The Water and Electrolyte Content of the Human Heart in Congestive Heart Failure with and without Digitalization

By Norman E. Clarke, M.D., and Robert E. Mosher, Ph.D.

The hearts of 25 patients have been serially analyzed for water, chloride, sodium and potassium content. Sixteen hearts were of patients who died in circulatory heart failure; some received digitalis and some did not. The water content of all hearts was the same. In circulatory heart failure, the sodium increases and potassium decreases but the sum of the two remains the same as in normal hearts, indicating a reciprocal relationship. Digitalis in circulatory heart failure restores the alkali metal values and ratios of heart muscle to near normal levels. Digitalis exerts a direct chemical action on the heart muscle.

The onset and severity of congestive heart failure does not always conform to the objective evidence of heart damage, just as the anatomic findings in all instances do not correlate with the functional status of the heart. Therefore, one must suspect that congestive heart failure may result from either physical or chemical change in myocardial tissue, although critical chemical changes within the living heart muscle cell cannot be evaluated by present methods. According to Herrman, the creatinine content of heart muscle is reduced in congestive heart failure and is partially restored by digitalis therapy. It appeared possible that digitalis might influence other constituents of the failing heart muscle, and the action of this drug in heart failure be due in part to its effect on the chemical balances existing in the heart tissue. We have investigated this possibility by studying the chemical topography of the human heart. The particular components studied were sodium, potassium, chloride and water content.

Methodology

Sampling. An effort was made to secure samples as soon after the time of death as possible, the average elapsed time from death to autopsy being eight hours. Samples approximately 20 Gm. in size were taken from the following five areas of hearts at autopsy: right auricle, midzone of right ventricle, midzone of ventricular septum, base of left ventricle and apex of the left ventricle. These samples were wiped dry of surface fluids and immediately subjected to analysis. All samples analyzed were trimmed so as to remove all visible fat and were carefully blotted before weighing to remove excess surface moisture.

Water Content of Tissue. Approximately 0.5 Gm. of tissue in thin slices was placed in a weighed aluminum dish and the dish reweighed. The difference in weight was taken to be the weight of the sample. The dish was then placed in an electric-air oven at 135 C. until it reached constant weight. The usual time required was two hours. The sample was then removed from the oven, cooled in a desiccator and reweighed. The loss in weight was taken to be the weight of water contained in the sample and calculations of per cent water content were made on this basis. This is essentially the method recommended by the Association of Agricultural Chemists for the determination of the water content of animal tissue.

Chloride Content of Tissue. A 0.500 Gm. sample of carefully trimmed tissue was carefully weighed and transferred to a 125 ml. Erlenmeyer flask, 5 ml. of five normal sodium hydroxide solution and 20 ml. of distilled water were added and the sample was heated gently on an electric hot plate until solution was complete. The solution was cooled and approximately 20 ml. of distilled water, 7 ml. of concentrated nitric acid and then exactly 5.0 ml. of 0.01 normal silver nitrate solution was added and titrated with 0.01 normal potassium thiocyanate to a faint pink endpoint. We found it advisable to run a reagent blank and to standardize the thiocyanate solution against the silver nitrate. The per cent
chloride was computed according to the following formula:

\[
\% \text{Cl} = \frac{V_{\text{ANO}_3} \times N_{\text{ANO}_3} - V_{\text{KCN}} \times N_{\text{KCN}}}{\text{Weight of sample in Gm.}} \times 0.0355 \times 100
\]

_Sodium and Potassium Content of Tissue._ A 0.300 Gm. sample of tissue was carefully weighed and transferred to a 50 ml. Erlenmeyer flask. Five ml. of concentrated nitric acid and 5 drops of 70 per cent perchloric acid were added and then slowly evaporated to incipient dryness on an electric hot plate in a hood. No charring should occur. If the sample did char, 5 ml. of concentrated nitric acid were added and the sample was evaporated to dryness once again. It has been found that 5 µL of vanadium as ammonium vanadate will accelerate this wet ashing procedure. After the sample reached dryness, it was cooled and 10 ml. of distilled water and one drop of concentrated hydrochloric acid added and warmed until all salts were in solution. It was cooled and transferred quantitatively to a 25 ml. volumetric flask and diluted to the mark with distilled water then mixed thoroughly by inversion. Then 1.0, 2.0, and 3.0 ml. aliquots of the standard solution were treated in the same manner as the tissue sample. Standards and unknowns were compared using the Beckman flame photometer. This technic is described by Mosher and co-workers.

