Interrelations Between Total Exchangeable Sodium, Potassium, Body Water, and Serum Sodium and Potassium Concentrations in Hyponatremic and Normonatremic Heart Disease

By Knud H. Olesen, M.D.

SUMMARY

Interrelations between total body water, total exchangeable cation (sodium + potassium), and cation (sodium + potassium) concentration of serum water were examined in 20 normonatremic and 11 hyponatremic edematous cardiac patients. The total exchangeable cation and total body water were highly significantly correlated in the normonatremic and hyponatremic groups. However, for the combined groups the correlation coefficient was lower than that found in the individual populations, and in covariance analysis the cation content in relation to total body water was significantly lower in the hyponatremic than in the normonatremic group. When it is assumed that the total exchangeable cation differs little from the total osmotically active cation, and that the cation concentrations of the extracellular and intracellular water are approximately equal, the ratio: total exchangeable cation / cation concentration in serum water, that is, the cation space, should reflect the total body water. The cation space and total body water were highly significantly correlated in the normonatremic and hyponatremic groups, and the correlation coefficient remained at the same high level for the combined groups. The relationship between cation space and body water was very close to unity, and in covariance analysis no significant difference was found in cation space in relation to total body water. These results were confirmed in 10 sequential studies. It is concluded that the cation space in hyponatremic and normonatremic cardiac patients has proved to reflect the total body water very closely, and the implications of this finding are discussed.

Additional Indexing Words:
Alteration in body composition
Cation space
Cardiac edema
Correlation and regression analysis

According to current knowledge sodium is the predominant cation of the extracellular phase, and potassium is the preponderant cation of the cell mass, while small amounts of potassium are present in the extracellular compartment, and minor quantities of sodium are found in the cells. In actual concentrations the sums of sodium and potassium in extracellular and intracellular water are approximately equal, and with their anions these cations account for the great majority of the total osmotic activity of the two compartments. Since with few exceptions osmotic gradients are not sustained across cell membranes, the sum of osmotically active sodium and potassium in the body may be considered as the determinant of the body water content.

The total exchangeable sodium \( (Na_e) \) and total exchangeable potassium \( (K_e) \) as
measured by isotope dilution are only slightly larger than the total osmotically active quantities of these cations, and in accordance with the concepts outlined above, isotope dilutional studies of body composition in normal man have shown a highly significant correlation between total body water (TBW) and total exchangeable cation \((Na_e + K_e)\). This relationship is expressed in regression equation 1, where \(a\) indicates the intercept, and \(b\) represents the regression coefficient:

\[
Na_e + K_e = b \cdot TBW + a \tag{1}
\]

In chronic illness where the most frequent pattern of alteration in body composition is an expansion of the extracellular phase and a shrinking of body cell mass, the highly significant correlation between total body water and total exchangeable cation appears to be sustained as long as the normal serum cation (serum sodium) concentration is maintained, and the amount of exchangeable, osmotically inactive cation is unchanged.\(^3\)

However, in chronic illness with hypotonicity or hypertonicity (that is, hyponatremia or hypernatremia) the relationship between body water and total exchangeable cation must presumably be different from the findings in normotonic states, and in a population of patients with a wide variation of serum cation concentrations, the correlation coefficient of equation 1 must be expected to be decreased. For this situation the following relationship between the sodium concentration of serum water \((Na)s\) and the total exchangeable cation concentration \((Na_e + K_e)/TBW\) has been defined:\(^4\):

\[
(Na)s = b \cdot \frac{Na_e + Ke}{TBW} + a \tag{2}
\]

The significance of this relationship has been improved through the addition of the potassium concentration to the sodium concentration of serum water as shown in equation \(3^5\):

\[
(Na)s + (K)s = b \cdot \frac{Na_e + K_e}{TBW} + a \tag{3}
\]

This formula, which relates the cation concentration of serum water to the total exchangeable cation concentration, may be re-written as follows:\(^6\):

\[
\frac{Na_e + Ke}{(Na)s + (K)s} = b \cdot TBW + a \tag{4}
\]

With the assumption that the cation concentrations of the extracellular and intracellular water are equal, the term \(\frac{Na_e + K_e}{(Na)s + (K)s}\) represents the cation space, or the volume of dilution of cations, the variations of which should reflect the variations in total body water to the extent that the amount of exchangeable, osmotically inactive cation is unchanged. Since the variables of equation 4 cover a wider range than the variables of equations 2 and 3, the relationship expressed in equation 4 should be most suitable to include hypotonic, normotonic, and hypertonic disease states in a highly significant correlation.

