Clinical Studies

Sodium and Potassium Concentrations in Erythrocytes of Patients with Congestive Heart Failure

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SUMMARY

To study the changes in electrolyte concentrations in cells of patients with congestive heart failure, we measured the sodium and potassium concentrations in erythrocytes obtained from 34 stabilized patients treated with only digoxin and not with diuretics in order to avoid the effects of miscellaneous drugs and acute water overload. Patients were divided into classes I–III according to the NYHA classification. The values of urea nitrogen, hematocrit, and plasma sodium and potassium were not different among these groups. Serum digoxin concentration had a tendency to increase from class I to III, although not significantly. However, sodium concentration was significantly lower and potassium concentration was significantly higher in erythrocytes of class III, compared to class I patients. The erythrocyte sodium concentration was inversely related to the erythrocyte potassium concentration, but it was not related to the plasma sodium concentration or to the serum digoxin concentration. These results suggest that the reduced sodium concentration in patients with congestive heart failure was manifested earlier in erythrocytes than in plasma during long-term treatment with digoxin.

Additional Indexing Words:
Hyponatremia Congestive heart failure Electrolytes
Digoxin concentration

It is well known that patients with congestive heart failure develop an imbalance of plasma electrolytes resulting in such conditions as hyponatremia. Since most of them are treated with loop diuretics, hyponatremia observed in heart failure may well be induced by the diuretics. However, hyponatremia has also been reported in congestive heart failure not treated with loop diuretics.1,2) Hyponatremia can often be observed in patients in the acute phase or severe stage of congestive heart failure associated with marked edema of the
feet and body. There are a few reports on electrolyte levels in erythrocytes in heart failure. In most of these however, the values were modified by drugs, since digitalis and diuretic therapy change electrolytes not only in plasma but also in erythrocytes. Although plasma digoxin has been shown to induce an increase in erythrocyte sodium concentration, there was no significant correlation between the plasma digoxin concentration and erythrocyte sodium concentration reported in patients during chronic treatment with digoxin.

In the present study, sodium and potassium concentrations were examined in erythrocytes from patients in an unstable condition who were treated only with digoxin and compared in relation to the severity of congestive heart failure in order to elucidate the significance of electrolyte levels in erythrocytes in congestive heart failure.

**Subjects and Methods**

Thirty-four patients who were all being administered digoxin for heart diseases were divided into 3 groups ranging from class I to class III according to the New York Heart Association classification. No patient was treated with diuretics or oral potassium agents. Class I: 14 patients (9 males and 5 females) who had suffered from chronic congestive heart failure or arrhythmias (atrial fibrillation and extrasystoles). Class II: 13 patients (10 males and 3 females) with chronic congestive heart failure secondary to valvular disease, ischemic heart disease or cardiomyopathies. Class III: 7 patients (all males) with the same diseases as the class II patients. All patients were well controlled with digoxin therapy. Patients with hepatic or renal disease were eliminated from the study. The class I group consisted of patients aged from 28 to 76 years (50.1±14.6, mean±SD), the class II group from 16 to 73 years (54.8±15.3) and the class III group from 36 to 76 years (55.6±17.4). The ages of the 3 groups were relatively well matched (Table I). All patients were administered daily doses of digoxin of 0.125 mg to 0.375 mg orally (31 patients, 0.25 mg; 2, 0.375 mg; and 1, 0.125 mg).

Sodium and potassium concentrations in erythrocytes were determined by the method described in an earlier report. Blood drawn in a heparinized syringe was immediately centrifuged at 2,500 rpm for 5 min at room temperature. Plasma in the supernatant was used for the determination of plasma sodium and potassium concentrations. The precipitate was transferred to soft polyethylene tubes (400 µl). Following centrifugation at 2,000 g for 30 min at 20°C, the buffy coat and superficial layer were discarded. Thirty µl of the precipitate were lysed in 5 ml of lithium chloride as an internal stan-
standard and measured with a flame photometer (Hitachi 205). The value was corrected for the plasma volume trapped between erythrocytes, which was estimated to be approximately 3.8% calculated by the method using indocyanine green as a marker.11)

Serum digoxin concentration was determined by an Emit Digoxin Assay Kit (Syva) using an enzyme immunoassay technique. The blood samples were collected more than 6 hours after the last administration of digoxin.

Data are expressed as averages±SEM. One-way analysis of variance was used for statistical analysis and Duncan's multiple range test was applied to determine the significance of differences between pairs of means. A p value of less than 0.05 was considered a significant difference.

Results

The mean values of urea nitrogen were 12.6±1.0, 15.0±0.6 and 12.3±1.4 mg/dl, and hematocrit 42.4±1.4, 42.0±1.3 and 46.0±1.0%, respectively for each of the 3 groups; there were no significant differences (Table I). The values of (Na+ + K+ − Cl−), which seemed to indicate bicarbonate in these cases, were 42.9±1.3, 42.6±0.9 and 43.0±0.6 mEq/l, respectively. The bicarbonate concentration is of importance for estimation of the sodium concentration in erythrocytes, because it increases the passive transport of sodium through membranes.12)

Serum digoxin concentrations were 1.20±0.19, 1.31±0.15 and 1.59±0.20 ng/ml, respectively for each group. The level showed a tendency to increase from class II to class III, but not significantly (Fig. 1).