One liter of the stock standard solution contained 0.255 Gm. of sodium, 0.625 Gm. of potassium, 0.016 Gm. of magnesium, and 0.310 Gm. of phosphorus. The weighing forms were: sodium and potassium as chlorides, magnesium as distilled magnesium metal, and phosphorus as diammonium hydrogen phosphate.

A total of 50 human hearts were analyzed, using the above technic. The data obtained from 25 of these hearts is presented. Of this group, 16 were patients who died in Providence Hospital with the clinical diagnosis of congestive heart failure. This study was to correlate special chemical changes in the myocardium with this clinical diagnosis. The criteria for selection of these hearts included the presence of severe congestive heart failure, the absence of obvious renal insufficiency and confirmation of heart disease as the chief cause of the congestive heart failure by postmortem examination. The etiologic diagnosis, confirmed by necropsy, was rheumatic heart disease in five, coronary heart disease in four, ancient coronary infarction in three and hypertensive heart disease in four patients. Five of these patients had received digitalis and 11 had not. All of the digitalized patients had received preliminary digitalization and been maintained on daily maintenance dosage of the drug. The hearts of seven patients were normal from both clinical and autopsy examination.

Since some variation in water content occurs in different hearts and in different areas of the same heart, it is advisable to express concentrations of elements on a dry tissue basis. Routine fat determinations were not made and we have calculated ratios of potassium to sodium to eliminate the effect of the fat content of trimmed heart tissue which we have found by analysis to be normally 1 to 3 per cent. It is impossible to be sure of fat content, as present methods must show ether or other solvent extractables which may not represent solely fatty or lipid materials. Likewise, as collagen tissue comprises only 0.7 per cent of heart substance, it causes no major error in this data. These analyses, therefore, should be characteristic of heart muscle and its immediate fluid environment.

### RESULTS

As presented in table 1, the water content of the normal auricle is 81.2 per cent and the septum, base and apex of the left ventricle average about 79 per cent or the lowest water content, while the 80.7 per cent value for the right ventricle stands intermediate to the right auricle and left ventricle. There is a slight difference in the left ventricular water content of normal, diseased or digitalized diseased hearts, while that of the right auricle of cardiac

<table>
<thead>
<tr>
<th>Table 1.—Average Composition of Heart Muscle (per cent Composition of Wet Tissue)</th>
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<tbody>
<tr>
<td>A. Normals (7 Hearts)</td>
</tr>
<tr>
<td>Right Auricle.............. 81.2 0.15 0.120 0.139</td>
</tr>
<tr>
<td>Right Ventricle........... 80.7 0.14 0.112 0.196</td>
</tr>
<tr>
<td>Septum.................... 79.2 0.12 0.094 0.309</td>
</tr>
<tr>
<td>Base Lt. Vent............... 78.9 0.12 0.092 0.316</td>
</tr>
<tr>
<td>Apex Lt. Vent............... 79.4 0.12 0.089 0.311</td>
</tr>
<tr>
<td>B. Cardiacs (11 Hearts)</td>
</tr>
<tr>
<td>Right Auricle.............. 78.8 0.16 0.138 0.120</td>
</tr>
<tr>
<td>Right Ventricle........... 79.0 0.15 0.130 0.179</td>
</tr>
<tr>
<td>Septum.................... 79.7 0.15 0.130 0.200</td>
</tr>
<tr>
<td>Base Lt. Vent............... 79.1 0.16 0.131 0.224</td>
</tr>
<tr>
<td>Apex Lt. Vent............... 80.1 0.14 0.128 0.217</td>
</tr>
<tr>
<td>C. Digitalized Cardiacs (8 Hearts)</td>
</tr>
<tr>
<td>Right Auricle.............. 82.1 0.16 0.130 0.130</td>
</tr>
<tr>
<td>Right Ventricle........... 80.0 0.13 0.104 0.226</td>
</tr>
<tr>
<td>Septum.................... 79.3 0.14 0.104 0.285</td>
</tr>
<tr>
<td>Base Lt. Vent............... 79.5 0.13 0.096 0.290</td>
</tr>
<tr>
<td>Apex Lt. Vent............... 79.6 0.14 0.105 0.284</td>
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patients drops to 78.8 per cent. These variations in water content are not great enough to hold any significance.