The interrelations between total body water, total exchangeable cation, and serum cation concentrations have so far been examined in populations of patients with a wide variety of diseases.\(^4-6\) They have not been studied specifically in the entity of congestive heart failure, which demonstrates the most marked alterations in body composition,\(^5,7\) and in which the question of osmotic inactivation of cation has been raised.\(^8\) The objective of this paper is, therefore, to examine the relationships between body water, total exchangeable cation, and serum cation concentrations in hypernatremic and normonatremic heart disease.

**Patients and Methods**

The patients included in the study were subjects with an unequivocal diagnosis of organic heart disease. The clinical categories of cardiac disease and the degree of congestive heart failure are indicated in tables 1 and 2. For purposes of comparison the material is divided into two groups: the normonatremic group (range of serum sodium from 137 to 148 milliequivalents per liter of serum) and the hypernatremic group (range of serum sodium 117 to 133 milliequivalents per liter of serum).

The treatment included digitalis, a thiazide diuretic (chlorothiazide, 1 g, or cyclopenthiazide, 1 mg) and either 3 g of potassium chloride
Table 1

Clinical Data and Body Composition in Normonatremic Cardiac Patients

<table>
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<tr>
<th>Patients</th>
<th>Age, sex</th>
<th>Type of heart disease</th>
<th>Edema</th>
<th>Weight (kg)</th>
<th>Na⁺ serum water (mEq/L)</th>
<th>K⁺ serum water (mEq/L)</th>
<th>Na⁺ + K⁺ serum water (mEq/L)</th>
<th>N̄Na, total exchangeable sodium (mEq)</th>
<th>K̄o, total exchangeable potassium (mEq)</th>
<th>TBW (L)</th>
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Abbreviations in tables 1 and 2: AI, aortic insufficiency; ASD, atrial septal defect; ASHD, arteriosclerotic heart disease; CA, aortic coarctation; CoPe, constrictive pericarditis; CP, cor pulmonale; MI, mitral insufficiency; MS, mitral stenosis; Myo, myocarditis; Na⁺, sodium concentration in serum water; K⁺, potassium concentration in serum water; Nā, total exchangeable sodium; K̄, total exchangeable potassium; TBW, total body water.
or 100 mg of spironolactone to prevent potassium depletion. Additional injections of thiomerin had been required in two of 20 normonatremic patients and in five of 11 subjects in the hyponatremic group who had received the most intensive diuretic therapy.

Total exchangeable sodium (Na\textsubscript{e}) and total exchangeable potassium (K\textsubscript{e}) were measured by help of the isotopes \textsuperscript{24}Na and \textsuperscript{42}K according to methods previously described.\textsuperscript{7} The period of equilibration was 24 hours. Total body water was measured by dilution with deuterium oxide according to the method described by Friis-Hansen.\textsuperscript{9} The period of equilibration was 6 hours. The serum sodium and potassium concentrations were measured by flame photometry, and the concentrations per liter of serum water were calculated after determination of the serum protein content.\textsuperscript{10}

The results are analyzed according to conventional statistical methods.\textsuperscript{11} In all regression analysis a linear relationship is assumed.

The results of body compositional measurements are expressed as percentages of predicted normal values with use of the formulas given by Moore and associates.\textsuperscript{3} This procedure takes into account the influence of age, sex, and body weight upon body composition. Since no correction for excess of edema has been applied, the predicted normal values used will tend to be too high and the increments of water and electrolytes above normal will tend to be underestimated.

In 10 patients sequential studies were performed with intervals from 2 to 6 months, and the interrelations of variations in body compositional values were analyzed statistically.

### Results

The clinical and laboratory data for the 20 normonatremic and the 11 hyponatremic patients are given in tables 1 and 2. The departures from predicted normal body composition are shown in table 3. The results of correlation and regression analysis are illustrated in tables 4 and 5 and in figures 1 to 3.

The results obtained in the sequential studies are shown in table 6 and in figure 4.

