The Persistence of High Body Sodium in Previously Edematous Patients with Heart Disease

By Hugh J. Carroll, M.D., and Saul J. Farber, M.D.

In patients with heart disease the presence of edema is indicative of an increase in extracellular fluid volume. Since the sodium concentration of extracellular fluid is about 140 mEq. per liter, expansion of the extracellular space is accompanied by the accumulation of large quantities of sodium. The magnitude of sodium accumulation has been demonstrated through measurement of total exchangeable sodium in edematous cardiac patients by the sodium-isotope dilution technic.¹⁻⁵ When edematous cardiac subjects are rendered free of edema, there is a marked drop in the body content of sodium, but one study showed that in over half of the cases the total exchangeable sodium remains either absolutely high or disproportionately high in terms of the body weight and total body water.¹

The present investigation was undertaken to re-examine the body composition of the cardiac patient without edema and in particular to determine whether the total body sodium remains elevated or eventually returns to normal levels. The data support earlier observations indicating that the majority of previously edematous cardiac patients have a body content of sodium that is absolutely or relatively high. In addition, the study showed that while some patients gradually lost their sodium excess over a period of months, others maintained a disproportionate elevation in body sodium as long as they were observed.

Subjects and Methods

In 18 patients with heart disease of various types (table 1) measurements were made of body weight, total body water, and total exchangeable sodium. The measurements were made when the weight of the patients became stable following the loss of edema, and in six of the 18 patients the studies were repeated at intervals for periods of 2 to 5 months. The diagnosis of congestive heart failure had been made in these patients on the basis of accepted criteria and all had been edematous except one (no. 6). The therapeutic regimen included bed rest, salt restriction, digitalis, and, whenever necessary, diuretics.

Total body water was determined by the antipyrine-dilution technic. Total exchangeable sodium was determined by the dilution technic with Na₂⁻¹⁴C; 7 100 microcuries of Na₂⁻¹⁴C were injected into the antecubital vein from a calibrated tuberculin syringe. Twenty-four hours were allowed for equilibration and, when the plasma radioactivity had become stable, the counts were recorded. The complete output of urine for the 24-hour period was collected and, if the total radioactivity was greater than 1 per cent of the injected dose, it was subtracted from the injected dose. Plasma and urinary radioactivities were measured with an end-window Geiger-Muller tube. Sodium measurements were made with a Baird internal-standard flame photometer.

The data that are accepted as control values for this study are contained in reference no. 1. They consist of body weight, total exchangeable sodium, and antipyrine space measurements in a group of 27 hospitalized individuals with no evidence of heart disease.

Results

As a group these patients demonstrated a total body sodium higher than what would have been predicted on the basis of their body weight and total body water. Of the seven patients on whom serial measurements were made, three gradually lost their excess of sodium over a period of months without a fall in body weight or total body water. The remaining four maintained throughout the period of study the same high level of

*The data from serial studies on a seventh patient, reported in a previous publication from this laboratory, are included in this report.¹
body sodium that had been observed following compensation.

**Total Body Water (AS)**

The antipyrine space, measured in 14 of the 18 patients, averaged 32.6 liters or 52.2 per cent of the body weight (table 1). The mean figure of 52.2 per cent for body water as the per cent of body weight is the same as that observed in the control group.

**Total Exchangeable Sodium (TENa)**

The mean total exchangeable sodium for this group of 18 patients was 3,140 mEq. (table 1). Although the difference between this level and the mean of 2,896 mEq. in the control group is not statistically significant, it is important to note that the mean body weight of this group was 60.8 Kg. or 6.0 Kg. less than that of the control group (table 5). Twenty patients whose mean body weight was 60.1 Kg. were selected from the control group, and their mean TENa was 2,630 mEq. or 510 mEq. less than that of the cardiac subjects without edema (table 5). It is concluded that there is a significantly larger amount of sodium in the bodies of compensated cardiac patients than in control subjects having the same body weight.

**Body Concentration of Sodium**

Under normal circumstances, the prime determinant of the amount of sodium in the body is the amount of extracellular fluid. In the absence of accurate determination of the extracellular fluid volume the most meaningful expression of body sodium content is in terms of the body weight and total body water. Accordingly, the data are presented as milliequivalents of exchangeable sodium per kilogram of body weight and milliequivalents of exchangeable sodium per liter of water.

**Total Body Sodium/BODY WEIGHT**

Seventeen of the 18 patients had ratios of total body sodium/body weight above the normal mean (table 1). The mean ratio for the compensated cardiac subjects was 52.7 mEq. per Kg. as compared with the control level of 43.7, a statistically significant difference.

**Total Body Sodium/Antipyrine Space**

The ratio of body sodium to body water expressed as mEq. per liter was significantly higher 98.3 mEq. per liter, in the compensated cardiac subjects than in the control group 81.3 mEq. per liter (table 1). Of the fourteen patients whose total body water was measured, all had ratios TENa/AS above the normal mean.

