Rapid Water and Slow Sodium Excretion of Acetated Ringer's Solution Dehydrates Cells

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Acetated Ringer's solution is a slightly hypotonic infusion fluid (osmolality 270 mosmol/kg) that has inspired the belief that the fluid causes a shift of water volume to the intracellular space. We assessed the role of the kidney in modifying this volume shift by infusing 25 mL/kg of Ringer's acetate solution (mean, 1565 mL) over a time period of 15, 30, 45, and 80 min on different occasions in 5 healthy female volunteers. Regardless of the rate of administration, the excreted urine contained only half as much sodium (mean, 67 mmol/L) as the infused fluid. As there was only a slight increase of 0.9 mmol/L in the serum sodium level, mass balance calculations indicated that 274 mL of water had shifted from the intracellular to the extracellular space 30 min after the infusions ended ($P < 0.001$). This fluid shift was also maintained over the subsequent 90 min. In conclusion, infusion of Ringer's acetate solution does not promote cellular swelling as a result of the excretion of urine that is low in sodium. A slight dehydration of fluid from the intracellular space still persisted when our measurements ended 2 h after completing the infusion.

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Intravenous Ringer's solution is widely used for hydration of the extracellular fluid (ECF) space (1). The ion composition of the solution closely resembles that of the ECF, although for technical reasons bicarbonate is replaced by lactate or acetate. The osmolality of the solution is 270 mosmol/kg, which is less than the osmolality of the body fluids (2), and the sodium concentration (130 mmol/L) is less than in plasma (139 mmol/L). This would normally imply that a fraction of the infused water is translocated to the intracellular fluid (ICF) space. By the same osmotic mechanism, water moves in the opposite direction when hypertonic saline is infused. Therefore, isotonic or hypertonic saline are more suitable choices of infusion solutions if cellular swelling is to be avoided.

This report examines the role of the kidney in modifying the distribution of Ringer's acetate solution between the ICF and ECF spaces. Preliminary comparisons between the distribution and urinary excretion of sodium indicated that, in contrast to the current view, infusion of Ringer's acetate solution in healthy volunteers could translocate water from the ICF space to the ECF space. Our hypothesis was that those findings can be explained by water and sodium being excreted at different rates after infusion of this crystalloid fluid.

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Methods

Twenty IV infusions of Ringer's acetate were given to 5 healthy female volunteers 27–46 yr of age (mean age, 31 yr) and weighing between 50 and 75 kg (mean weight, 60 kg). The study was approved by the local Ethics Committee. Each volunteer gave her informed consent to participate after having received oral and written information about the purpose and implications of the study. None of them used regular medication and routine blood testing, including serum creatinine, showed values within the normal range for our hospital.

The volunteers received, in random order and at intervals of at least 1 day, an IV infusion of 25 mL/kg of Ringer's acetate solution over 15, 30, 45, and 80 min (sterile water containing the following electrolytes: sodium 130, potassium 4, calcium 2, magnesium 1, acetate 30, and chloride 110 mmol/L). The average amount of infused Ringer's solution was 1565 mL, and the various infusion times were used to examine whether the results were dependent on the intensity of the intravascular fluid administration program.

The volunteers ate only a light meal in the morning before each experiment, consisting of one cup of coffee, tea, or water and a sandwich. They rested comfortably on a bed, and at least 20 min of equilibration

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was allowed before the experiments started. Cannulae were placed in the antecubital veins of both arms and Ringer's acetate solution was infused into one of these veins at a constant rate with the aid of one or several infusion pumps (model 560; IVAC, San Diego, CA). Blood samples were withdrawn from the other arm. After a blood sample was drawn, the cannula was flushed with 2 mL of Ringer's solution.

The volunteers voided just before the experiments started, which was between 8 and 10 AM. All urine was collected 30 and 120 min after the infusion, the first collection period being called "Period 1" and the second "Period 2." The first period thus also included the urine excreted during the infusion. The two urinary volumes were measured in a calibrated tube and the urinary sodium (U-Na) and potassium (U-K) concentrations were analyzed using a Hitachi 747 (Hitachi, Naka, Japan).

Blood for measuring the serum concentrations of sodium (S-Na) and potassium (S-K) was drawn from the arm not used for the infusion before the infusion started and at the end of Period 1 and Period 2. The samples were analyzed by means of an ion-selective, direct potentiometry technique using an IL BGE analyzer (Instrumentation Laboratory, Milan, Italy) with a coefficient of variation of between 1% and 2%.