### Alterations in Body Composition

The normonatremic and hyponatremic groups embraced a wide range of body compositional values as shown in tables 1 and 2. For the normonatremic group the range of total exchangeable cation varied from 3,340 to 8,100 milliequivalents, and the total body water had a range from 23.0 to 54.9 liters.
For the hyponatremic group the corresponding ranges were from 3,360 to 9,250 milliequivalents and from 25.8 to 68.6 liters. The major differences between the two groups were found in the sodium and the cation concentrations of serum water, which were significantly lower in the hyponatremic than in the normonatremic group.

The nature and extent of alterations in body composition in relation to predicted normal values are shown in table 3. In the normonatremic group the total exchangeable sodium was increased to a mean value of 138% of normal, while total exchangeable potassium was decreased to a mean value of 79% of normal. The total exchangeable cation amounted to 108% of normal, and total body water to 116% of normal.

For the hyponatremic group the trends were similar. The total exchangeable sodium had a mean value of 147% of normal, while total exchangeable potassium had a mean of 72% of normal. The total exchangeable...
cation represented a mean of 106% of normal, and total body water a mean of 129% of normal.

Correlation and Regression Analysis
Total Exchangeable Potassium, Sodium, and Total Body Water

In the normonatremic group a strikingly high correlation \((r = 0.978)\) was found between total exchangeable cation \((\text{Na}_e + \text{K}_e)\) and total body water \((\text{TBW})\) as shown in table 4 and in figure 1. This correlation was significantly higher than the individual correlations between \(\text{K}_e\) and TBW \((r = 0.599)\) and between \(\text{Na}_e\) and TBW \((r = 0.933)\), which are shown in figure 2. While the disproportionate changes in \(\text{K}_e\), \(\text{Na}_e\), and TBW in cardiac failure tended to decrease the individual correlations between these parameters as compared to the findings in normal individuals, it appeared that the correlation between total exchangeable cation and total body water was maintained. This last finding suggested that the total body water was still determined by the total cation content.

As shown in table 4, the correlation analysis in the hyponatremic group showed exactly the same trends as found in the normonatremic group. When the groups were combined, however, the correlation coefficient for the relationship between total exchangeable cation and total body water was lower.
Correlation and natremic tolation in the result, this and 0.978 group lower in total body water.

**Figure 3**

Correlation between cation space \( \frac{Na_e + Ke}{Nd_e + K_s} \) and total body water for the combined groups of hyponatremic and normonatremic cardiac patients.

\[ \Delta \frac{Na_e + Ke}{Na_e + K_s} = 0.978 \cdot TBW - 0.19 \]

\[ Syx = 1.37 \]

\[ r = 0.981 \]

\[ p < 0.001 \]

**Table 3**

Correlation between cation space \( \frac{Na_e + Ke}{Nd_e + K_s} \) and total body water for the combined groups of hyponatremic and normonatremic cardiac patients.

\( r = 0.952 \) than found in the subgroups \( r = 0.978 \) and \( r = 0.982 \). In accordance with this result, covariance analysis revealed that the total exchangeable cation content in relation to total body water was significantly lower in the hyponatremic than in the normonatremic group (table 5). This significant difference in body composition between the

nornonatremic and hyponatremic groups may be related to the significant difference in serum cation concentrations mentioned above.

Cation Space \( \frac{Na_e + Ke}{(Nd)_e + (K)_s} \) and Total Body Water

When a correction for the differences in cation concentrations in serum water was applied to the comparison between the normonatremic and hyponatremic groups, the significant difference in body composition disappeared. As shown in table 4, the correlation between cation space and total body water for the combined groups remained at the same high level \( r = 0.980 \) as found in the subgroups \( r = 0.978 \) and \( r = 0.983 \). Accordingly, in covariance analysis no significant difference was found between the two groups in the relationship between cation space and body water. As shown in figure 3, the two groups may be combined in a regression equation with a relationship close to unity.

In the sequential studies where changes in total body water varied from +9.8 to −18.6 liters and cation space changes ranged from +9.1 to −17.8 liters, the alterations in these parameters were correlated highly significantly \( r = 0.981 \), and, similar to the findings above, the relationship was close to unity (table 6 and fig. 4).

**Discussion**

Our results showed in accordance with previous observations\(^5\,\,4\,\,7\) that normonatremic edematous patients presented a severe distortion of the pattern of body composition: A marked increase of total exchangeable sodium, a moderate increase of total exchangeable cation and of total body water, and a tendency to reduction of total exchangeable potassium. For the hyponatremic group the tendencies were similar. The major difference between the two groups was that the sodium and cation concentrations in serum water were significantly lower in the hyponatremic than in the normonatremic group.