When digitalis has been given, the auricular muscle chloride is 0.15 per cent and the lowest chloride content is 0.12 per cent in the septum, base and apex of the left ventricle. The sodium is highest or 0.12 per cent and potassium lowest or 0.139 per cent in the auricle but the reverse is true of these elements in the left ventricle where they appear to be distributed uniformly, with sodium at approximately 0.092 per cent and potassium at 0.312 per cent. In congestive heart failure the same relative relationship of the auricle and ventricle with respect to sodium and potassium persists but, in general, sodium increases and potassium decreases in all sections of the heart. When digitalis had been given for the congestive heart failure, there was a definite reversal of the electrolyte pattern toward normal levels. In all analyses the right ventricle figures stand intermediate to the auricular and left ventricular findings.

The effect of digitalis on the heart muscle electrolytes in congestive heart failure is illustrated by figure 1. This represents heart sections from the left ventricle only, with the figures for the ratio of potassium to sodium in milliequivalents on the abscissa and the number of samples of normal, diseased and digitalized diseased hearts on the ordinate. The samples from normal hearts fall between the ratios of 1.25 and 2.50, and for hearts of cardiac patients between 0.25 and 2.00. The sections from diseased hearts which had been digitalized all lie closer to normal values than they do to the values for undigitalized diseased hearts, although there is a certain amount of overlap. Apparently digitalis acts on the heart muscle in congestive failure so as to restore the cellular electrolytes (sodium and potassium) to within normal ratios.

To determine whether there was a change in the total amount of electrolytes in the failing heart, computation was made of the total milliequivalents of chloride and of the alkali metals per 100 Gm. of dried heart tissue. As presented in table 2, the normal left ventricular chloride level of 16 mEq. increases to 21 mEq. in the left ventricle muscle of undigitalized cardiac patients, but remains at 21 and 20 mEq. in the right auricle and right ventricle, respectively, of normal and diseased hearts. The sodium increases and potassium decreases in all muscle sections of the cardiac patients, but the total milliequivalents of sodium and potassium in the various muscle sections of the cardiac patients remain about the same as in the corresponding sections of the normal hearts, except that the right auricle decreases to 42.8 mEq., the normal being 47.8 mEq. Due to the natural variability of the auricle, it is doubtful if this difference has any statistical significance. The potassium-sodium ratios on the basis of milliequivalents also increase progressively from the right auricle to the left ventricle. The hearts of digitalized cardiac patients show lower chloride and sodium and higher potassium values than do the hearts of undigitalized cardiac patients. The total milliequivalents of sodium and potassium of all heart muscle sections in the digitalized cardiac pa-

![Fig. 1. The effect of digitalis on the potassium-sodium ratio of the left ventricular heart muscle in circulatory heart failure.](http://circ.ahajournals.org/)

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tients are about equal to those for normal hearts except for a greater than normal increase in the right auricle. It is significant that in contrast to the great change in potassium-sodium ratios between the normal and diseased heart, the total number of milliequivalents of alkali metals in 100 Gm. of dry heart tissue is essentially the same in all corresponding heart sections of both groups.