**Serial Measurements of Total Exchangeable Sodium and Total Body Water**

In order to determine whether the patient who remains compensated loses his excess sodium, studies were performed at intervals of one to several months in a group of patients whose ratio of total exchangeable sodium to body weight was high following loss of edema. The measurements of body water, TENa, and body weight that were obtained in serial studies of seven such patients are recorded in tables 2 and 3. Three patients showed a fall in TENa over a period of months without a simultaneous loss of body weight or total body water. When normal levels were reached, there was no further fall in TENa. Four patients showed no tendency to lose excess sodium during a comparable period of time. One patient (no. 9) in the latter group gained weight without an increase in total body water (table 3). It is presumed that this gain in weight was in the form of fat.

**Correlation of Sodium Retention with Clinical State**

No correlation was observed between the tendency to maintain or lose excess sodium and such factors as the type of heart disease, age, number of previous episodes of congestive heart failure, the amount of edema previously observed.

**Discussion**

The studies of Farber and Soberman (33 patients)¹ and Birkenfeld et al. (3 patients)² show that cardiac subjects who have lost edema generally have a higher level of total body sodium than would be predicted on the basis of their body weight. The data from this present study are in agreement with the previously reported findings. It has also been
shown in this study that previously edematous cardiac patients may retain an increment of sodium for varying periods of time. The mechanism by which this excess quantity of sodium is retained in the body is not readily apparent. Several explanations may be proposed.

If the retained sodium is osmotically active, it must either be in the extracellular space and accompanied by retention of isosmotic quantities of water or in an intracellular compartment in exchange for another cation. Intracellular cations that might be exchanged for sodium include potassium and magnesium.

With regard to the possibility that the excess sodium is in the extracellular space and osmotically active, there are three lines of contrary evidence.

a. The theoretical increase in extracellular water calculated on the possibility that the increment in TENa in each patient is to be explained solely as an augmentation of the extracellular space is shown in table 4. The assumption was made that the starting extracellular fluid volume is 20 per cent of body weight or 40 per cent of total body water. (The data would not change appreciably if allowance were made for Donnan effect and difference in water content between plasma and extracellular fluid in calculating extracellular sodium concentration.) Table 4 indicates that eight of the 18 patients would have required extracellular space expansion of 41 to 75 per cent over normal, quantities of excess fluid that would probably be detectable in most individuals. No patient in this series
had demonstrable fluid collections in the extremities, sacrum, or peritoneal, pleural, or pericardial space when body sodium and water were measured.

b. The concept that an increase in body sodium represents an increased extracellular fluid volume is challenged by the observation on the three compensated cardiac subjects who showed a gradually diminishing TENa without a concomitant loss of body weight or body water. These three patients, nos. 18, 6, and W. McL. (table 2), lost respectively 500, 1,600, and 1,000 mEq. of sodium. It seems likely that if such quantities of sodium were in the extracellular space, clinical edema would have been apparent.

c. The total body water as the per cent of body weight is normal in compensated cardiac subjects, so that any excess of extracellular water would occur at the expense of the intracellular fluid. If larger quantities of water were to leave the intracellular space, a marked reorganization of intracellular osmotically active cation would be required. This might be accomplished in several ways.

1. Intracellular potassium might become osmotically inactive, a possibility that cannot at present be ruled out.

2. The intracellular osmolarity might be much greater than the extracellular osmolarity, an event that would contradict good physiologic evidence.

3. Intracellular potassium might be markedly depleted. Since most of the body potassium is intracellular, this would necessitate marked depletion of body potassium. Evidence against this possibility is cited below.

If the excess of sodium in the compensated cardiac patient were in an intracellular site in place of potassium, the majority of subjects would be profoundly depleted of potassium. Total body potassium was not measured in these patients. The literature contains studies on the metabolism of potassium in congestive heart failure that indicate a depletion of body potassium in the edematous phase but this deficit probably does not exist when the pa-
of magnesium are compared with the general hospital population.

Birkenfeld et al.10 Also, evidence of heart disease11 was demonstrated in the compensated cardiac patients. However, no evidence of heart disease was found in normal persons. The external balance of sodium was positive only in a few patients.

The compensated cardiac patients have been compared with the general hospital population because they are chronically ill and it would be unreasonable to compare their total body electrolytes with those of normal persons. The evidence reviewed appears to support the view that the compensated cardiac patients are merely sick people with no specific deficit of total body potassium.

Measurements of the external balance of magnesium in five patients during recovery from congestive heart failure were made by Mader et al.10 It was shown that the magnesium balance may be positive or negative, but only small quantities of this cation are involved. It appears improbable that the retention of large quantities of sodium can be explained by depletion of potassium or magnesium.

It is possible that strategic combinations of occult edema and potassium depletion in the same patient might explain sodium retention by some compensated cardiac patients, especially if the amount of sodium retained is small. Another solution, however, is compatible with the data. Some of the sodium may be osmotically inactive.

