ELECTROLYTE AND WATER CONTENT OF THE VENTRICULAR MUSCULATURE OF THE HEART-LUNG PREPARATION WITH SPECIAL REFERENCE TO THE EFFECTS OF CARDIAC GLYCOSIDES

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The studies of Harrison and his co-workers (1, 2) have demonstrated that heart failure in humans is associated with changes in the electrolyte composition of the cardiac musculature. The potassium content of hearts from patients dying of heart failure was found to be decreased. A similar change was found in the hearts of dogs receiving toxic doses of digitalis (3). More recent studies have demonstrated that toxic doses of digitalis cause a decrease in the potassium content of striated muscle (4), the ventricular musculature of the heart-lung preparation (5), the Langendorff perfused rabbit heart (6), and isolated strips of the ventricular musculature of the turtle (7). The reported effects of "therapeutic doses" of digitalis bodies on the potassium content of heart muscle are controversial. Calhoun and Harrison (3) reported a slight decrease of questionable significance in the cardiac potassium content of the intact dog, the blood potassium findings of Wood and Moe on the heart-lung preparation (5, 8) indicated a loss of potassium from the heart and/or the lungs, Wedd (7) could demonstrate no change in potassium content of the heart of the intact cat or in isolated strips of the turtle heart, Hagen (6) found the potassium content of Langendorff perfused rabbit hearts was increased after "therapeutic doses" of Lanatoside C, and Boyer and Poindexter (9) found that therapeutic digitalis dosage increased the potassium content of the hearts of intact cats.

Results of potassium, sodium, chloride and water analyses of the ventricular musculature of failing heart-lung hearts with and without treatment with cardiac glycosides are reported in this paper.

METHODS. The heart-lung preparations were set up as described by Peters and Visscher (10) so that oxygen consumption and external diastolic volume could be recorded continuously, and the measurements necessary for the calculation of the external work and hence the external mechanical efficiency of the preparation could be made at suitable intervals.

The preparation and analysis of the ventricular musculature were carried out as described by Wood and Moe (11) and Wood (12).

RESULTS. The ventricles of forty heart-lung preparations receiving none or

1 An excerpt from a thesis submitted to the graduate faculty of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1940.

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various doses of digitalis glycosides2 have been analyzed for potassium and water. Some of these hearts have also been analyzed for sodium and chloride.

The average values and the range of variation in the potassium and water analyses are given in table 1. The "digitalis hearts" are subdivided according to whether they received "toxic" or "therapeutic" doses of a digitalis glycoside. In this paper toxic and therapeutic doses are defined in reference to the heart-lung preparation in accordance with Moe and Visscher (13). A toxic dose of a digitalis glycoside is one which produces cardiac arrhythmias in the heart of the heart-lung preparation. A therapeutic dose is one which will increase the external mechanical efficiency of the heart-lung without the production of cardiac arrhythmias within a period of 150 minutes after administration of the drug.

### TABLE 1

*Heart lung ventricles, average values*

<table>
<thead>
<tr>
<th>(no.) HEARTS OF</th>
<th>WATER CONTENT PER 1000 GRAMS FRESH TISSUE</th>
<th>POTASSIUM CONTENT PER 1000 GRAMS FRESH TISSUE</th>
<th>POTASSIUM CONTENT PER 100 GRAMS DRY WEIGHT</th>
<th>DURATION OF PREPARATION</th>
<th>EDema CONTENT OF VENTRICLES AS CALCULATED BY</th>
<th>K CONTENT PER 1000 GRAMS FRESH TISSUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>grams</td>
<td>mM</td>
<td>mM</td>
<td>minutes</td>
<td>Lung edema method*</td>
<td>H2O content method*</td>
</tr>
<tr>
<td>Normal dogs</td>
<td>(768-799)</td>
<td>81.5</td>
<td>37.4</td>
<td>183</td>
<td>20.0</td>
<td>10.6</td>
</tr>
<tr>
<td>Control Heart-lungs</td>
<td>(784-825)</td>
<td>71.6</td>
<td>35.6</td>
<td>183</td>
<td>20.0</td>
<td>10.6</td>
</tr>
<tr>
<td>Therapeutic dose</td>
<td>(781-812)</td>
<td>63.1</td>
<td>31.6</td>
<td>249</td>
<td>25.0</td>
<td>10.6</td>
</tr>
<tr>
<td>Toxic dose</td>
<td>(781-810)</td>
<td>59.2</td>
<td>28.6</td>
<td>185</td>
<td>21.5</td>
<td>7.8</td>
</tr>
</tbody>
</table>

* Wood and Moe (1941).
† Calculated by lung edema method (Wood and Moe, 1941).

