Alterations in Exchangeable Sodium Content, “Sodium$^{24}$ Space” and Body Weight During The Treatment of Congestive Failure

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Serial determinations of the exchangeable sodium content and sodium$^{24}$ (Na$^{24}$) space were made by the radioisotope dilution method in patients with congestive failure during the course of intensive therapy. In most instances, the decrease in body weight was too great to be accounted for solely on the basis of the change in sodium$^{24}$ space or exchangeable sodium content. This excess weight loss is attributed to loss of intracellular fluid.

INCREASE in body weight, which occurs during congestive heart failure, was generally assumed to be due to the retention of sodium and water in the extracellular fluid compartment. However, some recent studies have suggested that changes also occur in the intracellular phase.$^{1,2}$ The external balance method, which has been used in most previous studies of this problem does not permit the direct measurement in vivo of the sodium content of the body. This difficulty can be overcome by the use of the isotope dilution technic, and one group of investigators$^3$ has previously reported such an application of this technic.

The purpose of the present study was to determine, by the use of the in vivo isotope dilution technic, whether or not the weight loss which occurs during diuresis can be accounted for solely on the basis of a decrease in the extracellular content of sodium and water. Serial determinations of the exchangeable sodium content were made and the changes in this value were correlated with the alterations in body weight. Observations were also made on the effects of intensive therapy with mercurial diuretics on sodium and potassium metabolism.

Material and Methods

Subjects. Thirteen patients, 9 men and 4 women, with advanced congestive failure were studied. Their ages ranged from 53 to 77 years. In five subjects, the cause of the congestion was pulmonary fibrosis and emphysema with cor pulmonale; in six subjects, coronary arteriosclerotic heart disease; and in two, hypertensive cardiovascular disease. Most of these individuals had previously been followed in the Outpatient Clinic and had received maintenance doses of digitalis, ammonium chloride and aminophylline, and periodic injections of a mercurial diuretic. Only one patient (case 2) had not previously been treated with digitalis or a mercurial diuretic. When admitted to the hospital, all were edematous.

The general plan was to make serial determinations of the exchangeable sodium content, the radio-sodium space, the serum concentrations of sodium and potassium, and the body weight during hospitalization.

All patients received a salt-free or low-salt (200 to 400 mg.) diet; water was given without restriction. Except in one case, mercaptomerin sodium (Thiomerin) was administered subcutaneously or intramuscularly whenever mercurial diuretics were indicated. A summary of the clinical data and the type of therapy employed is given in table 1.

Isotopes. Isotopic sodium (Na$^{24}$)* was prepared for injection in the manner previously described.$^4$

Measurement of Radioactivity. The activity of the urine and serum specimens was determined with a well-type scintillation counter and a scaling circuit.

* Na$^{24}$ was supplied by the Oak Ridge National Laboratory, Oak Ridge, Tenn., on allocation from the U. S. Atomic Energy Commission.

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A total of 10,000 counts were made on each sample. All determinations were corrected for decay.

**Determination of Serum Sodium and Potassium.** The total sodium and potassium concentrations in the serum were determined with a Baird flame photometer, using the lithium internal standard method.

**Procedure**

**Determination of Exchangeable Sodium Content (Na-e).** Each subject received from a calibrated syringe 1.5 µc. of Na<sup>24</sup> per Kg. of body weight, contained in sterile 0.9 per cent sodium chloride solution. All urine voided for the next 24 hours was collected, and the Na<sup>24</sup> content of the pooled specimen was determined. A blood specimen was obtained 24 hours after the injection of Na<sup>24</sup> and the specific activity of the sodium in the serum was determined.