The diffusion of fluid into and out of the cells was calculated by the sodium dilution method (3–5), which is based on a mass balance concept implying that sodium ions (Na) and water in the ECF space remain constant over time except for additions and losses. In principle, all these additions and losses are known except for fluid exchange between the ECF and ICF spaces. Because Na is distributed throughout the ECF space, the S-Na concentration at any time (t) during or after an IV infusion of fluid ($S\text{-}Na_t$) equals the amount of Na in the ECF volume divided by the current ECF volume. This relationship can be expressed as:

$$S\text{-}Na_t = \frac{\text{Added Na} + (S\text{-}Na_o \times ECF_o - Na_{loss})}{(ECF_o + \text{infused volume} - \text{urine volume} - \Delta ICF)}$$

where $S\text{-}Na_o$ and ECF_o are the serum sodium concentration and the ECF volume at baseline, Na_{loss} is the natriuresis (in mmol), and ΔICF is the change in the water content of the ICF compartment. As ECF_o corresponds to 20% of the body weight (2), ΔICF could be calculated from the following rearrangement:

$$\Delta ICF = ECF_o + (\text{infused} - \text{urine}) \text{ volume} - \frac{\text{Added Na} + (S\text{-}Na_o \times ECF_o - Na_{loss})}{S\text{-}Na_t}$$

The results are expressed as the mean ± SEM when $n = 5$. Statistical evaluation was made using repeated-measures analysis of variance (ANOVA) and linear regression analysis. $P < 0.05$ was considered significant. When no significant differences among the 4 series of experiments were found, the results were alternatively presented as the mean followed by the 95% confidence interval (CI) in parenthesis for the pooled data ($n = 20$). Other results from the same experiments have been used to study the hemoglobin kinetics in response to intravascular fluid administration (6).

Results

The S-Na concentration increased slightly, the average increase being 0.9 (95% CI, 0.8–1.8; $P < 0.04$) mmol/L from before the infusion to 120 min after (Fig. 1, top). The S-K concentration also changed very little, usually in the direction of the infused fluid, which contained 4 mmol/L of potassium (Fig. 1, bottom).

The U-Na and U-K concentrations of the urine excreted during the infusions and within the first 30 min thereafter (Period 1) were quite consistent, the U-Na concentration of all 20 infusions being 67 (50–85) mmol/L and the U-K concentration amounting to 15 (11–19) mmol/L.

During the subsequent 90 min (Period 2), however, the U-Na concentration was 133 (120–146) mmol/L, which is close to that of the infused fluid, whereas the U-K concentration was approximately 10 times larger than in the infused fluid (mean, 30 mmol/L; 95% CI, 23–37). These trends were valid for all 4 series of infusions, regardless of the baseline urinary concentration of these electrolytes (Fig. 2).

The urine volumes were also very similar regardless of the infusion rate; the pooled average for all infusions was 760 mL (95% CI, 632–887 mL) during Period 1, whereas an additional 281 (226–336) mL was excreted during Period 2 (Fig. 3, top). The small content of sodium in the first portion of urine apparently created an osmotic imbalance between the ECF and ICF that was corrected by a shift of water. The sodium dilution method suggests that 274 (152–396) mL ($P < 0.0002$) had been added to the ECF volume from the ICF volume 30 min after the infusion. This volume was virtually unchanged, 261 (144–377) mL, at 120 min (Fig. 3, bottom).

There were no statistically significant differences among the 4 infusion rates with respect the changes in serum electrolytes, urinary excretion of electrolytes, urine volume, and to the reduction of the ICF volume (repeated-measures ANOVA).