Without chloride analyses there is no adequate means of correcting for edema in heart-lung hearts. Table 1 includes the amount of cardiac edema as calculated by the water content and lung edema methods, the only available means of estimating the edema content in this group of hearts since they were not analyzed for chloride (11). The actual cardiac edema probably correlates more closely with the calculated edema based upon the simultaneously occurring lung edema (11). Therefore the ventricular potassium content has been computed on the basis of edema corrected (lung edema method) fresh tissue weight in an effort to gain a better idea of the exchanges occurring in the actual cardiac tissue. The inadequacy of this correction is shown by the fact that these calculations (table 1) show higher potassium concentrations in control and therapeutically treated hearts.

2 The pure glycosides of Digitalis lanata, Lanatosides A, B, or C, were used in the majority of these experiments.
ELECTROLYTE AND WATER CONTENT OF PERFUSED HEART

peutic dose hearts than are obtained with normal hearts. Average edema values as obtained by this method have been shown to overcorrect for edema (11).

In spite of the difficulty of interpretation due to cardiac edema, several definite indications can be drawn from table 1: 1, heart-lung ventricles have an increased water content, presumably due to the accumulation of edema fluid; 2, with the doses used in these experiments the magnitude of this increase is apparently not affected by digitalis glycosides; 3, all heart-lung ventricles have a decreased potassium concentration compared to the normal dog heart when concentrations are expressed on either a fresh tissue or a dry weight basis; 4, hearts receiving toxic doses of digitalis glycosides show a much greater decrease in potassium concentration than the control heart-lung hearts; this decrease is much too large to be explained on the basis of edema content; 5, hearts receiving therapeutic doses of digitalis glycosides show a greater decrease in potassium concentration than do control hearts. However, it must be noted that the average duration of the preparation was about one-third greater in the therapeutic dose digitalis experiments than in either the controls or the toxic dose experiments. This greater time would favor spontaneous potassium loss and edema formation. The correction for edema leaves a small apparent loss of potassium in comparison with control hearts which is slightly less than one-third that found with toxic doses of digitalis glycosides.

More decisive information can be derived from the hearts which were analyzed for sodium and chloride in addition to the potassium and water analyses. The average values and range of variation of these analyses are given in table 2. The wet and dry weight potassium and water concentration changes in this group of hearts are similar to those shown in table 1. The chloride concentration in heart-lung ventricles is increased; the magnitude of this increase is apparently not significantly affected by the doses of digitalis glycosides used in these experiments. The sodium concentration in heart-lung ventricles is likewise increased; the magnitude of this increase is significantly larger in preparations which received a toxic dose of a digitalis glycoside.

The amount of cardiac edema occurring in this group of hearts was calculated from both the sodium and chloride analyses as described by Wood and Moe (11). A knowledge of the edema content of the heart makes possible the calculation of the approximate exchanges which occurred in the actual ventricular musculature. The average results of some of these calculations are given in table 3.

The average edema contents of the control heart-lung ventricles as calculated either from the sodium or chloride concentrations were not significantly different and amounted to 17.5 grams per cent of the final ventricular weight. The potassium content when calculated on the basis of edema corrected fresh tissue was not significantly different from normal, 80.0 mM per kilo as compared to—81.5 mM per kilo, the average normal figure. The gains in chloride and sodium were “equivalent” when calculated on the basis of their concentrations in serum; hence the increase in sodium and chloride content can be explained on the basis of edema formation alone.

The average edema content of the toxic dose heart-lung ventricles was 25.3
grams per cent on the basis of chloride analyses. The potassium content when calculated on an edema corrected fresh tissue basis was significantly reduced, 66.1 mM per kilo as compared to 81.5 mM per kilo, the average normal value.