In table 2, average deviations are given for normal hearts and for hearts from patients dying in congestive heart failure who had or had not received digitalis. In general, the deviations for hearts of undigitalized cardiac patients are greater than the corresponding values for the other two categories. Generally, the deviations for the right auricle and right ventricle are greater than those for the left ventricle. Computed percentage-wise, the deviations of potassium-sodium ratios are smaller than for sodium and potassium individually. This would indicate that the ratio is more reliable than individual sodium or potassium values as an index or criterion of the status of electrolyte balance in a heart. In diseased hearts the deviations for the left ventricular samples are the same as or greater than those for samples from the right auricle or right ventricle. This condition does not occur with normal or digitalized diseased hearts.

To establish that there is a relationship between potassium and sodium, as suggested by the fact that there may be wide variation in potassium-sodium ratio between samples having the same combined amounts of these ele-

| Table 2.—Milliequivalents of Chloride and Alkali Metals per 100 Gm. of Dried Heart Tissue with Average Deviations of Analysis. |
|--------------------|-----|-----|-----|-----|-----|-----|-----|
|                    | Cl  | Cl A.D.* | Na | Na A.D.* | K  | K A.D.* | Na-K | Na-K A.D.* | K/Na | K/Na A.D.* |
|--------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| A. Normals (7 Hearts) |
| Right Auricle      | 21 ± 4.3 | 27.5 ± 4.5 | 20.3 ± 8.2 | 47.8 ± 9.0 | 0.74 ± 0.31 |  |
| Right Ventricle    | 20 ± 3.6 | 25.6 ± 4.1 | 26.1 ± 3.6 | 51.7 ± 5.6 | 1.02 ± 0.29 |  |
| Septum             | 18 ± 2.5 | 19.6 ± 2.2 | 38.1 ± 3.2 | 55.7 ± 2.9 | 1.94 ± 0.30 |  |
| Base Lt. Ventricle | 16 ± 1.1 | 19.1 ± 1.2 | 38.6 ± 2.6 | 57.7 ± 3.2 | 2.02 ± 0.10 |  |
| Apex Lt. Ventricle | 16 ± 1.5 | 18.5 ± 1.6 | 38.1 ± 2.6 | 56.6 ± 4.2 | 2.06 ± 0.13 |  |
| B. Cardiacs (11 Hearts) |
| Right Auricle      | 21 ± 4.7 | 28.3 ± 7.7 | 14.5 ± 5.1 | 42.8 ± 12.1 | 0.50 ± 0.18 |  |
| Right Ventricle    | 20 ± 2.6 | 28.8 ± 4.7 | 21.8 ± 4.7 | 50.6 ± 7.6 | 0.76 ± 0.18 |  |
| Septum             | 21 ± 3.2 | 27.8 ± 8.9 | 29.9 ± 5.9 | 57.7 ± 6.5 | 1.08 ± 0.42 |  |
| Base Lt. Ventricle | 22 ± 3.3 | 27.2 ± 5.3 | 27.4 ± 6.4 | 54.6 ± 6.0 | 1.00 ± 0.29 |  |
| Apex Lt. Ventricle | 20 ± 3.4 | 28.0 ± 4.4 | 27.9 ± 7.9 | 55.9 ± 3.0 | 1.00 ± 0.32 |  |
| C. Digitalized Cardiacs (5 Hearts) |
| Right Auricle      | 28 ± 6.0 | 32.1 ± 7.2 | 20.0 ± 2.9 | 52.1 ± 6.1 | 0.58 ± 0.22 |  |
| Right Ventricle    | 18 ± 2.0 | 21.5 ± 2.7 | 29.1 ± 6.2 | 50.6 ± 6.7 | 1.38 ± 0.32 |  |
| Septum             | 19 ± 1.0 | 22.4 ± 2.5 | 35.1 ± 1.5 | 57.5 ± 3.3 | 1.57 ± 0.15 |  |
| Base Lt. Ventricle | 18 ± 1.2 | 20.4 ± 2.0 | 36.1 ± 2.1 | 56.5 ± 2.5 | 1.77 ± 0.19 |  |
| Apex Lt. Ventricle | 19 ± 1.6 | 22.4 ± 2.8 | 35.6 ± 2.3 | 58.0 ± 3.1 | 1.63 ± 0.29 |  |