For all 20 experiments, there was a significant linear relationship between the total urine volume and the total Na excretion ($r = 0.67$; $P < 0.004$) and between

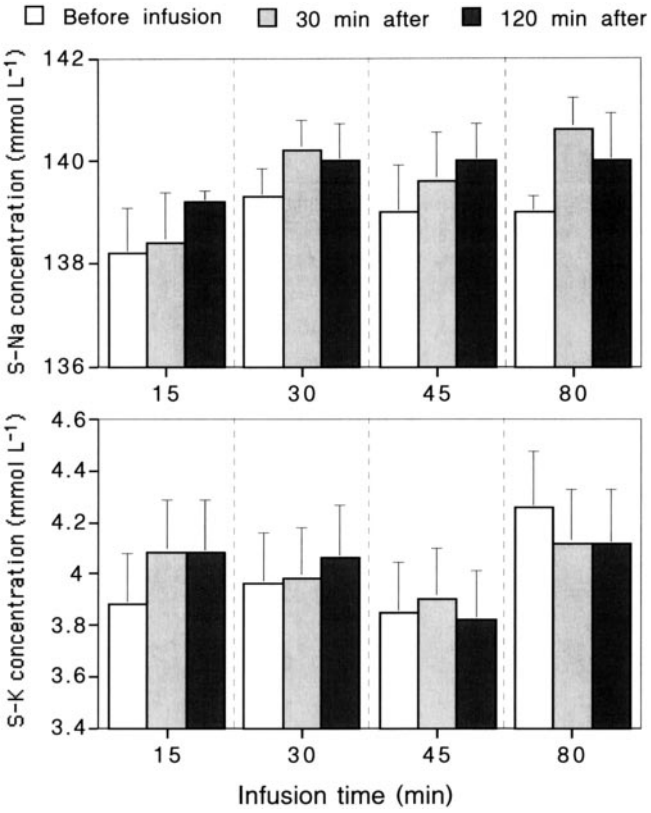

Figure 1. The serum sodium (top) and serum potassium (bottom) concentrations just before, 30 min after (end of Period 1), and 120 min (end of Period 2) after an IV infusion of 25 mL/kg of Ringer's acetate solution over 15, 30, 45, and 80 min in 5 healthy volunteers. Data are mean ± SEM.

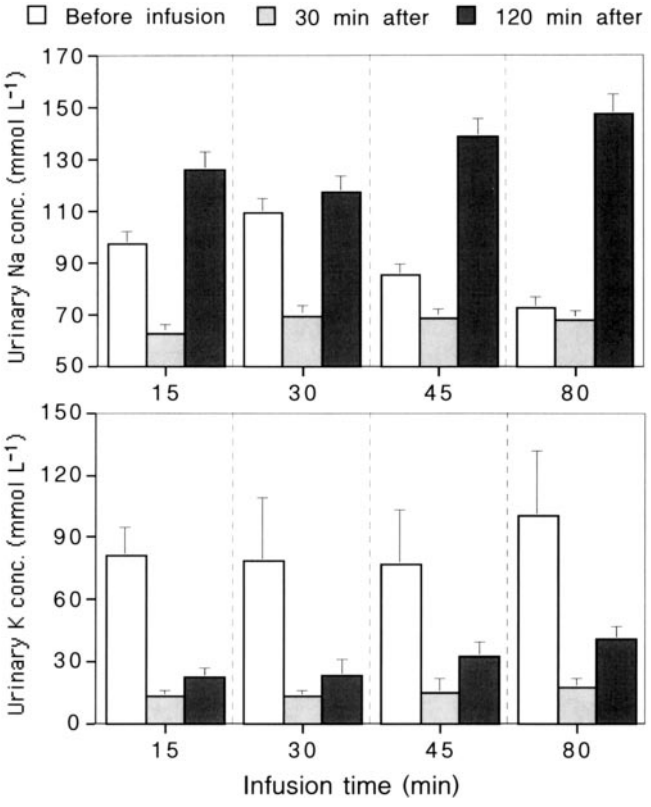

Figure 2. The urinary concentrations of sodium (top) and potassium (bottom) in the urine recovered just before, 30 min after (Period 1), and 120 min after (Period 2) an IV infusion of 25 mL/kg of Ringer's acetate solution over 15, 30, 45, and 80 min in 5 healthy volunteers. Data are mean ± SEM.

the total urinary excretion and the reduction of the ICF volume ($r = -0.52$; $P < 0.04$).

Discussion

Sodium remains almost exclusively outside the cells (2) and serum sodium changes after additions and losses of water may therefore be used to estimate the translocation of water to and from the intracellular space by means of mass balance equations. The result is surprising when the sodium dilution method is applied to the fluid balance after infusion of Ringer's acetate solution. This fluid is slightly hypotonic, leading one to believe that the fluid would hydrate the cells. However, we recorded just the opposite effect on administering 1500 mL of the fluid to female volunteers. Approximately 275 mL of water had been translocated from the cells to the ECF fluid space at 30 min after the infusion (end of Period 1), and the situation was the same 90 min later (end of Period 2). These fluid shifts would even be slightly larger if evaporation losses through the airways had been considered. The fluid balance was only followed for a limited period of time, but we assume that the baseline ICF volume was eventually restored.