**TABLE 2**

*Heart-lung ventricles, average values*

<table>
<thead>
<tr>
<th>(NO.) HEARTS OF HEARTS OF NORMAL DOGS</th>
<th>WATER CONTENT PER 1000 GRAMS FRESH TISSUE</th>
<th>CONCENTRATION IN mM PER:</th>
<th>MINUTES DURATION OF PREPARATION</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>grams</td>
<td>Potassium</td>
<td>Sodium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1000 grams fresh tissue</td>
<td>100 grams of dry weight</td>
</tr>
<tr>
<td>Normal dogs</td>
<td>783 (766-799)</td>
<td>81.5 (73.4-87.0)</td>
<td>37.4 (31.6-40.0)</td>
</tr>
<tr>
<td>Control Heart-lungs</td>
<td>810 (784-835)</td>
<td>66.7 (60.7-75.1)</td>
<td>35.1 (32.3-37.7)</td>
</tr>
<tr>
<td>Toxic dose Heart-lungs</td>
<td>810 (791-852)</td>
<td>50.8 (44.0-60.0)</td>
<td>25.8 (21.3-30.4)</td>
</tr>
</tbody>
</table>

Average serum values

<p>| | | | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal dogs</td>
<td>937</td>
<td>4.69</td>
<td>141</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>Control Heart-lungs</td>
<td>3.82</td>
<td>144</td>
<td>119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxic dose Heart-lungs</td>
<td>5.72</td>
<td>143</td>
<td>117</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 3**

*Calculated electrolyte and water exchanges of heart-lung ventricles, average values*

<table>
<thead>
<tr>
<th>(NO.) HEARTS OF HEARTS OF</th>
<th>CALCULATED EDema CONTENT FROM: Chloride content</th>
<th>POTASSIUM CONTENT ON BASIS OF &quot;EDema CORRECTED&quot; FRESH Tissue</th>
<th>CI GAIN</th>
<th>Na GAIN</th>
<th>Na &quot;SERUM EQUIVALENT&quot; OF CI GAIN</th>
<th>Na GAIN IN EXCESS OF &quot;SERUM EQUIVALENT&quot; OF CI GAIN</th>
<th>K GAIN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>grams</td>
<td>mEq per 1000 grams of fresh tissue</td>
<td>mM</td>
<td>mM</td>
<td>mM</td>
<td>mM</td>
<td></td>
</tr>
<tr>
<td>Control Heart-lungs</td>
<td>175</td>
<td>173</td>
<td>80.0</td>
<td>20.9</td>
<td>25.0</td>
<td>25.2</td>
<td>-0.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.5</td>
</tr>
<tr>
<td>Toxic dose Heart-lungs</td>
<td>253</td>
<td>370</td>
<td>66.1</td>
<td>29.6</td>
<td>48.7</td>
<td>36.3</td>
<td>12.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-11.6</td>
</tr>
</tbody>
</table>

The gain in sodium was in excess over the "serum equivalent" of the chloride gain. This excess amounted to 12.4 mM per kilo of fresh tissue, and is presumably due to the entrance of sodium into the muscle cell in exchange for the lost po-
tassium. The loss in potassium was 11.6 mM per kilo of fresh tissue, approximately the chemical equivalent of the sodium gain.

A better concept of the actual cardiac muscle cell exchanges which occurred can be gained by calculating the "extracellular water" content of these heart-lung hearts. This makes possible a calculation of the approximate intracellular space composition as described by Hastings and Eichelberger (14).

In calculating the "extracellular water" of the heart-lung ventricles it was assumed that the extracellular fluid had the same protein content as the serum

\[ \text{Per cent extracellular water gram} = \frac{100 \text{ (mM per kilo ventricular chloride)}}{\text{(mM per kilo serum chloride)}} \]

The average results of these calculations are given in table 4. The "extracellular water" of heart-lung ventricles is significantly increased over normal due to edema formation which is extracellular in position. The differences in the "extracellular water" values for the control and the toxic dose heart-lung ventricles are probably due to the longer duration of the toxic dose preparations (table 2) rather than to an effect of the digitalis glycoside.

\[ \text{"Extracellular water" has been used (15) as a non-committal term for the calculated chloride space, since this calculated value is actually neither the "chloride space" nor "extracellular space" but only a good approximation of these two phases of tissue.} \]
Intracellular water, potassium, sodium and chloride content of control heart-lung ventricles is apparently not significantly different from the normal ventricle. The intracellular composition of the toxic dose ventricles, however, shows definite and significant variations from the controls and normal ventricles. The intracellular potassium content is significantly decreased; 122 mM per kilo of water as compared to 145 mM per kilo of water, the average normal value. The intracellular sodium content is increased. The loss of intracellular potassium is apparently an exchange with an equivalent amount of sodium, since the average increase in intracellular sodium content of 26 mM per kilo of water is approximately chemically equivalent to the corresponding intracellular potassium loss of 23 mM.