If the sodium is osmotically inactive, it may be bound to some intracellular constituent or to an extracellular constituent of tissues such as bone, cartilage, or connective tissue. There is some evidence that intracellular constituents such as nucleotides can bind sodium in an osmotically inactive form in vitro, but there are no studies of the physiologic importance of this binding.12

The possibility of sodium storage in bone in disease states has recently been studied. Bone sodium concentration was measured in a series of patients who died with a variety of electrolyte disorders including heart disease, and no abnormality in bone sodium concentration was demonstrated.13

Connective tissue and cartilage are known to be capable of storing cations in an osmotically inactive state and of acting as ion exchangers.14, 15 These tissues are rich in chondroitin sulfate, a long chain polyanion,

Table 3

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Date</th>
<th>Wt. (Kg.)</th>
<th>AS (liters)</th>
<th>TENa (mEq.)</th>
<th>TENa/AS (mEq./L)</th>
<th>TENa/Wt. (mEq./Kg.)</th>
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</table>

Comments

Patient no. 15 required repeated injections of mercurials in order to maintain his dry weight. He gained about 1 Kg. of water weekly but never demonstrated edema or other signs of frank decompensation.

Patient no. 9 gained 7.5 Kg. of weight during the study without a change in TENa. Since there was no change in his total body water, it is presumed that this increase in weight represents very largely an accumulation of fat.
Theoretical Calculations

### Table 4

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>&quot;Extra&quot;* exch. Na mEq.</th>
<th>AS</th>
<th>Calculated extracellular space (liters)</th>
<th>% &quot;Extra&quot; ECF† on basis of AS of body wt.</th>
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<td>11</td>
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<tr>
<td>18</td>
<td>770</td>
<td>31.4</td>
<td>12.6</td>
<td>12.0</td>
</tr>
</tbody>
</table>

*Observed TENa minus normal TENa (Body wt. × 43.7 mEq.).
† "Extra" exch. Na divided by plasma Na concentration gives the number of liters of water required to contain this amount of Na at a concentration equal to plasma. This number of liters divided by the extracellular fluid volume equals the % "Extra" ECF.
‡This patient's TENa was below normal.
§AS could not be measured. This figure represents 52.2% of body weight.

### Table 5

Summary of Mean Values and Statistical Analysis

<table>
<thead>
<tr>
<th></th>
<th>Compensated cardiac patients (N = 18)</th>
<th>Controls (N = 27)</th>
<th>Controls with same body weight (N = 20)</th>
<th>Controls with same body weight vs. compensated cardiac patients</th>
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</thead>
<tbody>
<tr>
<td>Weight (Kg.)</td>
<td>60.8</td>
<td>66.8</td>
<td>NS‡</td>
<td>60.1</td>
</tr>
<tr>
<td>Antipyrine space (liters)</td>
<td>32.6†</td>
<td>35.0</td>
<td>NS</td>
<td>32.8</td>
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<tr>
<td>TENa (mEq.)</td>
<td>3140</td>
<td>2896</td>
<td>NS</td>
<td>2630</td>
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<tr>
<td>TENa/AS (mEq./L)</td>
<td>98.3†</td>
<td>81.3</td>
<td>&gt;0.01</td>
<td>81.3</td>
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<tr>
<td>TENa/wt. (mEq./Kg.)</td>
<td>52.7</td>
<td>43.7</td>
<td>&gt;0.01</td>
<td>44.7</td>
</tr>
</tbody>
</table>

*p = Probability of t.‡
‡N = 14.
‡NS = not significant.

and in the case of cartilage at least, the cation-binding capacity of the tissue appears to depend upon its chondroitin sulfate content. The ability of chondroitin sulfate to bind sodium has been demonstrated by equilibrium dialysis studies with sodium chondroitin sulfate isolated from bovine nasal cartilage.

In these studies a significant portion of the sodium associated with the polyanion failed to behave as osmotically active ion. It appears possible that sodium binding by chondroitin sulfate may be of importance in those disease states in which storage of osmotically inactive sodium is thought to occur.

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The fact that compensated cardiac patients generally have a TENa higher than would be predicted on the basis of body weight and total body water may be taken as evidence that in patients with heart disease sodium retention need not be accompanied by equivalent water retention. Further support for this view may be found in the observation that compensated cardiac subjects with high TENa may lose large quantities of sodium without losing water as they remain in a compensated state. Retention and loss of sodium without concomitant changes in body water suggest that sodium may enter some tissue where it is bound in an osmotically inactive form. The evidence that chondroitin sulfate can bind sodium and the widespread occurrence of chondroitin sulfate in the connective tissues of man make it reasonable to postulate that storage of osmotically inactive sodium in connective tissue may be an important feature of heart disease.

Summary

Measurements of total body water and total exchangeable sodium were made in patients with heart disease rendered free of edema following congestive heart failure.

The total exchangeable sodium in most of the patients was higher than would have been predicted on the basis of their body weight and total body water. Serial measurements showed that some patients gradually lose their excess sodium over a period of months without a loss of body water; others maintain an elevated ratio of body sodium to body weight and body sodium to body water for periods of at least several months.

The data imply the possibility of significant quantities of osmotically inactive sodium in patients with heart disease.

References


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