y.</td>
<td>51</td>
<td>m.</td>
<td>Aortic valvular disease</td>
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<td></td>
</tr>
<tr>
<td>16</td>
<td>T. S.</td>
<td>58</td>
<td>m.</td>
<td>Hypertensive heart disease</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>K. Y.</td>
<td>37</td>
<td>m.</td>
<td>Aortic stenosis with mitral stenosis</td>
<td>II</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>M. S.</td>
<td>19</td>
<td>m.</td>
<td>Coarctation aortae</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>S. Y.</td>
<td>56</td>
<td>f.</td>
<td>Obstructive aortoarteritis, Hypertension</td>
<td>I</td>
<td></td>
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<tr>
<td>20</td>
<td>K. Y.</td>
<td>63</td>
<td>f.</td>
<td>Hypertension, Arrhythmia perpetua</td>
<td>I</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>R. F.</td>
<td>62</td>
<td>m.</td>
<td>Paroxysmal tachycardia, Myocardial fibrosis, Arach. adv. cerebrothoracalis</td>
<td>C</td>
<td></td>
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</table>

Concentrations in red cells were determined by the following formula:

\[ Ec = \frac{Ew - Es(1 - Ht.)}{Ht.} \]

where Ec means red cell Na or K concentration in mEq/L.
Ew means whole blood Na or K concentration in mEq/L.
Es means serum Na or K concentration in mEq/L.

Hematocrits were determined by spinning for 30 minutes at 1,460 g in tubes of the Kato-type. The mean value of two hematocrit determinations of each sample was applied in this formula. FINCH and HUNTER (1941), using Evans blue to determine plasma volume, showed that the volume of fluid trapped between packed red cells is not greater than 4 per cent of the total volume. SOLOMON (1952) showed that the ratio of the true hematocrit value to the observed hematocrit value at 1.610g is 0.971 ±0.003 by the addition of trace amount of isotonic Na\(^{24}\)Cl to whole blood. MAIZELS (1955) found that intercellular plasma of erythrocytes centrifuged at 2,000 g for 30 minutes is 1.88±0.15 per cent of the packed cell volume. But, since these correction factors were very small, and in this study it is more important to observe relative changes than to obtain the true value of Na, K concentrations in red cells, the observed hematocrit values were not corrected.

**RESULT**

I) Normal ranges of sodium and potassium concentration in red cells.

Many investigators reported normal ranges of sodium and potassium concentrations in red cells, but there is marked variation in values. Table II shows sodium and potassium concentration in serum and red cells obtained from healthy physicians and nurses by the method used in this study. Their means and standard deviations are in good agreement with those.
Table II  Sodium and potassium concentrations in serum and erythrocytes in normal subjects

<table>
<thead>
<tr>
<th>Case</th>
<th>Name</th>
<th>Age</th>
<th>Sex</th>
<th>Serum</th>
<th>Erythrocyte</th>
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<tr>
<td>22.</td>
<td>K. K.</td>
<td>31</td>
<td>m.</td>
<td>148.1</td>
<td>4.50</td>
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<tr>
<td>23.</td>
<td>A. H.</td>
<td>27</td>
<td>m.</td>
<td>145.7</td>
<td>4.40</td>
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<tr>
<td>24.</td>
<td>H. M.</td>
<td>32</td>
<td>f.</td>
<td>143.7</td>
<td>4.08</td>
</tr>
<tr>
<td>25.</td>
<td>T. K.</td>
<td>23</td>
<td>f.</td>
<td>142.7</td>
<td>4.28</td>
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<tr>
<td>26.</td>
<td>A. S.</td>
<td>26</td>
<td>m.</td>
<td>143.0</td>
<td>4.70</td>
</tr>
<tr>
<td>27.</td>
<td>F. K.</td>
<td>21</td>
<td>f.</td>
<td>142.3</td>
<td>4.00</td>
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<tr>
<td>28.</td>
<td>T. K.</td>
<td>28</td>
<td>m.</td>
<td>148.0</td>
<td>4.44</td>
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<tr>
<td>29.</td>
<td>M. K.</td>
<td>26</td>
<td>f.</td>
<td>140.6</td>
<td>3.79</td>
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<tr>
<td>30.</td>
<td>H. H.</td>
<td>22</td>
<td>m.</td>
<td>140.3</td>
<td>4.46</td>
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<tr>
<td>Mean</td>
<td></td>
<td></td>
<td></td>
<td>143.8</td>
<td>4.20</td>
</tr>
<tr>
<td>S. D.</td>
<td></td>
<td></td>
<td></td>
<td>±2.88</td>
<td>±0.29</td>
</tr>
</tbody>
</table>

