Exchangeable Sodium, Body Potassium, and Body Water in Previously Edematous Cardiac Patients

Evidence for Osmotic Inactivation of Cation

By HUGH J. CARROLL, M.D., RITA GOTTERER, M.D., AND BERNARD ALTSHULER, PH.D.

Previous studies from this laboratory have indicated that cardiac patients who have been successfully treated for congestive heart failure and who have become free from edema have a larger than normal concentration of sodium in their bodies. The suggestion was advanced that part or all of the sodium excess in such patients represented osmotically inactive cation because the patients studied did not have increases in body water comparable to the excess of sodium and because those patients whose body concentration of sodium fell to normal with time did not show a simultaneous loss of body water. The conclusion that previously edematous cardiac subjects have a pool of osmotically inactive cation requires proof that the sodium excess does not merely represent compensation for a deficiency of the principal intracellular cation, potassium. In the studies described above the work of other investigators was cited which made it appear unlikely that potassium depletion was present in the previously edematous cardiac subjects, but no measurements were made of body potassium concentration. The present study was undertaken to evaluate directly the possibility that the excess of exchangeable sodium in previously edematous cardiac subjects might be a consequence of potassium depletion. To this end measurements were made simultaneously of total body water, total exchangeable sodium, and total body potassium in a group of 13 previously edematous cardiac subjects (“dry cardiac” group). Identical determinations were made in a group of 20 hospitalized individuals with no evidence of heart disease and no history of having been edematous (“control” group). The results showed that in both groups the body water as the per cent of body weight was the same. The whole body potassium concentration in both groups was the same, but in the “dry cardiac” group the characteristic elevation in total exchangeable sodium was found.

Patients and Methods

Thirteen patients who had been treated for congestive heart failure with edema were studied when loss of edema had ceased and weight had been stable for periods of 2 weeks to 4 months. Two of the patients had rheumatic heart disease, nine arteriosclerotic heart disease, and two heart disease of unknown type. The study was limited to male patients. The diagnosis of heart failure was made on the basis of accepted criteria and was unequivocal in each case. No patient was accepted for the study who had any evidence of edema in the extremities or fluid collection in the pleural or abdominal spaces. The 20 patients in the “control” group had the same age distribution as the “dry cardiac” group and suffered from a wide variety of noncardiac diseases. An attempt was made to avoid gross disparity in body composition between the two groups of patients by matching them as closely as possible with regard to body build and state of nutrition. Total exchangeable sodium and total body water were measured by dilution technics with use of Na24 and antipyrine as previously described.2
Body Composition in Previously Edematous Cardiac Patients ("Dry Cardiac" Group)

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*RH, rheumatic heart disease; AS, arteriosclerotic heart disease; UNK, unknown heart disease.
†In all tables: A.S., antipyrine space; TENa, total exchangeable sodium; TENa/A.S., total exchangeable sodium per liter of antipyrine space (body water); TENa/wt., exchangeable sodium per Kg. of body weight; TBK, total body potassium; TEK, total exchangeable potassium; TBK/wt., total body potassium per Kg. of body weight; TEK/wt., total exchangeable potassium per Kg. of body weight.

The total body potassium was estimated by counting endogenous potassium radioisotope in a whole body counter. This technic takes advantage of the facts that significant amounts of K⁴⁰ are naturally present in the body and that the specific activity of natural potassium is everywhere the same. In this system, to reduce background, the subject is placed in a small room whose walls, ceiling, and floor are made of iron, 7 inches in thickness. He is seated in a straight-backed aluminum chair reclined at 45°. The scintillation detector is placed above the hips, 50 cm. from the lowest point of the seat, facing downward. This detector consists of a thallium-activated sodium iodide crystal 8 inches in diameter and 4 inches in thickness. It is viewed by five photomultipliers each 3 inches in diameter. A 400-channel transistorized pulse-height analyzer is used to obtain the pulse-height spectrum of the detector output. The analyzer is calibrated for 10 KeV of gamma-ray energy per pulse-height channel. The counts in the recorded spectra are integrated from the 1.20-Mev channel to the 1.60-Mev channel for potassium measurement. In this geometry the efficiency of counting the whole body is taken as 1.22 times the efficiency of counting a point source located at the lowest point in the seat of the chair. This geometry factor was derived by conventional calibration technics for whole body isotope counting. It was confirmed in eight subjects in this series by comparing the counts per minute recorded from 1 microcurie of Na²⁴ at the point source with the cpm recorded from the patient in the body counter 24 hours after intravenous injection of the same microcurie of Na²⁴. For these eight patients the geometry factor was 1.218 ± .035 S.D. The background of the counting system is measured periodically for 1,000 minute periods and is stable within the limits of counting statistics. Patients are counted for 30 minutes.