* Average deviations of analysis.
value for our data is $-0.67$, we can conclude that there is a high probability of correlation between sodium and potassium levels in tissue, probably in the nature of some type of equilibrium.

The limits of variation of alkali metals in the right auricle, right ventricle and left ventricle are presented in figure 3. The sum total of milliequivalents of sodium and potassium per 100 Gm. of dried heart tissue was used, since this value was found to be fairly constant for both normal and diseased hearts. The values are from normal, diseased and digitalized diseased hearts. The greatest variation occurs in the auricle where the values range between 20 and 80, or a range of 60, while the least variation occurs in the left ventricle with a range between 40 and 70, or a variation of only 30. The right ventricle once again stands intermediate with a variation from 25 to 75, or a range of 50. The great difference in the total milliequivalents of alkali metal between the right auricle and left ventricle may reflect the different function of these two chambers.

Heart enlargement is an important clinical sign of heart disease and edema of congestive heart failure, so it seemed important to determine whether the two necessarily bear any relationship. In figure 4, heart weights in grams on the abscissa are plotted against per cent water content on the ordinate. It is apparent that there is no relationship between heart weight and water content of heart muscle, for hearts weighing between 500 and 650 Gm. have the same average water content as hearts weighing between 200 and 300 Gm. This graph is representative of normal, diseased and digitalized diseased hearts. The relationship of heart weight and congestive heart failure to heart muscle chloride, sodium and potassium content is presented in table 3. The two hearts selected are representative of others in our series. The heart weighing 575 Gm. was that of a man dying suddenly from cerebral thrombosis. Prior to death he had had no pronounced heart symptoms and analysis showed the chloride, sodium and potassium content of his heart to be essentially normal despite its size.
The second heart weighing 250 Gm. was from a man dying with the clinical picture of congestive heart failure which followed intestinal surgery, prolonged use of gastric drainage by Levine tube and the administration of three liters of 5 per cent glucose in sterile water daily for 11 days. He received no saline solutions. He died after increasingly severe dyspnea, orthopnea, anasarca, weakness and ultimate collapse. The chemical changes in his heart are extreme, the left ventricular chlorides being 0.05 as compared with the normal of 0.12 with marked depletion of sodium to 0.062 per cent and potassium to 0.280 per cent, normal values being 0.0917 and 0.312 per cent respectively. He died with the clinical picture of congestive heart failure and with marked electrolyte change in the myocardium although with a heart of normal weight and no previous history of heart disease.

**DISCUSSION**

It has been stated that the reduction in heart muscle potassium in congestive heart failure is the result of heart muscle edema. Our experience is to the contrary, as no real difference in average water content between normal and diseased hearts was found, although the latter show definite decrease in potassium content. Further, the potassium content of heart muscle of digitalized cardiac patients is higher than that of undigialized cardiac patients with no or very slight change in the water content. Since heart muscle does not become edematous in congestive heart failure, changes in chloride or alkali metal content are not related to change in total heart muscle water.

There are distinct differences between the right auricle and left ventricle in chloride and electrolyte content and their behavior in congestive heart failure. Although the right auricle is more resistant than the left ventricle to quantitative change in individual metal content when congestive heart failure occurs, as shown by potassium-sodium ratios, nevertheless the right auricle has a wider range of total alkali metal content than does the left ventricle. These findings may reflect the varied importance of these electrolytes in the different functions of these two heart chambers.