Reported by Solomon (1952) and by D'Amico (1958). The value of sodium concentration in red cells was found to be slightly higher in comparison with Solomon's "true value". This may be due to uncorrected hematocrit values.

II) Sodium and potassium concentrations in

![Graph 1](image1)

**Fig. 1.** Relation between sodium concentrations in serum and the severity of congestive heart failure. (C. H. F.: Congestive heart failure, I, II, III, IV: The Classification of New York Heart Association.)

![Graph 2](image2)

**Fig. 2.** Relation between sodium concentration in red cells and the severity of congestive heart failure.

*Japanese Circulation Journal Vol. 30, July 1966*
Fig. 3. Correlation between sodium concentrations in serum and those in red cells. 
(r = 0.307, P > 0.05) ●: Congestive heart failure ○: Normal subject

Fig. 4. Relation between potassium concentrations in serum and the severity of congestive heart failure.

Fig. 5. Relation between potassium concentrations in red cells and the severity of congestive heart failure.

serum and red cells in patients with congestive heart failure.

1) Sodium
   i) The average value of serum sodium concentrations in congestive heart failure was significantly decreased. \( F = 5.74, \ P < 0.01 \) (Figure 1)
   ii) There was no significant change in sodium concentration in red cells, except for increased standard deviation. \( F = 0.71 \) (Figure 2)
   iii) There was no correlation between sodium concentrations in serum and those in red cells. \( r = +0.307, \ P > 0.05 \) (Figure 3)

2) Potassium
   i) There was no significant difference between serum potassium concentration in patients with congestive heart failure and that in normal subjects. \( F = 1.95 \) (Figure 4)
   ii) As for potassium concentration in red cells, the difference between normal subjects and patients with congestive heart failure was statistically significant, and furthermore the differences between each grade of congestive heart failure were also statistically significant \( F = 3.88, \ P < 0.05 \), so that they increased in proportion to the clinical grades of heart failure. (Figure 5)
   iii) There was a positive correlation between potassium concentration in red cells and venous pressure including the cases which were given digitalis. (Figure 6) \( r = +0.543, \ P < 0.01 \) except one case of digitalis intoxication which is marked with an X
   iv) There was no correlation between potassium concentrations in serum and those in red cells. \( r = +0.199, \ P > 0.05 \) (Figure 7)

3) Correlation between sodium concentration and potassium concentration in each compartment.
   i) There was a positive correlation between sodium concentrations and potassium concentrations in serum. \( r = +0.400, \ P < 0.05 \) (Figure 8)
   ii) There was no significant correlation between sodium concentrations and potassium concentrations in red cells. \( r = -0.257, \ P > 0.05 \) (Figure 9)

4) K/Na ratio
   i) The mean value of serum K/Na ratio in patients with congestive heart failure appeared a little higher than that in normal subjects, but the difference was not statistically significant. \( t = 1.39, \ P > 0.05 \) (Figure 10 left column)
   ii) The mean value of K/Na ratio in red cells in patients with congestive heart failure appeared also a little higher than that in normal subjects, but the difference between them was not statistically significant. \( t = 1.93, \ P > 0.05 \) (Figure 10 right column)
   iii) There was no significant correlation between K/Na ratios in serum and those in red cells. (Figure 11)

5) The sum of sodium and potassium concentration in red cells in patients with congestive heart failure was significantly higher than that in normal subjects principally due to the increases in potassium concentrations. \( t = 2.40, \ P < 0.05 \) (Figure 12)
Fig. 7. Correlation between potassium concentrations in serum and those in red cells. 
\( r = 0.199, P > 0.05 \)

Fig. 8. Correlation between sodium concentrations and potassium concentrations in serum. 
\( r = 0.400, P < 0.05 \)
III) Influence of digitalis on serum and red cell electrolytes in patients with congestive heart failure.