In spite of the fact that the severe alterations in body composition in the normonatremic patients caused a decrease of the
correlations between \( K_e \) and TBW and between \( Na_e \) and TBW as compared to the findings in normal subjects, the correlation between total exchangeable cation \((Na_e + K_e)\) and body water (TBW) was still highly significant \((r = 0.978)\). This finding is compatible with the concept that the total body water content is still determined by the total cation content.

The results obtained in the hyponatremic group showed exactly the same trends as found in the normonatremic group. However, the correlation between \( Na_e + K_e \) and TBW for the combined normonatremic and hyponatremic groups was lower \((r = 0.952)\) than the correlations for the individual groups \((r = 0.978, \text{and } r = 0.982)\). In accordance with this finding a significant difference was found between the two groups in covariance analysis. The adjusted means for \( Na_e + K_e \) in relation to TBW was lower in the hyponatremic than in the normonatremic group. It would appear likely that this significant difference in body composition between the two groups was a reflection of the significant difference in serum cation concentrations.

Continued analysis of the relationship between total exchangeable cation and total body water taking into account the influence of cation concentrations in serum water revealed that the relationship between the cation \(\left(\frac{Na_e + K_e}{(Na)_s + (K)_s}\right)\) and total body water was not significantly different in the hyponatremic and normonatremic groups. For the combined groups the correlation coefficient remained at the same highly significant level \((r = 0.980)\) as found for the individual groups \((r = 0.978, \text{and } r = 0.983)\). Accordingly, in covariance analysis no significant difference was found in adjusted means for cation space in relation to total body water. Actually, the regression equation for the combined groups defined a relationship close to unity.

The results obtained in sequential studies demonstrated a highly significant correlation between the variations in cation space and in total body water \((r = 0.981)\) with a regression coefficient close to unity (fig. 4 and table 6), and supported strongly the previous findings.

It may be concluded, therefore, that equation 4:

\[
\frac{Na_e + K_e}{(Na)_s + (K)_s} = b \cdot TBW + a,
\]

has proved to be able to unify the interrelations between total body water, total exchangeable cation and cation concentrations in serum water in hyponatremic and normonatremic cardiac patients. In the present study the cation space proved to reflect the total body water very closely, suggesting that the basic assumption of approximately equal cation concentrations in extracellular and intracellular water holds true. When this assumption was accepted the results appeared to indicate that the amount of exchangeable, osmotically inactive cation in hyponatremic patients was not significantly different from that of normonatremic patients. It would appear unlikely, therefore, that the hyponatremia was caused by osmotic inactivation of exchangeable cation (or sodium).

In terms of body compositional findings the hyponatremia may be ascribed to a decreased ratio: \( Na_e + K_e/TBW \). Since in our series all hyponatremic patients demonstrated an absolute excess of sodium, the hyponatremia could not have been caused by a loss of sodium, but must have been related to a deficit of potassium or an excess of body water. It would appear from table 3 that although the \( K_e \) in relation to predicted normal values was slightly lower in the hyponatremic than in the normonatremic group, reflecting either a potassium depletion caused by more intensive diuretic treatment or a shrinking of body cell mass due to more advanced disease, the major cause of the hyponatremia was most likely found in an excess of total body water. It is our conclusion, therefore, that the hyponatremia in cardiac edema is largely dilutional.

**References**

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Nature's Experiments

... "Peradventure this is not fortune's work neither, but Nature's; who perceiving our natural wits too dull to reason of such goddesses has sent this natural for our whetstone..."

All scientists, including clinical scientists, are products of their culture and society. Indeed, in a very real sense, we are the very servants of our poets, artists, philosophers, theologians, and academicians. We must now be prepared to adapt to a new era. It is one in which we can play a formulating role if we will but accept the challenge. We must not be hypersensitive to criticism; we must be communicative; we must contribute in the most positive way possible to the development of a cultural philosophy that will continue to foster the most effective interpretation of Nature's experiments, and the attainment and utilization of scientific knowledge to the welfare of our patients and all mankind.—Robert A. Good: Presidential Address: The Whetstones. J. Lab Clin Med 69: 7; 13, 1967.
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KNUD H. OLESEN

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