The formula for calculating total body potassium (TBK) is as follows. TBK = S [total body cpm - background cpm], where the counts in channels 120 to 159 inclusive are summed and divided by the counting time.

S is the sensitivity factor determined by counting 1,000 Cpm. of reagent-grade KCl (535 Cpm. of potassium) as a point source and correcting through the geometry factor 1.22.

\[ S = \frac{1.22 \text{ (cpm per Kg. of KCl - background cpm)}}{535} \]
### Results

The data on body composition in the “dry cardiac” group and in the “control” group are shown in tables 1 and 2, respectively. A summary and comparison of mean values appear in figure 1 and a statistical analysis is given in table 3.

#### Total Body Water (AS)

The antipyrine space in the “dry cardiac” group averaged 32.7 liters or 53.2 per cent of the body weight. In the “control” group the total body water averaged 35.2 liters and the body water as per cent of body weight was 54.0 per cent. These differences are not significant.

#### Total Exchangeable Sodium (TENa)

The mean TENa for the “dry cardiac” group was 3,393 mEq and for the “control” group, 2,846 mEq. The difference, 547 mEq., is statistically significant. Since the amount of a particular cation in the body depends upon the size of the body and the size of the fluid compartments in which the cations are contained the results of body electrolyte determinations are more meaningful when expressed as the ratio of the particular cation to the body weight and the total body water. The ratios of exchangeable sodium to body weight (TENa/wt.) were 44.7 mEq./Kg. for the “control” group and 54.0 for the “dry cardiac” group. The ratios of exchangeable sodium to body weight and the total body water (TENa/wt.) were 44.7 mEq/Kg. for the “control” group and 54.0 for the “dry cardiac” group.

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![Figure 1](http://circ.ahajournals.org/)

**Figure 1**

Body composition in “controls” and “dry cardiacs.” Summary and comparison of mean values.
Body Composition in Hospitalized Patients with No Heart Disease and No History of Edema ("Control" Group)

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<th>Patient</th>
<th>Age</th>
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<th>Serum sodium (mEq./L.)</th>
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Mean 59.1 64.1 139.1 35.2 2846

Standard deviation 13.8 10.1 3.26 6.25 361.5

Standard error 3.09 2.26 0.73 1.43 80.83

Sodium to total body water (TENa/AS) were 82.5 mEq./L for the “control” group and 103.4 for the “dry cardiac” group. These differences are highly significant.

**Total Body Potassium (TBK) and Total Exchangeable Potassium (TEK)**

The mean total body potassium content in the “control” group was 2,750 mEq. and in the “dry cardiac” group 2,671. In terms of the body weight the mean concentrations of potassium were 42.7 mEq. per Kg. in the “controls” and 42.2 in the “dry cardiace.” These differences are not significant. The possibility could be proposed that the members of the “dry cardiac” group actually are in a state of potassium depletion but that they appear to have a normal body potassium concentration because they have lost more fat than the “control” group and hence have a relative increase in lean body mass. That this is not the case is strongly suggested by the fact that in both groups the body water as the per cent of body weight is the same. If one group had lost significantly more fat than the other, a relative increase in total body water would be anticipated because of the low water content of fat.

The whole body counter provides a measure of all the potassium in the body, the nonexchangeable as well as the exchangeable. Since only the exchangeable potassium participates significantly in metabolic events in the body it is necessary to determine what portion of the body potassium in these patients is exchangeable. Total body potassium, estimated by whole body counting, and total exchangeable potassium, estimated by K⁴² dilution, have been compared by simultaneous measurements in young adults. These measurements indicated that TEK was 90 per
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<th>TENa wt.</th>
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<td>7.03</td>
<td>526.2</td>
<td>6.07</td>
</tr>
<tr>
<td>1.83</td>
<td>2.41</td>
<td>1.24</td>
<td>146.10</td>
<td>1.82</td>
<td>127.62</td>
<td>1.57</td>
</tr>
</tbody>
</table>