1) Case reports

i) Case 1—T. Y., a 60-year-old gilder was admitted to the Kyoto University Hospital on December 11, 1962, complaining of palpitation, dyspnea, cough, and oliguria. The diagnosis was coronary heart disease with cardiac decompensation (grade IV). He had been well until 1961, when he could not lift a heavy burden, because of palpitation and shortness of breath. In March 1962, the second attack of palpitation and dyspnea became better with administration of digitalis. For a week before admission, he was in acute distress with dyspnea and palpitation, and his urine volume decreased to 250 ml a day. At the time of admission, the patient was severely dyspneic. The blood pressure was 100/73 mmHg, the pulse was 94 and irregular, and the respiration was 30 per minute. The venous pressure was 255 mmHg, and the liver was enlarged, extending five fingerbreadths beneath the right costal margin. The ascites was observed.
The systolic murmur was heard at the apex. C. T. R. (0.58), BSP (30%–30 min.), CRP (+), and there was moderate disturbance in renal clearance test.

Following 3 days of bed-rest, O₂-tent and low sodium diet (NaCl: 3 gr/day, K: 60 mEq/day), lanatoside C was used intravenously 0.6–0.4 mg a day. The clinical course of venous pressure, body weight, urine volume, blood pressure, vital capacity, circulating time (arm-lung), aldosterone excretion in urine, total sodium and potassium excretion in urine, and sodium and potassium concentrations in serum and red cells were illustrated in Figure 13.

Marked sodium diuresis was observed and venous pressure fell into normal range in two weeks. The aldosterone excretion in urine was reduced rapidly. The sodium concentration in serum was not changed so much. The potassium concentration in serum and the sodium concentration in red cells increased temporarily and were kept in relatively high concentrations for about 30 days.

On the contrary, potassium concentration in

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Fig. 11. Correlation between serum K/Na ratios and red cell K/Na ratios.

Fig. 12. Relation between red cell concentrations of (Na + K) and the severity of congestive heart failure.
red cells decreased from the relatively high zone to the middle zone within the normal range. The high concentrations of serum potassium and red cell sodium were reduced to the normal range at the time when the vital capacity became normal.

ii) Case 2—T.S. a 42-year-old man was admitted to the Kyoto University Hospital on January 15, 1964, complaining of dyspnea, palpitation and malaise. The diagnosis was mitral valvular disease with cardiac decompensation (grade III), and secondary pulmonary hypertension. Seven years before admission, he complained of shortness of breath as he was walking up a hill, and heart disease was indicated. Two years before admission, he was administered digitalis because of palpitation, cyanosis and swelling of the legs.

Physical examination: Pulse 68 per minute and irregular, blood pressure 125/80 mmHg, venous pressure 188 mmHg, circulating time (arm-lung) 20 sec., cyanosis (+), systolic and diastolic murmurs were heard at the basis; the second pulmonary sound was intensified, and the liver edge extended five finger breadths below the costal margin. The renal clearance test revealed mild disturbance. The clinical course is illustrated in the Figure 14.

During the 10 days of bed rest and low sodium diet (Na: 3 gr/day, K: 60 mEq/day),

Fig. 13. Case 1. T. Y. a 60-year-old man. Coronary heart disease.
(NaCl in diet: 3 gr/day)
the sodium concentration in serum was not changed, the potassium concentration in serum was slightly increased, the sodium concentration in red cells was not changed, the potassium concentration in red cells was slightly increased and sustained at the high level.

