Electrolyte Studies in Heart Failure

I. Cellular Factors in the Pathogenesis of the Edema of Congestive Heart Failure

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CIRCULATORY insufficiency in cardiac failure appears to produce changes in cellular metabolism, resulting in extrusion of certain cations out of the cells and in migration of water into the cells. These changes, presumably, follow activation of cellular base and an increase in cellular osmolarity. Along with these intracellular alterations, the extracellular fluid tends to become hypertonic.

The relationship between cellular and extracellular changes in the pathogenesis of congestive heart failure remains obscure, not only because of distortions produced by therapeutic factors, but also because of the fact that studies on the extracellular fluid have not been correlated with the degree or the trend of the circulatory failure at the time of the study.

The present report attempts to elucidate the cellular factors involved in the pathogenesis of the edema of congestive cardiac failure. The following data obtained from direct muscle analysis show potassium deficits in skeletal muscle during congestive failure and restitution with recovery.

**Method and Material**

Two muscle samples, weighing 0.25 to 0.50 Gm., were obtained with extreme care from the deltoid muscle of 10 patients shortly after their admission to the hospital in frank congestive heart failure. Regional block anesthesia was attained with 1 per cent procaine by infiltration of the skin at least 2.5 cm. away from the site of the biopsy. The muscle samples were rolled lightly and quickly over dry gauze and placed immediately into tared covered crucibles and weighed. One sample was heated to 100 C. for four to six hours, cooled in a desiccator and reweighed. This procedure was repeated until a constant dry weight was obtained. The sample was then digested with perchloric-nitric acid mixture and analyzed for potassium and sodium. The second sample was not heated to dry weight, but digested with strong sodium hydroxide and analyzed for chloride. Concurrent with muscle biopsy, plasma samples were obtained for determination of sodium, potassium and chloride levels.

These studies were then repeated 9 to 56 days later, well after restoration of cardiac compensation. Body weight, venous pressure, circulation time, and vital lung capacity were obtained periodically to follow the clinical progress of cardiac compensation. Five of the 10 patients received no mercurial injections. Four received one to two injections during the first five days of therapy, but none received any during the seven days preceding the second muscle biopsy. One patient (C. G.) required several mercurial injections during the four weeks before compensation, but received no injection during the next four weeks preceding the second muscle biopsy study.

Calculations of intracellular and extracellular distribution of water and potassium were made, utilizing the chloride content and the plasma chloride concentrations. Corrections were made for the theoretical inactive chloride content of 1 mEq. per 100 Gm. of fat free tissue solids. The plasma chloride concentration was corrected for Donnan's effect and plasma water content by multiplying with 1.08. In view of the recent studies performed by Nichols and coworkers, the chloride space corrected for the inactive intracellular moiety of Yammel and Darrow, which would more than allow for the slightly higher concentration of chloride in connective tissue water, would appear to be the most accurate measure of the extracellular space. Tissue fat content was assumed to be 1 per cent. Since the muscle samples, by necessity, were small, it was not considered feasible to extract and analyze for fat; however, because of the smallness of the samples, it was relatively simple to obtain samples which contained no fascia or septum and hence only minimal quantities of fat.

**Chemical Methods.** Plasma sodium and potassium were analyzed on the flame photometer, according to the method previously described. Plasma chloride

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was determined either by polarographic or by titration methods. Plasma carbon dioxide combining power was measured by vacuum extraction. Tissue sodium and potassium were analyzed on the flame photometer after suitable preparation of the sample. Tissue chlorides were analyzed by microtitration, using Volhard's method.

**RESULTS**

The results of analyses of muscle tissue obtained during and after congestive heart failure and the derived values for distribution of water and potassium are given in table 1.

The average loss of weight of these 10 patients during the 9 to 56 day period of compensation was 16.8 Kg. and the range was from 5.32 to 26.90 Kg. The average venous pressure fell from 243 mm. H2O to 112 mm. and the average circulation time (arm-to-tongue Decholin) decreased from 36 to 27 seconds.

During the height of congestive failure, the average water, potassium and chloride contents of muscle were 78.2 Gm., 5.81 mEq., and 3.53 mEq. per 100 Gm. of wet tissue, respectively. After compensation these values were 75.9 Gm., 8.33 mEq., and 2.52 mEq., respectively. The decrease in water content occurred in each of the 10 cases, although it was hardly significant in four of the cases. There was a significant increase in potassium content of muscle in eight cases, a slight increase in one, and an actual decrease in one. Eight of the 10 cases showed a decrease in the chloride content, but two cases showed an increase.