**Calculations.** The following formula was used to calculate the value for the exchangeable sodium content of the body:

\[
Na-e = \frac{Na-i^{24} - Na-u^{24}}{Na-s^{24}/Na-s^{23}}
\]

- \(Na-e\) = quantity of exchangeable sodium in milliequivalents (mEq.).
- \(Na-i^{24}\) = quantity of radiosodium administered.
- \(Na-u^{24}\) = quantity of radiosodium excreted in the pooled specimen of urine.
- \(Na-s^{24}\) = concentration of radiosodium in the serum at 24 hours.
- \(Na-s^{23}\) = concentration of nonradioactive sodium in the serum at 24 hours.
- \(Na-s^{24}/Na-s^{23}\) = specific activity of the serum at 24 hours.

Preliminary studies in this laboratory revealed that the Na-e measurement was reproducible within five per cent in edema-free, hospitalized subjects with various chronic diseases whose condition was stabilized. This finding agrees with those previously reported by Miller and Wilson.<sup>3</sup>

**Sodium<sup>24</sup> Space.** The volume of dilution of the injected Na<sup>24</sup> was calculated as follows:

\[
Na^{24} \text{ space in liters} = \frac{\text{total sodium}^{24} \text{ activity injected}}{\text{serum Na}^{24} \text{ concentration per liter at 24 hours}}
\]

A total of 35 determinations of exchangeable sodium content and radiosodium space were made on 13 subjects, usually at weekly, but occasionally at biweekly intervals.

**Results (table 1 and 2)**

**Weight Changes.** All 13 subjects lost weight during the period of observation. The maximum decrease in body weight (25 per cent of the original value) occurred in the subject (case 2) with the shortest duration of acute congestive heart failure (one week). This subject, on intensive mercurial therapy, rapidly lost 14.1 Kg., in spite of which the serum sodium concentration remained normal and unchanged. Transient small increases in weight (1 and 3 per cent) occurred in two subjects (cases 3 and 4), and were followed by subsequent decreases in weight. One of these subjects (case 4) died in congestive heart failure four days after completion of the third determination of exchangeable sodium content (Na-e).

**Exchangeable Sodium Content.** The mean exchangeable sodium content in older adult male subjects with congestive heart failure has been previously reported to be 56.7 ± 1.9 mEq. per kilogram.<sup>3</sup> In the present series, the mean of the initial values was 65.3 ± 3.2 mEq. per kilogram. In only one instance (case 13) was the original value for Na-e/Kg. within the normal range (40.6 ± 1.5 mEq. per kilogram).<sup>3</sup> This subject was a markedly obese woman who had clinical evidences of congestive heart failure and in whom the Na-e value subsequently decreased during therapy.

In 11 of the 13 patients, the final values for exchangeable sodium content per kilogram were above the range previously reported (3) in individuals who had cardiovascular disease without congestive heart failure (42.8 ± 2.4 mEq. per kilogram.)

In all instances except one (case 4), the absolute values for Na-e decreased during the period of observation. This decrease was greater than 30 per cent of the original value in five subjects (cases 2, 3, 8, 9 and 11); in absolute values the decrease ranged from 1310 to 2132 mEq. The patient who failed to show any decrease was a man who did not respond to intensive treatment and who died four days after the last determination (case 4).

In figure 1 the change in weight has been plotted against the change in exchangeable sodium content and serum sodium concentration. If 1 Kg. of weight loss is assumed to represent 1 L. of extracellular fluid water, then each kilogram of weight loss should be accompanied by a loss of sodium equivalent to its concentration in the serum at that instant. This nor-
### Table 1—Determinations of Exchangeable Sodium Content, Radiosodium Space, and Body Weight During Intensive Therapy of Congestive Heart Failure