After the administration of digitalis, the sodium concentration in serum was not changed, the potassium concentration in serum increased temporarily, the change of the sodium concentration in red cells was difficult to decide, but the potassium concentration in red cells decreased. Marked decrease in aldosterone excretion in urine was also observed.

iii) Concerning the next eleven cases (from the third to the thirteenth) only the doses of digitalis, the sodium and potassium concentrations in serum and red cells, the aldosterone excretion in urine are illustrated in Figure 15, 16, 17. Among them, case 10, 11, 12, were the cases that had no clinical symptom of cardiac decompensation. It is very difficult to decide whether the sodium and potassium concentration increased or decreased after the administration of digitalis, because of the difference of intervals from the administrations of digitalis to the determinations of the sodium and potassium concentrations in serum and in red cells. Table III roughly summarizes these results.

iv) A case of digitalis intoxication is shown in Figure 18. A 58-year-old man was diagnosed as having myocardial fibrosis with cardiac decom-

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**Fig. 15.** The effect of digitalis on Na, K concentrations in serum and those in red cells. Aldosterone: Aldosterone excretion in urine.

**Fig. 16.** The effect of digitalis on Na, K concentrations in serum and those in red cells.

pensation (grade III). He complained of Stokes-Adams attacks. Extremely low potassium concentrations and on the contrary extremely high sodium concentrations in red cells were observed. Because of bradycardia and bigeminal rhythm, digitalis that had already been administered before hospitalization was discontinued, and then marked natriuresis was observed.

2) Figure 19 summarizes all the data of potassium concentrations in red cells in cases 1–13, taking no account of the number of determinations and their intervals. High potassium concentration in red cells which had been obtained before digitalis administration decreased to the normal range with recompensation.

3) Figure 20 shows a correlation between aldosterone excretion in urine and potassium concentration in red cells before and after digitalis administration. It is hereby somewhat noteworthy that one of two cases marked with X (left upper, high aldosterone excretion with low potassium levels in erythrocytes) is a case with digitalis intoxication and the other is a case that had received digitalis during a long term administration of trichlormethiazide.

Discussion

The attempt of this study is to investigate

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Case 10</th>
<th>Case 11</th>
<th>Case 12</th>
<th>Case 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lantoside C</td>
<td>1.0 mg</td>
<td>i.v.</td>
<td>i.v.</td>
<td>i.v.</td>
</tr>
<tr>
<td>mEq/l</td>
<td>15</td>
<td>106</td>
<td>K</td>
<td>Na</td>
</tr>
<tr>
<td>RED CELL Na</td>
<td>92</td>
<td>92</td>
<td>92</td>
<td>92</td>
</tr>
<tr>
<td>SERUM Na</td>
<td>150</td>
<td>4.9</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>SERUM K</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
</tbody>
</table>

Fig. 17. The effect of digitalis on Na, K concentrations in serum and those in red cells.

the intracellular electrolyte metabolism, and particularly its fluctuations following digitalization in patients with congestive heart failure. For this purpose the electrolyte concentrations in the erythrocytes and the serum were measured.

1) Sodium and potassium levels in serum and red cells before the onset of treatment in patients with congestive heart failure.

i) Sodium

As shown in Figure 1, sodium concentrations in serum in patients with congestive heart failure were significantly lower than those in normal subjects. As for the hyponatremia observed in patients with congestive heart failure, Friedberg stated that he had noted a tendency to an increased frequency and an increased degree of hyponatremia with increased severity of heart failure, apparently unrelated to therapeutic agents. And he interpreted these observations to indicate that increasing hyponatremia represents a parallel consequence or metabolic adjustment to advancing heart failure.

There are many reports on sodium concentration in serum in patients with congestive heart failure, they report increased\textsuperscript{10}, unchanged\textsuperscript{11,12,13}, decreased\textsuperscript{14,15,16,17} sodium concentrations in serum.

Sodium concentrations in red cells in patients with congestive heart failure vary too much to reveal any significant difference from those in the control group, as seen in Figure 2. On the other hand, Riecker, Bubnoff\textsuperscript{10}, and D'Amico\textsuperscript{7} reported increased sodium concentrations in red cells in patients with congestive heart fai-

![Diagram of electrolyte concentrations](image)

**Fig. 18.** U.F., a 58-year-old man. Myocardial fibrosis with digitalis intoxication. In red cells, extremely high sodium concentrations and extremely low potassium concentrations were observed.

*Japanese Circulation Journal Vol. 30, July 1966*
lure. Furthermore D'Amico described that a rise in erythrocyte Na is proportional to degree of heart failure and of sodium retention.