This effect on the equilibrium of water between cells and noncells can be accounted for by the urinary excretion of fluid that contained only half as much sodium (67 mmol/L) as the infused fluid. At 30 min after infusions, 56% of the infused water volume, but only 26% of the infused sodium, had been excreted. The sodium concentration was larger in the next collection of urine but it did not consistently exceed that of the infused fluid, resulting in a status quo with respect to the distribution of infused fluid. At that time, 77% of the infused water volume and 45% of the sodium had been excreted. In contrast to the urinary data obtained before the infusion, these findings were quite consistent and the scattering of the data relatively small. No effect of the infusion time on the natriuresis and the translocation of water could be discerned. Reid et al. (7) recently described the same pattern of rapid water and slow sodium elimination after infusion of normal saline, but not after Hartmann's solution, which has a composition similar to Ringer's lactate. They suggested that the phenomenon is attributable to the larger chloride content of normal saline.

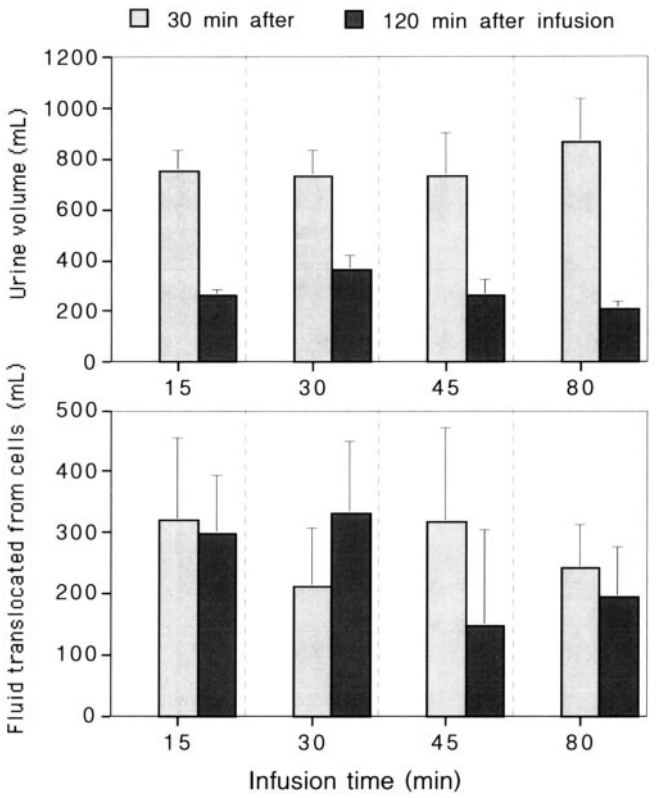

Figure 3. The urine volume (top) and the calculated translocation of fluid from the intracellular to the extracellular fluid space (bottom) 30 min after (Period 1) and 120 min after (Period 2) an IV infusion of 25 mL/kg of Ringer's acetate solution over 15, 30, 45, and 80 min in 5 healthy volunteers. Data are mean ± SEM.

Excretion of urine that is low in sodium creates a situation similar to treatment with hypertonic saline. A relative excess of sodium remains in the ECF space, which attracts water from the ICF by virtue of osmosis. Our volunteers showed a slight increase in the serum sodium concentration, whereas the mass balance calculations indicated that the increase (i.e., the difference between S-Na_t and S-Na_o) should be four times larger to keep the ICF volume unchanged. Hence, the increase in serum sodium in response to the brisk diuresis was smaller than expected, and the serum level could be kept low only by dilution with intracellular water.

The sodium dilution method used to calculate the fluid shift between cells and noncells is simplistic. The method assumes that sodium ions are evenly distributed in the ECF volume and that absorption from the gut is of negligible importance for the calculations, which are not particularly sensitive to erroneous assumptions for the baseline ECF. Setting this volume to a 20% larger value than the one used in the study reduced the translocation of fluid from the ICF volume by as little as 10 mL. Conversely, setting the baseline ECF to a 20% smaller value increased the calculated translocation by 10 mL. However, one must also consider that complete equilibration of sodium in the ECF space requires approximately 10 minutes (8) and that the formation of urine takes some time as well.