### Table 3

**Summary of Mean Values and Statistical Analysis**

<table>
<thead>
<tr>
<th></th>
<th>&quot;Controls&quot;</th>
<th>&quot;Dry cardinals&quot;</th>
<th>&quot;Controls&quot; vs &quot;Dry cardinals&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight (Kg.)</td>
<td>64.1</td>
<td>63.5</td>
<td>N.S.†</td>
</tr>
<tr>
<td>2. Antipyrine space (liters)</td>
<td>35.2</td>
<td>32.7</td>
<td>N.S.</td>
</tr>
<tr>
<td>3. AS/Wt. (% Body water)</td>
<td>54.0</td>
<td>53.2</td>
<td>N.S.</td>
</tr>
<tr>
<td>4. TEKtNa (mEq.)</td>
<td>2846</td>
<td>3393</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5. TEKtNa/AS (mEq./L.)</td>
<td>82.3</td>
<td>103.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6. TEKtNa/Wt. (mEq./Kg.)</td>
<td>44.7</td>
<td>54.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7. TEK (mEq.)</td>
<td>2393</td>
<td>2336</td>
<td>N.S.</td>
</tr>
<tr>
<td>8. TEK/Wt. (mEq./Kg.)</td>
<td>37.3</td>
<td>37.1</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

*P = probability of t.
†N.S. = not significant.

In older and chronically ill individuals the figure would be expected to be slightly lower, since potassium bound in bone is less likely to change with age and illness than is muscle potassium. In one study a figure of 37.2 mEq per Kg. of body weight was established as the exchangeable potassium concentration for a group of hospitalized male "control" patients whose mean age was close to the mean age of the patients in this series. If this figure is compared with the figure of 42.7 mEq/Kg. for the total body potassium (TBK). In older and chronically ill individuals the figure would be expected to be slightly lower, since potassium bound in bone is less likely to change with age and illness than is muscle potassium. In one study a figure of 37.2 mEq per Kg. of body weight was established as the exchangeable potassium concentration for a group of hospitalized male "control" patients whose mean age was close to the mean age of the patients in this series. If this figure is compared with the figure of 42.7 mEq/Kg. for the total body weight.
body potassium concentration in the "control" group of the present series, the exchangeable fraction of TBK is calculated at 87.3 per cent. With use of this figure, total exchangeable potassium and its ratio to body weight have been calculated for the two groups of patients in the present series. The results are as follows. For the "control" group the mean TEK is 2,400 mEq. and the ratio of TEK/wt. 37.3 mEq./Kg. For the "dry cardiac" group the mean TEK is 2,335 and the ratio of TEK/wt. 37.1 mEq./Kg. This calculation is based on the assumption that the ratio of inexchangeable to exchangeable potassium is the same in "control" patients and "dry cardiax." Such an assumption appears to be warranted, since there is little likelihood that heart failure is accompanied by an increase in the potassium content of compact bone. It is concluded therefore, that there is no difference in exchangeable potassium content or concentration between the two groups of patients. Both groups have a somewhat lower body potassium concentration than healthy males of the same age (58 to 59 years). In the latter group body potassium concentration quantitated in the whole body counter is 45.0 mEq./Kg. of body weight.7

Discussion

Part of the exchangeable pool of body sodium is bound to the surface of bone, in cartilage, in dense connective tissue, and possibly in other sites where negative charges are fixed.8-10 Since this quantity of sodium is not free in the body fluids, it does not contribute to the osmotic pressure of the body fluids. In normal individuals the osmotically inactive portion of exchangeable sodium is a fairly constant fraction of the exchangeable pool. Exchangeable but osmotically inactive potassium is thought to represent a very small amount of this ion.7, 11

The question of whether the binding of cations to extracellular and perhaps to intracellular sites can vary as a result of disease or an induced physiologic abnormality has been the subject of much investigation. It seems well established that sodium bound to bone can be released in exchange for hydrogen in acutely induced acidosis.12 Whether or not the opposite phenomenon occurs, i.e., that the tissue capable of binding cations can increase the amount of cation over that normally found, has not been resolved.