As seen in Figure 3, there is no definite correlation between sodium concentrations in serum in patients with congestive heart failure and those in normal subjects. This indicates that sodium concentrations in red cells are not so strictly influenced by sodium concentrations in serum.

ii) Potassium

Serum potassium levels: Reports of many investigators on the potassium concentrations in serum in patients with congestive heart failure vary from normal\(^{19}\) to mild elevated values\(^{6,17}\) but the present study revealed no statistically significant difference from the normal, in spite of the presence of several cases with high potassium concentration, as seen in Figure 4.

Potassium levels in red cells: As to the intracellular potassium content in patients with congestive heart failure, numerous studies were made since the initial report of Harrison et al. in 1930 which reported the decrease in potassium content in cardiac muscle in patients who died of congestive heart failure.

Many of these reported the decrease in potassium content, some investigators in the studies of biopsied skeletal muscle, others in the studies with the radioisotope dilution method. Recently Bliss and Adolph\(^{19}\) reported that the myocardium from animals with experimental congestive heart failure contained significantly less potassium per kilogram of dry fat-free and blood-free myocardium than the myocardium from normal animals.

In regard to the erythrocyte potassium concentration, Riecker and Bubnoff\(^{30}\) reported the decreased level in patients with congestive heart failure. On the contrary, D'Amico\(^{7}\) reported the elevated erythrocyte potassium concentrations in patients with severe congestive heart failure, which are in good accord with the results of this paper. As seen in Figure 5, the present study revealed a significant statistical difference in the erythrocyte potassium level in patients with congestive heart failure from that in normal subjects, and generally speaking, the more the congestive heart failure was advanced, the more the potassium concentration in red cells was increased.

The systemic venous pressure, which is a good indicator of the grade of congestive heart failure, and the potassium concentration in red cells revealed a fairly good positive correlation, as seen in Figure 6, indicating some ground for the surmise that the elevated venous pressure in congestive heart failure may at the same time be taking part in the way of increasing potassium concentration in red cells. Meanwhile, as shown in Figure 7, potassium concentration in serum and potassium concentration in red cells do not correlate at all. Reasoning from all the facts above mentioned, the author may say that potassium concentration in red cells should be under an immediate influence of the mechanism of congestive heart failure rather than the potassium concentration in serum.

iii) The correlation between sodium and potassium concentrations in serum and erythrocytes.

The correlation between sodium and potas-

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Fig. 19. The effect of digitalis on potassium concentrations in red cells in patients with congestive heart failure.

sium concentrations in serum, as seen in Figure 8, showed a positive relation, thus providing enough reason for the surmise that the fluctuation of sodium and potassium concentrations in serum in patients with congestive heart failure is related to the dilution and concentration of serum itself. On the other hand, sodium and potassium concentrations in red cells have neither positive nor negative significant correlation, as seen in Figure 9. These facts suggest that the fluctuations of sodium and potassium concentrations in red cells may be subject to certain membranous or intracellular metabolic disturbances. In patients with congestive heart failure, in both serum and red cells, K/Na ratio tended to show an elevation, but the differences from the normal mean value were not statistically significant, as seen in Figure 10. Figure 12 shows that the summation of sodium and potassium concentrations in red cells has a higher average level in patients with congestive heart failure than that in normal subjects. Lastly, no correlation was noted between serum K/Na ratio and red cell K/Na ratio, as seen in Figure 11.

So far, sodium and potassium concentrations in serum and red cells in patients with congestive heart failure were discussed, and, as the main changes, a tendency of the decreased level of serum sodium concentration, and a more distinct elevation of red cell potassium level are recognized. From here on, some more detailed considerations on the latter item, which is the more important, will be given. As for the disturbed water metabolism in congestive heart failure, RIECKER and BURNOFF stated that the red cell water content in cardiac patients in a well-compensated state did not differ.

Fig. 20. Correlation between aldosterone excretion in urine and potassium concentrations in red cells in patients with congestive heart failure.

○: before the administration of digitalis.
●: during the administration of digitalis.

Japanese Circulation Journal Vol. 30, July 1966
from that in normal subjects, whereas in patients with prominent edema, the red cell water content was significantly increased. On the other hand, D'Amico reported that the water content of red cells in patients with congestive heart failure was not significantly different from normal. Anyway the water metabolism disturbance alone does not explain the mechanism of the selective elevation of potassium concentration in red cells.

