Long-Range Observations of Sodium Exchange in Patients with Congestive Heart Failure

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Long-term studies of sodium balance were made in three patients with congestive failure. The data indicate exchange of water and sodium between the intracellular and extracellular spaces. They suggest that a portion of the intracellular cation exists in a form which is not osmotically active. The term "quantometer" is applied to the previously described intracranial volume-regulating mechanism. An hypothesis is offered in which it is assumed that exhaustion of this quantometer may contribute to the retention of sodium as heart failure becomes manifest.

THE starting point of the reports from this laboratory was the desire to investigate the concept of a central homeostatic mechanism concerned with sodium retention as a means of protecting the body against various types of circulatory failure. With the exception of two reports these studies have been limited to normal subjects and are not, therefore, directly applicable to patients with cardiac failure, or to such problems as the importance of the orthopneic position in relation to edema formation. The observations reported thus far seem to indicate that a central homeostatic mechanism concerned with sodium exchange does exist, and that this mechanism is brought into play not by a decline in cardiac output or alteration of renal hemodynamics, but rather by alterations in the renal tubular activity initiated by a change in the distribution and volume of body fluids. Since the results of the data recently collected from studies on patients with congestive failure indicate that this homeostatic mechanism is greatly impaired or is inoperative in congestive failure, it seemed advisable to observe patients with congestive failure for longer periods of time. It was hoped that a clearer concept of the role of this homeostatic mechanism in the formation of edema in cardiac failure would emerge. The present report is concerned with the long-range observations of the sodium exchange in three patients with chronic congestive heart failure.

METHODS

The observations reported here were made on three patients with congestive heart failure due to rheumatic mitral stenosis (A.S.), senile heart disease (J.T.), and cor pulmonale with senile heart disease (J.M.). All were able to deliver urine with a maximum specific gravity of 1.025 or higher. The clinical course of each patient was followed by frequent determinations of venous pressure, circulation time, vital capacity, and blood pressure. Dietary sodium was calculated from weighed diets.\(^{6,7}\)

Water intake (distilled water), urine volumes and body weight were recorded daily.

Serum and urine analyses for sodium were made with a Beckman DU model photometer, utilizing an oxyacetylene type flame.

Calculations were based on the assumption that daily weight changes represented changes in extracellular water, that is, edema fluid.

Calculations

1. Extracellular sodium concentrations \([\text{Na}^{\text{ECF}}]\) were considered to be \(0.95 \times \) serum concentration.
2. Changes in extracellular sodium \(\Delta \text{Na}^{\text{ECF}}\) equalled change in body weight \(\Delta \text{wt.}\) \(\times \) extracellular sodium concentration \(\text{[Na}^{\text{ECF}}]\).
3. Total sodium balance \(\Delta \text{Na} = \) intake (Na\(_i\)) – output (Na\(_o\)) of sodium.
4. Changes in "nonextracellular" sodium (pre-

* The Lonalac used in the preparation of these diets was kindly furnished by Mead, Johnson and Company, Evansville, Ind.
sumably intracellular sodium) content $\Delta Na_{120} = \Delta Na - \Delta Na_{150}$.

**Fig. 1.** Patient J. T. On admission he was given a diet containing 2.5 mEq. of sodium per day. During the following 12 days his weight fell from 69.0 Kg. to 62.2 Kg., and the sodium balance was negative. Calculations revealed an initial loss of sodium from the extracellular space and an apparent increase in intracellular sodium. During the eleventh and twelfth days urine volumes declined, and serum sodium concentration fell to 126 mEq. per L. (It had previously been within normal limits.)

From the thirteenth to the seventy-third hospital day the patient received a 250 mEq. sodium diet daily. During the period from the thirteenth to the thirty-sixth day there was a slight weight gain, a positive sodium balance, with an increase in both extra- and intracellular sodium.

The next six days revealed a state of relative equilibrium in so far as sodium exchange was concerned. During the period from the forty-third to sixty-ninth day, J. T.'s subjective and objective condition showed little change. Weight changed only slightly. On the other hand, there was a strikingly positive sodium balance, practically all being taken into the intracellular space.

The next three days were characterized by a deterioration of the patient's condition, an increment in body weight, and an increase in extracellular sodium.

After the institution of a diet containing 2.5 mEq. of sodium per day on the seventy-ninth day, the changes noted during the first 12 days were observed.

**RESULTS**

I. Sodium-Rich Diets. (Figs. 1 and 2)

Patient J. T. (Fig. 1). Following an oliguric episode due to sodium depletion, patient J. T. (fig. 1, days 15 through 72) was placed on a diet containing an average of 250 mEq. of sodium per day, and digitalis therapy was discontinued. In so far as sodium exchange was concerned, his response to this high sodium intake may be divided roughly into four phases.