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (Yrs.)</th>
<th>Sex</th>
<th>Cause of Congestion</th>
<th>Pertinent Clinical Data</th>
<th>Therapy*</th>
<th>Days of Hospitalization</th>
<th>Weight (kg.)</th>
<th>Exchangeable Sodium Content</th>
<th>Radiosodium Space</th>
<th>Serum Concentrations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total (mEq.)</td>
<td>Na-e/ wt (mEq./Kg.)</td>
<td>Total (L.)</td>
</tr>
<tr>
<td>1</td>
<td>53</td>
<td>M</td>
<td>ASHD</td>
<td>Chr. congest.; readmitte 2 wks. after previous discharge. Disoriented between 5th and 12th hospital days.</td>
<td>1, 4, 7 (2 ml. q day x 7)</td>
<td>5 12</td>
<td>53.6 46.8</td>
<td>4282 3178</td>
<td>80.5 74.3</td>
<td>31.3 24.3</td>
</tr>
<tr>
<td>2</td>
<td>72</td>
<td>M</td>
<td>ASHD</td>
<td>One prev. episode 2 yrs. ago. Duration present bout, 1 wk.</td>
<td>2, 7 (1 ml. q day x 8)</td>
<td>1 9</td>
<td>56.6 42.5</td>
<td>4407 2275</td>
<td>78.0 53.5</td>
<td>31.3 16.0</td>
</tr>
<tr>
<td>3</td>
<td>77</td>
<td>M</td>
<td>ASHD</td>
<td>Chr. congest., initially refractory to therapy.</td>
<td>1, 3, 4, 7 (2 ml. q.o.d. x 10)</td>
<td>1 34</td>
<td>68.2 63.6</td>
<td>5246 5462</td>
<td>76.9 85.9</td>
<td>38.7 49.9</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>Cor P.</td>
<td>Chr. edema; died on 19th hospital day.</td>
<td>1, 3, 7 (2 ml. x 3 in 4 days)</td>
<td>2 15</td>
<td>73.0 70.9</td>
<td>5560 5691</td>
<td>76.2 79.6</td>
<td>44.7 38.8</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>F</td>
<td>Cor P.</td>
<td>Congest. for 4 yrs. Severe dyspnea 2 wks. Obese</td>
<td>1, 6, 3, 7 (2 ml. x 2)</td>
<td>2 9</td>
<td>67.8 60.5</td>
<td>4807 4130</td>
<td>72.2 68.3</td>
<td>35.1 30.5</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>Cor P.</td>
<td>Congest. for 3 mos.</td>
<td>1, 3, 4, 7 (1 ml. q day x 9)</td>
<td>8 16</td>
<td>56.4 51.4</td>
<td>3591 3220</td>
<td>63.7 62.7</td>
<td>27.0 23.0</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>Cor P.</td>
<td>Parox. dyspnea for 10 yrs.</td>
<td>1, 3, 4, 7 (2 ml. x 1)</td>
<td>1 8</td>
<td>45.5 42.3</td>
<td>2887 2230</td>
<td>63.5 52.7</td>
<td>21.2 18.1</td>
</tr>
<tr>
<td>8</td>
<td>68</td>
<td>M</td>
<td>ASHD</td>
<td>Periph. edema, 1 yr. Dyspnea, 2 wks.</td>
<td>1, 3, 4, 8, 7 (2 ml. x 1)</td>
<td>2 9</td>
<td>77.3 68.6</td>
<td>4893 3344</td>
<td>63.3 48.7</td>
<td>37.0 22.5</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>M</td>
<td>HCVD</td>
<td>Congest. 4 yrs. Mass. periph. edema, 6 wks.</td>
<td>1, 3, 4, 7 (1 ml. q.o.d. x 11)</td>
<td>7 15</td>
<td>68.2 60.5</td>
<td>4314 3497</td>
<td>63.3 57.8</td>
<td>30.2 25.8</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
<td>F</td>
<td>ASHD</td>
<td>Increasing dyspnea and leg edema for 2 mos.</td>
<td>1, 4, 6, 7 (2 ml. x 3)</td>
<td>2 16</td>
<td>65.2 58.1</td>
<td>4117 3876</td>
<td>63.1 66.7</td>
<td>31.1 28.2</td>
</tr>
<tr>
<td>11</td>
<td>63</td>
<td>F</td>
<td>HCVD</td>
<td>Massive edema for 3 wks.</td>
<td>1, 4, 7 (2 ml. x 3)</td>
<td>4 12</td>
<td>73.5 61.8</td>
<td>4245 2835</td>
<td>57.8 47.5</td>
<td>32.4 23.1</td>
</tr>
<tr>
<td>12</td>
<td>74</td>
<td>M</td>
<td>Cor P.</td>
<td>Congest. continually for 1 yr.</td>
<td>1, 7 (1 ml. q.o.d. x 7)</td>
<td>7 19</td>
<td>69.0 61.8</td>
<td>3100 3200</td>
<td>50.9 51.8</td>
<td>23.3 21.3</td>
</tr>
<tr>
<td>13</td>
<td>77</td>
<td>F</td>
<td>ASHD</td>
<td>Congest. 4 mos. Marked obesity.</td>
<td>1, 7 (1 ml.)</td>
<td>3 11</td>
<td>83.6 77.7</td>
<td>3328 2651</td>
<td>39.8 34.1</td>
<td>25.2 19.4</td>
</tr>
</tbody>
</table>