Lusk et al.13 performed balance studies on patients with heart disease who were allowed to develop congestive heart failure. They found that the amount of sodium retained exceeded the amount of water retained over a period of weeks. Since there was no elevation in serum sodium concentration they concluded that osmotic inactivation of sodium had taken place. Elsbach and Schwartz14 and Ashley and Whyte15 performed balance studies on obese subjects during weight reduction. They found striking discrepancies between changes in water balance and changes in the balance of sodium plus potassium which could best be explained by variations in cation binding. Farber and Soberman1 found that edematous patients with heart disease had a disproportionate accumulation of sodium to water and postulated that sodium binding could have occurred. Several other investigations with the balance technic have provided evidence for variations in cation binding, particularly in patients with congestive heart failure. In the patients observed, fluctuations in serum sodium concentration could not be attributed completely to measured exchanges in water and electrolyte.16, 17

The work of other authors, notably Wynn18 and Edelman et al.11 does not support the view that osmotic inactivation of electrolytes may be a prominent feature of disease states. Wynn measured total body water, serum electrolytes, and water and electrolyte balance in patients undergoing rapid fluctuations in serum tonicity and acid base balance. His results enabled him to construct an equation that allowed for the treatment of fluid and salt imbalance on the principle that the tissue cells as a whole acted like a perfect
osmometer and that no acute changes in cation binding had to be presumed.

Edelman and his associates\textsuperscript{11} studied interrelations between serum sodium concentration, serum osmolarity and total exchangeable sodium, total exchangeable potassium, and total body water. Their subjects consisted of 100 patients with widely varying levels of body fluid osmotic pressure. Two thirds of these subjects had either heart disease or cirrhosis of the liver and one third had other diseases. In this group of patients the authors found no evidence for osmotic inactivation of cation, and cast doubt upon the likelihood that such inactivation may occur as a manifestation of disease.

The data from the present study show that previously edematous cardiac subjects have a body content of sodium that is disproportionately high in terms of body weight and body water. Since this excess of sodium is not due to depletion of potassium or accumulation of water and since it does not produce hypernatremia, it is logical to suppose that osmotic inactivation has taken place. There is no incompatibility between the results of the present study and those of Edelman et al., since the present study was directed at a patient population that was not adequately represented in the studies described by Edelman's group.

The present studies make no contribution to the question of acute changes in ion binding. Studies in which previously edematous cardiac subjects were followed for several months showed that when TEna fell to normal levels it did so slowly.\textsuperscript{2} In many patients studied after periods of compensation up to 1 year, TEna was still abnormally high.\textsuperscript{1}

The data presented do not permit definite conclusions as to which cation is bound, the site of binding, or the physiologic significance of cation binding in heart disease.

At least three possibilities exist concerning the nature of the ion bound:

1. All the excess sodium is osmotically inactive.
2. The excess exchangeable cation represents bound potassium. In this case the excess sodium would provide an osmotically active replacement.
3. The bound ions consist partially of sodium and partially of potassium.

It appears likely that the bound ion is primarily sodium, since in some patients the amount of excess exchangeable cation would be equal to more than half of the body potassium. Binding of such amounts of potassium would be physiologically tantamount to extreme potassium depletion.

The possible binding sites for sodium have been discussed at length in a previous publication.\textsuperscript{2} It was concluded that although intracellular binding was a possibility, binding to bone or connective tissue was more likely. Of these two tissues connective tissue was thought to be a more probable binding site for several reasons. The polyanionic constituents of connective tissue have well-known properties as cation binders and exchangers.\textsuperscript{9,10} Studies on bone composition following prolonged heart failure in man showed no abnormality in sodium concentration.\textsuperscript{20}

The physiologic significance of cation binding in patients with heart disease also remains a subject for speculation. This mechanism could conceivably serve as a protection against the obligatory retention of water when salt is retained. It is also possible that activation of bound sodium and its entry into the body fluids could cause the retention of water even as dietary sodium was restricted. Such a phenomenon would be similar to that observed by Elsbach and Schwartz, whose patients apparently mobilized sodium and retained water during periods of weight reduction.\textsuperscript{14}

**Summary**

Measurements have been made of total exchangeable sodium, total body potassium, and total body water in a group of 13 previously edematous patients with heart disease, and in 20 "control" patients. The data show that while both groups have the same quantity of water as the per cent of body

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weight and the same body potassium concentration, the cardiac group has an excess of exchangeable sodium when compared with the "controls." Since the excess sodium in the cardiac group cannot be attributed to the loss of potassium or the accumulation of water, the results of these studies are taken as evidence that osmotic inactivation of a considerable amount of some cation, probably sodium, has taken place. It is suggested that a likely site for cation binding is in the polyanionic constituents of the connective tissues.

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References

Exchangeable Sodium, Body Potassium, and Body Water in Previously Edematous Cardiac Patients: Evidence for Osmotic Inactivation of Cation
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