Calculations of extracellular and intracellular water content in terms of per cent of wet tissue revealed an average extracellular volume of 29.05 per cent and an average intracellular volume of 49.1 per cent during the height of failure, and 20.9 and 55.0 per cent, respectively, after compensation. Individually, the per cent of extracellular water per unit mass of wet tissue decreased in eight cases, but increased in two. As was to be expected from the minimal change occurring in total water, the change in intracellular water was

**Table 1. Analysis of Muscle During Congestive Heart Failure and After Recovery**

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Sex</th>
<th>Age</th>
<th>Cardiac Diagnosis</th>
<th>Date of Study</th>
<th>Body Weight Kg.</th>
<th>V. P. mm. H2O</th>
<th>H. O</th>
<th>C. T. Sec.</th>
<th>Plasma</th>
<th>Muscle Per 100 Gm. Tissue</th>
<th>Derived Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>J. B.</td>
<td>M</td>
<td>69</td>
<td>Cor. P.</td>
<td>10/14</td>
<td>101.0</td>
<td>245</td>
<td>40</td>
<td>140</td>
<td>3.80</td>
<td>116.0</td>
<td>28</td>
</tr>
<tr>
<td>W. W.</td>
<td>M</td>
<td>54</td>
<td>AHD</td>
<td>12/1</td>
<td>70.5</td>
<td>100</td>
<td>45</td>
<td>140</td>
<td>3.90</td>
<td>107.0</td>
<td>23</td>
</tr>
<tr>
<td>C. R.</td>
<td>M</td>
<td>53</td>
<td>RHD</td>
<td>12/14</td>
<td>86.7</td>
<td>188</td>
<td>36</td>
<td>136</td>
<td>6.35</td>
<td>110.7</td>
<td>18</td>
</tr>
<tr>
<td>A. K.</td>
<td>M</td>
<td>50</td>
<td>HHD</td>
<td>12/29</td>
<td>72.4</td>
<td>78</td>
<td>18</td>
<td>137</td>
<td>4.45</td>
<td>106.7</td>
<td>16</td>
</tr>
<tr>
<td>C. G.</td>
<td>M</td>
<td>57</td>
<td>HHD</td>
<td>1/25</td>
<td>62.8</td>
<td>320</td>
<td>35</td>
<td>128</td>
<td>4.80</td>
<td>104.6</td>
<td>16</td>
</tr>
<tr>
<td>P. P.</td>
<td>M</td>
<td>50</td>
<td>AHD</td>
<td>3/21</td>
<td>91.0</td>
<td>385</td>
<td>50</td>
<td>140</td>
<td>4.90</td>
<td>124.0</td>
<td>13</td>
</tr>
<tr>
<td>J. A.</td>
<td>M</td>
<td>54</td>
<td>RHD</td>
<td>2/12</td>
<td>66.0</td>
<td>142</td>
<td>40</td>
<td>125</td>
<td>4.87</td>
<td>115.8</td>
<td>21</td>
</tr>
<tr>
<td>E. G.</td>
<td>M</td>
<td>45</td>
<td>HHD</td>
<td>6/5</td>
<td>61.4</td>
<td>140</td>
<td>146</td>
<td>5.00</td>
<td>91.9</td>
<td>26</td>
<td>76.0</td>
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<td>B. L.</td>
<td>M</td>
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<td>HHD</td>
<td>4/22</td>
<td>90.0</td>
<td>165</td>
<td>25</td>
<td>140</td>
<td>5.28</td>
<td>110.5</td>
<td>15</td>
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<tr>
<td>D. H.</td>
<td>M</td>
<td>55</td>
<td>RHD</td>
<td>4/10</td>
<td>74.2</td>
<td>140</td>
<td>40</td>
<td>140</td>
<td>5.30</td>
<td>94.2</td>
<td>16</td>
</tr>
<tr>
<td>Average</td>
<td></td>
<td></td>
<td></td>
<td>69.5</td>
<td>112</td>
<td>27</td>
<td>138</td>
<td>4.51</td>
<td>102.8</td>
<td>21</td>
<td>73.5</td>
</tr>
</tbody>
</table>

* Extracellular water.
† Intracellular water.
‡ Intracellular potassium.
§ Fat-free solids. Fat content assumed as 1%.
in the opposite direction to the change in the extracellular water.

The amount of intracellular water per 100 Gm. of "fat free" solids (fat content assumed to be 1 per cent of wet tissue) remained the same, averaging 239 Gm. during congestive failure and 244 Gm. after compensation, increasing in five and decreasing in five.