*1 = Digitalis in maintenance doses.  
2 = Rapid digitalization while hospitalized.  
3 = Aminophylline suppositories.  
4 = Ammonium chloride.  
5 = Potassium chloride.  
6 = Diamox.  
7 = Dosage of mercurial diuretic (Thiomerin).
mal relationship is indicated by the diagonal line. It is apparent that in 17 of 22 instances the weight changes were greater than could be accounted for solely on the basis of the sodium changes, whereas, in five instances, the decrease in body weight was less than could be accounted for solely on the basis of a change in exchangeable sodium.

Na\textsuperscript{24} Space. Warner and his co-workers\textsuperscript{8} have previously reported that the mean sodium\textsuperscript{24} space in elderly adults with decompensated cardiovascular disease was 41.7 per cent of the body weight. The mean of the initial values obtained in the present series (48.6 ± 2.4 per cent) was slightly higher than that in Warner's series. In all 13 subjects the sodium\textsuperscript{24} space decreased by at least 10 per cent of the original value. The maximum decrease (49 per cent) was observed in case 2.

In most instances the value for Na\textsuperscript{24} space per kilogram tended to decrease during therapy of congestive failure. In 9 of the 13 subjects, the changes in weight were too great to be accounted for solely on the basis of a change in Na\textsuperscript{24} space. This relationship parallels that observed with the exchangeable sodium content.

Serum Sodium Concentration. The initial serum sodium levels were below 135 mEq per liter in seven subjects. In all of these individuals, subsequent values obtained during therapy of the congestive heart failure were higher. In case 11, the initial value of 131.2 mEq per liter dropped to 127 mEq per liter and then rose to 139 mEq per liter; satisfactory diuresis was observed at this time the serum sodium concentration was lowest.

Initially normal values decreased to 129.1 mEq per liter and 123.0 mEq per liter, respectively, in two subjects (cases 7 and 9) during diuresis; no abnormal clinical symptoms or signs appeared at this time. There was no correlation between the presence of a serum sodium concentration below 135 mEq per liter and the development of the symptoms and signs of the "low salt syndrome," such as lethargy, weakness, and somnolence.

The changes in serum sodium concentration
were unpredictable and could not be correlated with the amount of mercurial diuretic which was given.

*Serum Potassium Concentration.* Serum potassium concentrations as low as 3.3 and 2.7 mEq. per liter were observed on only two occasions (cases 1 and 3). The value of 3.3 mEq. per liter was observed in case 3 at a time when the patient was responding poorly to treatment and was lethargic and somnolent. A dramatic clinical improvement occurred before the second determination, when the serum potassium concentration had risen to 5.1 mEq. per liter. Diuresis, however, did not occur for another week. The value of 2.7 mEq. per liter was obtained in case 1 during intensive mercurial therapy. This patient became disoriented and somnolent; potassium given orally in small amounts produced dramatic improvement, and he again became alert.