Discussion. The bearing of these cardiac electrolyte studies on heart failure and digitalis action are of some interest. The uniformity and magnitude of the cardiac edema which was found to occur in these preparations lends some support to Rühl's contention (16) that cardiac edema is at the basis of heart failure in the heart-lung preparation. However, since digitalis glycosides reverse the processes of failure and yet do not decrease edema, it is equally probable that the edema is an independent concomitant of spontaneous failure.

The finding that untreated failing heart-lung hearts lose little if any intracellular potassium does not agree completely with the results obtained in human heart failure (1, 2). This may result from the fact that failure in the heart-lung heart is much more rapid than that usually seen in clinical heart failure. It should be pointed out that chloride analyses were not carried out in the human heart studies so that calculations of the increase in extracellular space could not be made. Most types of clinical heart failure are associated with increases in the amount of connective tissue and of varying degrees of edema in the heart muscle; until these factors are determined results indicating a decrease in cardiac muscle cell potassium should be accepted with reservations. The fact that nearly all cardiac patients are treated with digitalis may also contribute to the decrease in cardiac potassium concentration which has been reported for such patients.

The electrolyte studies on the heart-lung ventricles receiving toxic doses of digitalis glycosides are in essential agreement with previous results obtained with preparations of other types. The sodium and chloride analyses carried out in this study have added additional information not available in previous studies. It is of interest that the ventricular muscle electrolyte exchanges which were found to result from digitalis action are very similar to the exchanges which occur in striated muscle during activity.

Due to cardiac edema the results concerning the effects of therapeutic doses of digitalis on the potassium content of the heart-lung ventricle are not as conclusive as could be desired. It can be definitely concluded, however, that therapeutic doses of digitalis did not cause an increase in the ventricular potassium content of this preparation. Actually the evidence gives some indication that “therapeutic dose hearts” had a decreased potassium content. This inability to confirm the findings of Boyer and Poindexter (9) on the intact cat and the findings of Hagen (6) on the Langendorff perfused rabbit heart may be due to the dif-
ferences in the preparations used. It may be significant that the average normal potassium content for the cat heart as given by Boyer and Poindexter is 17.0 mM per kilo of fresh tissue lower than the values reported from other laboratories (17, 7, 18).

SUMMARY

Studies of the electrolyte and water content of the heart-lung ventricle are reported.

The ventricles of the untreated (failing) heart-lung heart have: 1, an increased water content; 2, an increase in the wet and dry weight sodium and chloride concentrations; 3, a decrease in the wet and dry weight potassium concentration. Correction for edema and calculation of the "extracellular water" on the basis of chloride analyses indicate that: 1, the intracellular water and electrolyte content of the untreated heart-lung ventricles is not significantly different from normal ventricles; 2, the average edema content is 17.5 grams per cent of the final ventricular weight and is extracellular in position; 3, the increase of sodium and chloride content of these hearts can be accounted for on the basis of the extracellular edema formation.

The ventricles of heart-lung preparations which received therapeutic doses of a digitalis glycoside have: 1, an increased water content which is comparable to the control heart-lung ventricles; 2, an apparent decrease in potassium content which is larger than that found in the control heart-lung and does not appear to be accountable for on the basis of an increased edema content alone.

The ventricles of heart-lung preparations which received toxic doses of a digitalis glycoside show significant changes in their intracellular electrolyte compositions. The intracellular potassium content is decreased apparently in exchange for sodium since there is approximately a chemical equivalent increase in intracellular sodium content. The doses of cardiac glycosides used in these experiments did not significantly affect the water gain or edema formation which occurs in heart-lung ventricles.

The unphysiological factor or factors which are responsible for cardiac edema formation in the heart-lung preparation must exert their chief effect on the capillary membrane, since the electrolyte concentration gradients across the muscle cell membrane and the intracellular water content of untreated heart-lung hearts are apparently normally maintained.

REFERENCES