The intracellular potassium concentration increased from an average of 116 mEq. to an average of 151 mEq. per liter of intracellular water. Considerable variation was found in the actual potassium concentration during failure (range 74.5 to 176 mEq. per liter), but the trend with compensation was quite consistent, being increased in eight, unchanged in one, and decreased in one. Calculation of intracellular potassium content per 100 Gm. of tissue solids showed an increase from an average of 27.5 mEq. to an average of 36.5 mEq. There was an increase found in eight cases and a decrease in two.

Because of extreme variability in the results of sodium analysis, the data did not lend itself to any interpretation and hence are not presented.

**DISCUSSION**

The results of the muscle biopsy studies clearly indicate a deficit of cellular potassium in congestive heart failure and a repletion after recovery, thereby substantiating the conclusions reached from indirect metabolic studies. The magnitude of potassium deficit per unit mass of wet tissue (—30.1 per cent of total control content) was considerably greater than that obtained by Talso and associates (—22.3 per cent) or by Mokotoff and colleagues (—17.4 per cent) and could hardly be attributed to any difference in the extracellular or intracellular water content. The greater deficit of muscle potassium found in the present study may have been due to: (1) the fact that our comparisons were made on specimens from the same patient during the height of failure and after complete compensation, (2) the fact that these patients were studied immediately after admission to the hospital in profound and progressive congestive heart failure before any alleviation of the circulatory insufficiency, or (3) the fact that the muscle samples were obtained from the deltoid muscle rather than from the dependent muscles of the lower extremity, where hydrostatic pressure may influence not only the extracellular, but also the intracellular distribution of water and electrolytes.

In contrast to previous reports, the mean content of potassium per unit of tissue solids was significantly lower (—23.5 per cent) during cardiac failure than after compensation. Even though exact corrections could not be made for muscle fat, the increase in potassium content was too great to be explainable by a decrease in mean fat content. One would, moreover, expect an increase in mean fat content during recovery.

The deficit of potassium becomes more apparent after calculation of the concentration per liter of cell water. The mean value increased from 116 to 151 mEq. per liter. The intracellular potassium concentration during failure in this series was decidedly lower than in other reports, but the values after compensation were comparable.

The total water per unit of wet tissue was greater during cardiac decompensation than during compensation, although the percentile difference from the control (3 per cent) was less than that found by either Talso and coworkers (6.0 per cent) or Mokotoff and associates (9.5 per cent). The less marked difference in total water content was undoubtedly due to the fact that the muscle samples were obtained from areas not subjected to the hydrostatic collection of edema fluid. Nevertheless, the calculated mean extracellular water was increased during congestive failure by 43 per cent over the control period. This was comparable to the 48 per cent increase found by Talso and colleagues, but less than the 88 per cent increase found by Mokotoff. The intracellular water per unit of wet tissue was decreased and the calculated cellular water in terms of tissue solids was essentially the same before and after compensation. Mokotoff and coworkers also failed to demonstrate any significant change in intracellular water per unit of fat-free tissue solids; however, since there is little reason to believe that the quan-
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The concentration of intracellular potassium in congestive heart failure, whether it be by loss of potassium, by increase of cell water, or by both. This decrease in intracellular potassium concentration can be explained by osmotic activation of intracellular base, which forces potassium out of the cells and/or absorbs water into the cells. In this regard, it has been shown by direct means that intracellular muscle sodium is also decreased in the cells. It is obvious that precise studies of the extracellular compartment would be necessary to clarify the nature of the changes occurring within the cells. These studies will be reported in a later paper.

Summary

Muscle analyses for water, potassium, and chloride were made in 10 cardiac patients during and after congestive heart failure. The potassium content per unit of wet tissue during failure was 30.1 per cent less than that during compensation. The concentration of potassium in the intracellular water increased from 116 mEq. per liter to 151 mEq. per liter with compensation. Calculated extracellular water decreased, but no change in intracellular water per unit of tissue solids was found.

Summary in Interlingua

Specimens bioptic de musculo esseva anaysate pro aqua, kalium, e chlorido in 10 patientes cardiac durante e post congestive insufficienciae cardiacae. Le conteto de kalium

Per unitate de teixito non-desiccate esseva 30.1 pro cento minus que le contento de kalium durante compensation. Le concentration de kalium in le aqua intracellular accresceva per le compensation ab 116 mEq per litro a 151 mEq per litro. Le calculate valores de aqua extracellular decresceva, sed nulle cambiamento esseva constata in le quantitate de aqua intracellular per unitate de solidos textual.

Acknowledgment

We wish to express our appreciation to Dr. Ivan J. Mader, Miss Irene Parker, R.N., Mrs. Leona de Marky and Miss Vivian Kapuscinski for their invaluable assistance in this study.

References


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