As to the hypoxemia in congestive heart failure, there is the report by Jennings, Sommers, Kaltenbach and West of the decreased myocardial potassium content in experimental animals with acute myocardial ischemic injury. In regard to the role of CO₂, respiratory alkalosis due to the tachypnea is the common outcome in patients with congestive heart failure, but on the other hand, the severe disturbance in pulmonary ventilation may result in respiratory acidosis due to the increased Pco₂. Levitin, Amick and Epstein reported the decrease in muscle potassium in animals exposed to 8% CO₂. As to the relationship between the elevation of catecholamine level which is one of the humoral factors in congestive heart failure and the red cell potassium concentration, Kahn and Acheson employed human erythrocytes and showed that catecholamine failed to affect cation movements of red cells.

As to the role of corticosteroids as some of the humoral factors, Streiten and Solomon stated that infusions of ACTH or cortisone caused a gain in erythrocyte potassium content. Since aldosterone which was reported by J. O. Davis et al. to be increased in congestive heart failure suppressed the inhibitory effect of digitalis in the active cation transport across the red cell membrane, Wilbrandt suggested that aldosterone should promote the active cation transport there. In the present study, the correlation between aldosterone excretion in urine and red cell potassium concentration could not be made clear, because of the small number of observed cases as seen in Figure 20. In order to make clear the mechanism of a decrease in myocardial potassium content and an increase in erythrocyte potassium concentration in patients with congestive heart failure, further studies are requested, but from the above mentioned several points of view, there may be some participations from their humoral and intracellular metabolic disturbances.

2) Influence of digitalization on serum and red cell sodium and potassium concentrations in patients with congestive heart failure.

Many studies were made on the effect of digitalis on the intracellular electrolytes metabolism in congestive heart failure. In 1931, Calhoun and Harrison stated that the potassium content of the cardiac muscle was markedly less in a series of dogs receiving toxic doses of digitalis than in a group of control animals. Woon and More (1942) reported a decrease in potassium content of the ventricles of heart-lung preparations of dogs which received therapeutic doses of a digitalis glycoside.

In 1947, Friedman and Bine reported an effectiveness of excess potassium in inhibiting a loss of potassium from the heart caused by large or toxic amounts of digitalis glycoside. Holland, Greig and Dunn observed that concentrations of lanatoside C producing characteristic changes in the electrocardiogram, also cause a loss of potassium from cardiac muscle (1954). In all these studies, however, the extracellular water of the myocardium makes it difficult to determine whether there is an exact loss or gain of electrolyte in cardiac muscle cells themselves.

Then Regan, Talmers and Hellemes measured myocardial transfer of sodium and potassium in dogs by simultaneous collection of blood samples from a systemic artery and coronary sinus before and after the administration of acetyl strophantidin in doses of 0.05 to 0.1 mg per kg. And they observed an abrupt increase in coronary sinus potassium with less rise in arterial potassium concentration after strophantidin, giving a mean maximum negative A-V difference of 0.86±0.44 mEq/L, indicating loss of potassium from the myocardium. Concurrently, they observed greater uptake of sodium with a positive A-V difference of 6.0±4.0 mEq/L. Although both cation A-V differences resumed approximate control.
values at about 30 minutes, they concluded that the fact that the stroke work of the left ventricle in this group of animals declined from a control value of 23.8 gm meters to 17.7 gm meters after strophanthidin, suggested that the negative inotropic effect of strophanthidin in the normal animal might be affected by the increase in internal ionic content of the myocardium due to the greater influx of sodium over the egress of potassium.

But in these studies, all investigators employed normal hearts which were not really proper for the proof of the effects of digitalization in congestive heart failure. Page\textsuperscript{30} suggested that the answer to this question might have to await the development of a preparation of heart muscle simulating the changes that occur in the hearts of patients with failure. According to this proposal, Bliss and Adolph\textsuperscript{30} (1963) reported significantly less potassium content of the myocardium from animals with congestive heart failure produced by progressive pulmonary artery constriction than the myocardium from normal dogs. They reported, at the same time, significantly increased potassium in the myocardium from animals with congestive heart failure after acetyl strophanthidin, and concluded that digitalis exerted two opposing effects on ion transport through the myocardial cell membrane and that neither of these was fundamental to its inotropic action.