The plasma sodium concentrations were 141.5±0.55, 142.9±0.53 and 141.4±1.5 mEq/l, and the plasma potassium concentrations 4.06±0.14, 3.92±0.10 and 3.93±0.13 mEq/l, respectively. There was no significant difference among the groups (Fig. 1). On the other hand, the sodium concentration in erythrocytes in the class III group was significantly lower than in the class I group (9.46±0.52 vs. 11.65±0.63 mEq/l, p<0.05, Fig. 2). The potassium

Table I. Comparison of the 3 Groups with Regard to Number, Sex, Age, Urea Nitrogen, Hematocrit and Na+ + K+ − Cl−

<table>
<thead>
<tr>
<th>NYHA</th>
<th>Number of Patients</th>
<th>Sex</th>
<th>Age Range (years)</th>
<th>Mean Age (years, Mean±SD)</th>
<th>Urea Nitrogen (mg/dl, Mean±SEM)</th>
<th>Hematocrit (%) (Mean±SEM)</th>
<th>Na+ + K+ − Cl− (mEq/l, Mean±SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>14</td>
<td>M 9</td>
<td>F 5</td>
<td>28-76</td>
<td>50.1±14.6</td>
<td>12.6±1.0</td>
<td>42.4±1.4</td>
</tr>
<tr>
<td>II</td>
<td>13</td>
<td>M 10</td>
<td>F 3</td>
<td>16-73</td>
<td>54.8±15.3</td>
<td>15.0±0.6</td>
<td>42.0±1.3</td>
</tr>
<tr>
<td>III</td>
<td>7</td>
<td>M 7</td>
<td>F 0</td>
<td>36-76</td>
<td>55.6±17.4</td>
<td>12.3±1.4</td>
<td>46.0±1.0</td>
</tr>
</tbody>
</table>
Fig. 1. Plasma sodium, potassium and serum digoxin concentrations in the 3 groups classified according to the New York Heart Association. Plasma electrolytes were measured in the same blood collected for determination of electrolyte concentrations in erythrocytes. Bars represent mean±SEM.

concentrations in erythrocytes in the class II and III groups were significantly higher than that in the class I group (103.92±0.74 or 101.74±1.09 vs. 97.16±0.95 mEq/l, p<0.01 or p<0.01, respectively). In the same way, the sodium to potassium ratios in erythrocytes in the class II and III groups were signifi-
Fig. 3. Relationship between sodium and potassium concentrations in erythrocytes. ●: NYHA class I, ○: class II, □: class III.

Fig. 4. Relationship between sodium concentration in erythrocytes and plasma sodium concentration. ●: NYHA class I, ○: class II, □: class III.

cantly lower than that in the class I group (0.099±0.004 or 0.089±0.05 vs. 0.121±0.007, p<0.05 or p<0.01, respectively). The sodium concentration in erythrocytes had a significantly negative relationship to potassium concentration in erythrocytes ($r=-0.396$, $y=-0.829x+110$, p<0.05, Fig. 3), but no
relationship to either the plasma sodium concentration (Fig. 4) or to the serum digoxin concentration ($r = -0.0795$, data not shown in Figure).

**DISCUSSION**

Hyponatremia is a well-known condition in patients with congestive heart failure,\textsuperscript{11,21} and it may result from an increase in the amount of fluid or a decrease in the amount of dissolved sodium.\textsuperscript{18,14} The former mechanism may be due to the increased secretion of antidiuretic hormone,\textsuperscript{21} increased glomerulotubular collecting duct permeability\textsuperscript{15} or lowering of hypothalamic osmoreceptors (mediated by antidiuretic hormone).\textsuperscript{11} The latter mechanism may be ascribed to renal sodium depletion. It may be related to the increased secretion of atrial natriuretic polypeptides which inhibit the production of aldosterone.\textsuperscript{16}

However, even the patients in the class III group showed no plasma sodium or potassium imbalance, and the patients in this study were well medicated with digoxin and maintained in a stable condition. They were not administered diuretics, which are known to have serious effects on the plasma electrolyte balance.\textsuperscript{17} The present results demonstrate that the sodium concentration in erythrocytes of patients with congestive heart failure is lower than in patients with less serious heart conditions despite no apparent changes in the plasma sodium concentration and the serum digoxin concentration. If the plasma sodium could be assayed in patients with more severe congestive heart failure, it would presumably be at a lower level.

In healthy subjects the erythrocyte sodium concentration was inversely related to the total activity of the sodium pumps.\textsuperscript{18} It has been reported that digitalis increases the sodium concentration and decreases the potassium concentration in erythrocytes\textsuperscript{4,6} and that there is a close relationship between the plasma digitalis concentration and the increase in the sodium concentration in erythrocytes.\textsuperscript{5} The estimation of the sodium concentration in erythrocytes was found to be useful for predicting digoxin intoxication.\textsuperscript{7} These results suggest that the changes in erythrocyte sodium and potassium concentrations are due to Na\textsuperscript{+}, K\textsuperscript{+}-ATPase activity in membranes. Accordingly, it might be conceivable that patients with more severe congestive heart failure have higher erythrocyte sodium concentrations due to the higher digoxin concentration. However, the erythrocyte sodium concentration was not related to the plasma digoxin concentration as reported earlier,\textsuperscript{19} because congestive heart failure induced a depletion of sodium in erythrocytes as well as hyponatremia. The present findings suggest that the reduced sodium concentration in congestive heart failure was manifested earlier in erythrocytes than in
plasma. As an explanation for this, the lower sodium concentration in erythrocytes could be due to an increase in the number of sodium pumps present in the erythrocyte membranes caused by digitalis or a digitalis-like factor detected in plasma of patients with congestive heart failure. As another explanation, it is hypothesized that homeostasis of body fluid is maintained by adjusting the electrolyte concentrations in plasma rather than in cells as regards sodium and potassium.

The change in erythrocyte electrolytes may suggest the same change in tissues such as the myocardium. The imbalance of intracellular electrolytes may have important effects on cellular function, since intracellular electrolytes are greatly involved in excitation, contraction and secretion.

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