Phase I: Recovery from sodium depletion (days 12 to 36, fig. 1). During this period there was a slight gain in weight, with a positive sodium balance. On analysis it was found that this sodium was retained in both the extracellular and the calculated intracellular compartments, with slightly more sodium being held in the latter.

Phase II: Interval of relative sodium equilibrium (days 37 to 42). This period was characterized by its brevity and by a relative balance between intake and output of sodium. In general, both extracellular and calculated intracellular compartments showed equal uptake of sodium.

Phase III: Positive intracellular sodium balance (days 43 to 69). With a slight gain in weight, there was a strongly positive sodium balance, extracellular sodium showing comparative equilibrium and the calculated intracellular compartment receiving almost all of the retained sodium. Neither subjectively nor objectively (venous pressure, vital capacity, circulation time) were there noticeable changes in the patient's condition.

Phase IV: Development of clinical congestive failure (days 70 to 73). In contrast to the preceding phase, sodium was retained in both extra- and intracellular compartments. The patient rapidly gained weight, developed orthopnea, pedal edema, increased venous pressure and circulation time, and a diminished vital capacity. Daily urine volume which previously had been roughly equated to water intake became much less than fluid intake.

**Patient J. M.** (Fig. 2). The institution of a diet rich in sodium in this patient was, like the above patient, preceded by an episode of sodium depletion, which had been accomplished by a severe restriction of dietary sodium (3 to 5 mEq. per day). Digitalis was withdrawn in this instance and daily sodium intake was, on the average 220 mEq. Clinically, J. M.'s
cardiac failure was of a more severe degree than that of J. T.

The first two phases described for J. T. were either nonexistent or were too transitory to be apparent with daily collection periods. The phase of positive intracellular sodium balance was the only one observed with this patient.

This balance study was terminated before clinical manifestations of congestive failure were observed.

II. Sodium Restriction and Recovery from Congestive Failure. (Figs. 1, 2 and 3)

Patient A. S. (Fig. 3). On admission, this patient exhibited the usual signs of severe congestive failure, such as pulmonary edema, pedal edema, and marked orthopnea. His therapy consisted of digitalis, bed rest, and a restricted sodium intake. Initially, there was a sharp drop in weight, and a loss of sodium, with urine containing sodium at a lesser concentration than that of the extracellular fluid. Calculations revealed that concomitant with this there was an increase in intracellular sodium content. After this initially positive
intracellular sodium balance, there occurred an outpouring of sodium from this compartment. On the twelfth day a change in dietary sodium content from 13 mEq per day to one containing 6.5 mEq per day was followed by a decline in weight, a negative extracellular sodium balance, and a positive intracellular balance, though to a lesser extent than that following admission. The remainder of the study showed loss of sodium from both compartments. Objective and subjective clinical improvement was manifest over the entire period of study.

Patient J. T. (Fig. 1). This patient was ambulatory on admission and had only moderate pedal edema. There was no detectable pulmonary congestion, and measurements of the cardiac status indicated a moderate state of decompensation. Therapy again consisted of sodium restriction, bed rest, and digitalis. Following the institution of sodium restriction, the observed and calculated balances of sodium were parallel to those of A. S. (fig. 3).

Following the development of congestive failure described previously, sodium restriction was again instituted. The results were similar in all respects to those described previously.

Patient J. M. (Fig. 2). The degree of congestive failure presented by this patient was minimal. After institution of a diet with low-sodium content there was a negative balance of this cation, with practically all being withdrawn from the extracellular space.

Comment

As stated previously, it was initially assumed that changes in weight represented changes in extracellular fluid or edema, and all calculations were made on this basis. It can be seen (figs. 1, 2 and 3) that in patients recovering from congestive failure, water is excreted in such proportions to sodium that the urine contains a lesser concentration of sodium than the serum. This can be interpreted in one of two ways: either that sodium is temporarily taken into the cells, or that water was withdrawn from the cells to contribute to the production of a urine with a lower sodium concentration than extracellular fluid. In view of the observation that prior to the development of overt congestive failure, sodium is apparently stored intracellularly without an increase in body water, and that failure develops after what may be presumed to be a “cellular saturation” with sodium, it hardly seems possible for as much of this cation to move into the cells on recovery from failure as is shown by our calculations.

Squires and coworkers\(^9,10\) in their study found that patients recovering from edema by diuresis lost water from the intracellular space, and that urine contained less sodium than serum. Therefore, the initial assumption that water loss represents only extracellular fluid is not entirely correct, and the data presented will be discussed with this in mind.