In the isolated animal heart, stimulation of the vagus nerve increased the potassium content of the perfusion fluid which was Locke's solution. The potassium loss was supposedly from heart muscle, and because the vagus nerve exerts greatest influence on the heart auricles, these chambers should contribute a greater proportion of their electrolyte content. We find that the auricle functions under a wide range of total electrolyte content but resists great change in individual electrolyte values. The right auricle is the location for the dominant stimulus formation, and these peculiarities of its electrolyte content may be necessary for maintaining the primary heart stimulus. At least it appears that sudden vagus stimulation
would not alter to any extent its potassium content. The left ventricle functions as the energy source for maintaining circulation of the blood. The energy producing or muscle contracting function of the left ventricle permits wide variation in individual electrolyte content with retention of the essential muscle irritability but exercises greater control over its content of total alkali metals. It seems possible that under certain conditions, strong vagus stimuli might quickly disturb auricular muscle potassium, alter impulse conductivity and produce an auricular arrhythmia such as occurs with severe, acute upper abdominal disease as duodenal ulcer and severe, acute gall bladder disease.

Various investigators7–8 have noticed that potassium can abolish the extrasystoles that occur with overdigitalization. It has been assumed that the potassium content of heart muscle is reduced by such therapy but our studies show that digitalis restores rather than decreases the potassium content of heart muscle when in the state of congestive failure. On the basis of our findings it appears probable that, since digitalis does not fully replace the potassium-sodium balance, the giving of potassium may complete this restoration and thereby produce the results that have been observed.

A reciprocal relationship between sodium and potassium in heart muscle is suggested by this study. There is an increase in sodium and decrease in potassium when the heart muscle is in a state of congestive failure, although the total milliequivalents per 100 Gm. of dried heart tissue remain practically the same in normal and diseased hearts and the normal potassium-sodium ratios may be twice as large as in congestive heart failure. This suggests that the movement of one of these elements into or out of the muscle tissue is accompanied by the opposite movement of the other element.

The use of digitalis in congestive heart failure is reflected in nearer normal electrolyte values in all sections of digitalized diseased hearts as compared with undigitalized diseased hearts. This probably is produced by a direct chemical action of digitalis although central action through the vagus nerve under certain conditions may be a factor. We found that the lowered auricular muscle potassium in congestive heart failure is elevated toward normal by digitalis which indicates that the action of digitalis on the auricle is a direct chemical effect or that vagal stimulation does not decrease the auricular muscle potassium when the heart is in congestive failure.

As the total milliequivalents of alkali metals are the same in normal and diseased hearts, the giving of digitalis in congestive heart failure increases the potassium and decreases the sodium content of heart muscle, restoring the potassium-sodium ratio to nearer normal levels. However, the restoration by digitalis of the potassium-sodium ratios to within normal limits did not prevent death. Perhaps the reduced heart muscle potassium or the abnormal potassium-sodium ratio was of such long standing that irreversible myocardial cell damage was present. This could explain digitalis resistance or failure of clinical response and show the necessity for early and adequate digitalis therapy in cases of congestive heart failure.

Summary

A total of 50 human hearts, 16 from patients dying in congestive heart failure, were sectionally analyzed for water, chloride, sodium and potassium.

The total water content of normal, diseased and digitalized diseased hearts was the same. Therefore the water content of heart muscle is not the cause of changes in chloride or electrolyte content of heart muscle.

The milliequivalents per 100 Gm. of dried heart tissue of sodium increases and of potassium decreases in congestive heart failure but the sum of the two is the same in all hearts; this supports the existence of a reciprocal relationship between these cations in heart muscle tissue.

In congestive heart failure, digitalis restores the alkali metal values and ratios of heart muscle to near normal levels. The alkali metal changes produced by this drug in the right auricle and left ventricle are distinctly different. This may be related to the different function of these heart chambers.

Evidence is presented that digitalis exerts a
direct chemical action on the heart muscle and
the possibility of irreversible myocardial dam-
age with prolonged electrolyte unbalance sug-
gests the importance of early and adequate
digitalis therapy.

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