**Comment**

The exchangeable sodium content is a measure of the sodium in the body which is available for exchange with the radioisotopic atom and reflects a functional component of the body rather than an anatomic unit. Although there is some question as to whether this determination measures the total body content of sodium and whether the injected radioactive isotope of sodium ever reaches complete equilibrium with all the native sodium in the body, the values obtained are reproducible and the method is practical for serially following changes in sodium metabolism in the living subject.

The initial values for exchangeable sodium content per kilogram in the present series were higher than those previously reported, this suggests that the subjects in the present study were retaining more sodium. The results indicate that patients with exchangeable sodium contents twice as high as the usual value found in chronically ill, edema-free patients may have normal serum sodium concentrations. Indeed, in several instances, the serum sodium concentration was abnormally low at a time when the total body content of sodium was markedly increased. Clinically, most of the subjects did not attain an edema-free state during the period of observation, and this fact is reflected by the final values for exchangeable sodium content per kilogram, which were higher than those reported in edema-free subjects.

A decrease in body weight which exceeds the relative decrease in exchangeable sodium content and the radiosodium space can be most logically explained on the basis of some alteration within the intracellular compartment or in the non-aqueous tissues of the body, such as body fat. The interpretation that such a decrease in body weight is due to a loss of intracellular fluid is consonant with the conclusion reached by other investigators, using the external balance method.

In five instances the change in exchangeable sodium was greater than the change in total body weight due to loss of extracellular fluid. The most likely explanation of the discrepancy in this direction would be that, at the time of the first measurement, the patients had an abnormally high intracellular sodium content, possibly associated with potassium depletion; with diuresis and the associated improvement in the congestive state, some of this intracellular sodium was replaced with potassium.

In spite of intensive therapy with mercurial
diuretics, no untoward effects such as somnolence, weakness and disorientation, which have been previously associated with the "low salt syndrome," were observed concomitantly with a decrease in serum sodium concentration. Such symptoms and signs, in the present study, were noted in two subjects at a time when the serum potassium concentration was decreased; in one of these patients a dramatic improvement occurred when oral supplements of potassium were administered. This observation suggests that some of the adverse side effects of intensive mercurial therapy may be more closely related to a depletion of the body store of potassium than to a depletion of sodium.

SUMMARY

The radioisotope dilution method was used to make serial determinations of the exchangeable sodium content of the body in 13 subjects with congestive failure. The mean value (65.3 ± 3.2 mEq. per kilogram) was considerably higher than in elderly non-edematous subjects (40.6 ± 1.5 mEq. per kilogram). Body weight and exchangeable sodium content decreased with intensive therapy. In most instances the decrease in body weight was too great to be accounted for solely on the basis of the change in radiosodium space or exchangeable sodium content. This weight loss, in excess of the amount which can be explained by the decrease in sodium values, is attributed to loss of intracellular fluid.

SUMMARIO IN INTERLINGUA

Le metodo del dilution de radioisotopos esseva usate in determinationes serial del contento de natrium excambiabile in le corpore de 13 individuos con dysfuctionamento congestive. Le valor median (65.3 ± 3.2 milli-equivalentes per kilogramma) esseva considerabilmente plus alte que in non-edematose individuos de etate avantiata (40.6 ± 1.5 milliequivalentes per kilogramma). Le pesos corporee e le contentos de natrium excambiabile se abassava in le mesura que le therapia esseva intensificate. In le majoritate del casos le reduction del peso corporee esseva plus grande que lo que huberea essite explicabile integemente super le base del alteration del spatio de radionatrium o del contento de natrium excambiabile. Le exceso del perdita de peso—i.e. le perdita de peso non explicabile per le reduction del valores de natrium—es attribuite per nos al perdita de fluido intracellulare.

REFERENCES

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