It is realized that the patients studied here were probably undergoing changes in nitrogen balance and hence the weight change did not represent solely changes in body water. The previous dietary history obtained from these patients and the results of other studies\(^9,10\) indicated that a positive nitrogen balance was likely during the present studies. Therefore, the basis on which the data were calculated would show greater than actual increase in extracellular sodium. During periods of rapid weight changes it would seem unlikely that protein changes would be significant.

Discussion

The data presented show that during the diuresis which accompanies recovery from congestive heart failure, there was initially a loss of both extra- and intracellular water and extracellular sodium. As clinically manifest heart failure developed, there was apparently a large increment in intracellular sodium before extracellular sodium and total body water began to increase. After the retention of water began, clinical failure developed rapidly.

If the sodium does in fact enter the cells in large quantities as congestive heart failure develops, there would seem to be four possibilities in regard to osmolar changes:

(a) That there is a corresponding rise in intracellular osmotic pressure. Since extracellular sodium concentration (and therefore presumably extracellular osmotic pressure)
does not rise, it seems unlikely that intracellular osmolarity would increase.

(b) That as sodium enters, water also enters in corresponding quantities, so that no change in intracellular osmolarity occurs. The simultaneous lack of weight gain and of rise of extracellular sodium concentration mitigates strongly against this assumption.

(c) That excess intracellular sodium is balanced by equimolar losses of some other cation. The available evidence does not seem to support this conclusion in so far as potassium is concerned. It would appear that the amount of magnesium present in cells is not sufficient to balance this sodium gain, even if most of this ion were lost from the cells.

(d) That the increased intracellular sodium does not appreciably alter cellular osmolarity. Therefore, it would seem likely that the sodium, or some other ion, becomes bound into an unionized or inactive form, and minimal or no changes in osmotically active cellular base occur. It is not inconceivable that this inactivation of cellular base is due to changes in the size and degree of dissociation of various phosphate and proteinate molecules which take place during the processes of cellular metabolism. Other investigators have found that similar apparently paradoxical transfers of sodium occur with diuresis during recovery from congestive failure. Their conclusions are similar to those presented.

As stated previously, the initial purpose of these reports was to investigate the nature of a central homeostatic mechanism concerned with the regulation of sodium exchange as a means of protecting the organism against circulatory failure. Studies from this laboratory suggest that this mechanism does not function in patients with congestive failure. Why does it not operate in heart failure, and how does this affect sodium exchange? Does the failure of this volume-regulating center influence the formation of edema in heart failure? At the present time these questions can be answered only in a speculative way, and only by the use of inference and analogy.

The adjustments in effective osmotic pressure which are made by the body are apparently affected mainly through the regulation of water excretion via the posterior pituitary antidiuretic hormone. This mechanism has been nicely presented by Verney and O'Connor, and Peters has referred to this as the "osmometer."

The control of the volume of body fluids cannot be so easily defined as that of osmotic regulation. Although osmolarity is the same throughout the cardiovascular system, the

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**Hypothesis for Mechanism of Action of "Quantometer"**

<table>
<thead>
<tr>
<th>Effect</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excess of intracranial extravascular extracellular fluid</td>
<td>Deficit of intracranial extravascular extracellular fluid</td>
</tr>
<tr>
<td>Stimulation of &quot;quantometer&quot;</td>
<td>Depression of &quot;quantometer&quot;</td>
</tr>
<tr>
<td>Increased activity of &quot;unknown mechanism(s)&quot;</td>
<td>Reduced activity of &quot;unknown mechanism(s)&quot;</td>
</tr>
<tr>
<td>Blocking or antagonistic action on DCA-like substance</td>
<td>Greater activity of DCA-like substance</td>
</tr>
<tr>
<td>Enhanced excretion of sodium</td>
<td>Increased tubular reabsorption of sodium</td>
</tr>
<tr>
<td>Lowering of extracellular fluid osmolarity</td>
<td>Rise in serum sodium concentration and hence increased osmolarity of extracellular fluid</td>
</tr>
<tr>
<td>Depression of osmometer</td>
<td>Stimulation of osmometer</td>
</tr>
<tr>
<td>Diminished output of antidiuretic hormone</td>
<td>Elaboration of posterior pituitary diuretic hormone</td>
</tr>
<tr>
<td>Increased excretion of water</td>
<td>Increased renal reabsorption of water</td>
</tr>
</tbody>
</table>

**Fig. 4.** See text.

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distribution of body fluids is profoundly influenced by such factors as gravity and posture. The evidence seems to support the concept of a volume-regulating mechanism (hereinafter referred to as the "quantometer"), responding to volume changes and mediating its response through sodium excretion.

One hypothesis which explains a possible mechanism of action of this "quantometer" is presented in figure 4. This concept is to be
considered highly speculative, and final acceptance must await more definitive evidence than is presently available.