Summarizing the present results (Result III, 1.) digitalization for the patients with congestive heart failure caused; i) notable decreases in red cell potassium concentrations to the normal range in all cases; ii) increases in red cell sodium concentrations in 9 out of 10 cases; iii) and no changes in serum sodium concentrations in 8 out of 10 cases. These results coincide well with the effect of digitalis on the red cell electrolytes in vitro. Namely, it is reasonable to presume that not only in vitro, but also in vivo as well, the active cation transport through the normal erythrocyte membrane may be impeded by digitalis. This can be also inferred from the data of control cases 10–12, in which the decreases in red cell potassium concentrations were observed. This initial effect, however, should be understood as the direct effect of digitalis on red cell potassium concentration, as seen in case 1; and the persistent decreases in red cell potassium concentrations to the normal value in cases 1 and 2 might be due to the indirect effect of digitalis through the improvement of some humoral or intracellular metabolic disturbances in congestive heart failure which was mentioned previously in Discussion 1).

This is again confirmed by the results of comparison of the red cell potassium concentrations in patients with congestive heart failure before and after the administration of digitalis with those in normal subjects. In Figure 20, which shows the correlation between red cell potassium concentration and aldosterone excretion in urine, the cases receiving therapeutic doses of digitalis are not divided from the cases with congestive heart failure before treatment. This fact suggests that the return of red cell potassium concentration to the normal is due to the hemodynamic improvement with the increased myocardial contraction by digitalis. This consideration is in agreement, to some extent, with that of Bliss and Adolph.

In digitalis intoxication (Figure 18), marked decreases in red cell potassium concentrations and marked increases in red cell sodium concentrations are observed. But, as to the clarification of the delicate differences of the effect of digitalis on the intracellular metabolism in patients with congestive heart failure and that in normal subjects, further studies are expected.

**Summary**

1. For the purpose of studying intracellular electrolyte metabolism in patients with congestive heart failure and the effect of digitalis on them, sodium and potassium concentrations in erythrocytes in twenty-one patients with compensated heart disease or chronic congestive heart failure were measured. In 13 patients of these subjects, sodium and potassium concentrations in erythrocytes before and during administration of digitalis were measured. At the same time, sodium, potassium and aldosterone excretion in urine and venous pressure were estimated.
2. For determination of normal ranges of red cell Na, K concentrations by the method applied in the present study, 9 normal blood samples were obtained from healthy physicians and nurses.

Their means and standard deviations are given next. Sodium concentration in serum is 143.8 ± 2.88 mEq/L. Potassium concentration in serum is 4.29 ± 0.29 mEq/L. Sodium concentration in red cells is 12.0 ± 1.45 mEq/L. Potassium concentration in red cells is 99.3 ± 3.72 mEq/L.

3. Sodium and potassium concentrations in serum and red cells before the onset of treatment in patients with congestive heart failure.

i) Sodium concentration in serum was significantly decreased, whereas that in red cells was kept in almost normal range.

ii) Potassium concentration in red cells was significantly increased along with the clinical grades of heart failure, whereas that in serum was kept in almost normal range.


i) Sodium concentrations in red cells in 9 of 10 patients were increased, whereas those in serum in 8 of 10 patients were not changed.

ii) Potassium concentrations in red cells in all 10 patients were decreased to the normal range; on the other hand those in serum in 5 patients were increased, 3 were decreased and 2 were not changed.

5. One of the influences of therapeutic dose of digitalis on red cell electrolytes may be due to the direct effect of digitalis on erythrocytes (particularly on their membranes) especially in the early stadium of its administration, but during the late stadium with its maintenance dose, there may be some indirect effects due to haemodynamic improvement of congestive heart failure.

REFERENCES


19) Bliss, H. A. and Adolph, R. J., Effect of experimental congestive heart failure and acetyl strophanthidin on myocardial electrolyte and water...