It has been reported by Gaudino and Levitt\textsuperscript{14} that an adrenal cortical hormone [a desoxycorticosterone (DCA)-like compound] has a primary influence on the distribution of sodium between extracellular and intracellular compartments. Their report states that this desoxycorticosterone-like substance produces a decrease in intracellular fluid space, and an increase in the extracellular fluid space. Desoxycorticosterone caused an increase in total body sodium with an elevated intracellular concentration of this cation. Adrenalectomy reversed these effects. That the renal tubular cells are more sensitive than other body cells to this compound is a conclusion which naturally follows, since they report a rise in serum sodium concentration under its influence.

As shown in figure 4, the "quantometer," through unknown mechanisms, exerts an influence on the activity of circulating desoxycorticosterone (or desoxycorticosterone-like compounds). It has been shown that patients with therapeutically controlled Addison's disease respond to posture with changes in sodium excretion much the same as do normals.\textsuperscript{19} Therefore, it would seem unlikely that the "quantometer" would influence the secretion of a desoxycorticosterone-like substance. Consequently, it is assumed that stimulation of the "quantometer" leads to a depression of the activity of some desoxycorticosterone-like substance. This antagonistic action affects the renal tubular cells (and to a lesser extent other body cells), so that less sodium is reabsorbed from the glomerular filtrate.

In figure 5 an outline of a possible mechanism leading up to clinically manifest heart failure is shown.

It is assumed that in congestive heart failure there occurs with activity a redistribution of blood into the central vessels and great veins of the thorax.\textsuperscript{20} Since there is an accumulation of greater than normal quantities of blood away from the periphery, then a deficit must exist in the systemic circulation. The occurrence of this peripheral volume deficit is assumed to depress the "quantometer," thereby effecting a retention of sodium, and subsequently (via the osmometer) of water also. Thus the ambulant and active patient with congestive failure retains during the day quantities of sodium and water in excess of a normal subject. The elimination of this excess body fluid and sodium at night, when gravity and recumbency cause a redistribution of the volume of fluids toward the head, stimulates

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**Hypothesis for Role of "Quantometer" in Congestive Heart Failure**

1. Diminished cardiac reserve

2. Central accumulation of blood

3. Deficit of volume of extracellular fluid in the periphery, particularly in the cranial cavity

4. Depression of "quantometer"

5. Greater than normal retention of sodium; and through osmometer, increase in body water

6. Recumbency at night → Redistribution of volume of body fluids → Stimulation of "quantometer" → Increased excretion of sodium and water → NOCTURIA

7. Failure of effectiveness of "quantometer"

8. Progressively greater retention of sodium and water → Increased pooling of blood in central vessels → Pulmonary congestion

9. Orthopnea → Almost continual depression of residual activity of the "quantometer" (enhanced by gravity and posture)

10. Intensification of disturbed volume and distribution of body fluids, and development of imbalance of intracellular cation content

11. Clinically manifest congestive failure

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**Fig. 5.** See text.
seen in patients J. T. and J. M. (figs. 1 and 2) on sodium-rich diets. If this occurs (and it is yet to be proved) then an hypothesis exists to explain the nocturia of failure which occurs as one of the earliest symptoms of a weakening myocardium.

It has been found recently\(^6\),\(^7\) that patients with advanced congestive failure, requiring frequent injections of diuretics for maintenance, do not respond to compression of the neck with an increased sodium output; neither do these individuals exhibit a negative sodium balance, as do normal subjects\(^1\),\(^2\) when placed in a recumbent position. If, as is shown in figure 5, the "quantometer" of such patients has failed or is not functioning adequately, then an hypothesis exists which explains their lack of response to compression of the neck and to posture.

**Summary and Conclusions**

The results of sodium balance studies on three patients with cardiac failure have been presented. These patients apparently exhibited striking transfers of sodium and water between the intra- and extracellular spaces of the body. In one patient given large amounts of sodium, it was shown that expansion of the extracellular fluid space did not occur until after "saturation" of the intracellular fluid space with sodium had occurred.

The results of this study have been discussed. A speculative hypothesis concerned with a mechanism of sodium retention leading up to clinically manifest heart failure has been presented.

**Sumario Español**

Estudios por largo tiempo de balance del sodio fueron hechos en tres pacientes con decompensación cardíaca. Los datos indican intercambio del agua y el sodio entre los espacios intracelulares y extracelulares. Se sugiere que una porción del catión intracelular existe en una forma que es osmoticamente inactiva. El término "cuantómetro" se aplica el previamente descrito mecanismo de regulación volumétrica intracranial. Se sugiere una hipótesis en la cual se asume que el agotamiento de este cuantómetro puede contribuir a la retención del sodio a medida que la decompensación cardíaca se manifiesta.

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