The sodium dilution method has previously been applied to the distribution of electrolyte-free irrigating fluid in sheep (3,4) and humans (4) and the intracellular uptake of the water component of glucose solutions in humans (5). One animal study comprised control experiments that support the view that normal saline causes a shift of fluid from the ICF to the ECF (3). Similarly, in male volunteers, 1 L of Ringer's acetate solution had translocated 100 mL of fluid from the ICF to the ECF at 90 minutes after the infusion (5).

In the present study, the volunteers were allowed to have one cup of fluid and one sandwich in the morning, usually preceding the experiments by 2–3 h. In our experience, such a light meal in the morning maintains steady state in the fluid balance. Conversely, volunteers who are in a completely fasting state show evidence of dehydration, which also affects the results. If anything, we believe that the potassium balance might have been affected by residual absorption of the morning meal; we have therefore refrained from detailed calculations concerning this ion. However, provided that such confounding is small, our view that water must have left the intracellular space during the intravascular fluid administration is also supported by the potassium data. The excretion of potassium averaged 18.4 mmol, more than 3 times the infused amount. As the S-K level changed very little, this potassium was probably mostly derived from the ICF space, and such passage of ions is capable of carrying along more than 100 mL of water by virtue of osmosis. This view suggests that the fraction of the urine that is derived from the ICF space can be estimated from the ratio of excreted potassium to the sum of the potassium and sodium ions, in this case approximately 22%. The relatively large excretion of potassium is one reason why the kidney must concentrate the urine to be able to eliminate a nearly isotonic crystalloid fluid. The kidney excretes more potassium in response to an increased tubular flow rate, which occurs in response to intravascular fluid administration (9).

The present findings have implications for our view of how the body handles crystalloid infusion fluids. When intravascular fluid administration is performed, the time course for the excretion of sodium and water are apparently different. The kidneys reabsorb more sodium than water, and the net result is a translocation of water from cells to noncells. At 2 hours after the infusion, conventional mass balance calculations would seem to imply that the ECF space is hydrated by 400 mL, the difference between the infused volume and the urinary excretion at that time. However, on considering the effect of natriuresis, the ECF space is in fact hydrated by 660 mL, 65% more than originally

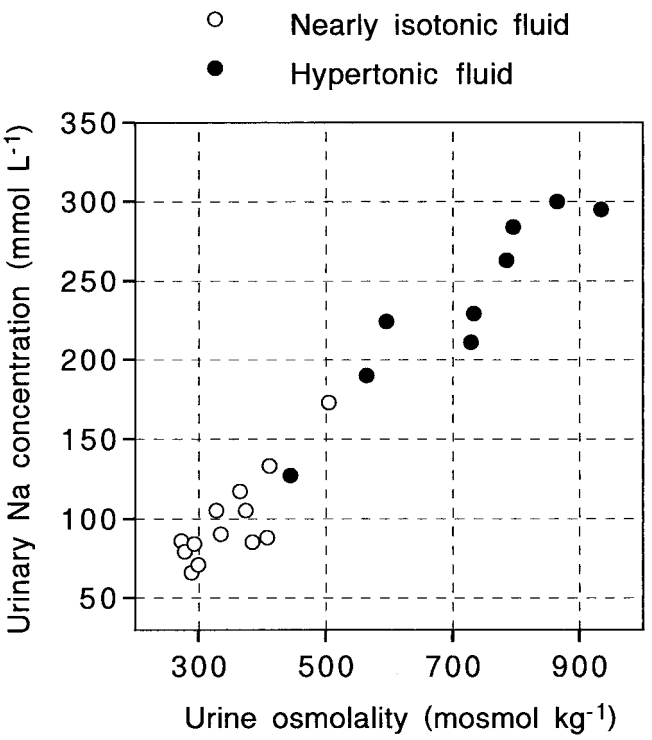

Figure 4. The urinary concentration of sodium versus the osmolality of the urine voided 210 min after an IV infusion of 25 mL/kg of Ringer's lactate, Ringer's acetate, or normal saline (open circles) or 3–5 mL/kg of a 7.5% saline solution with or without added dextran (closed circles). Each point represents one experiment in a male volunteer. Unpublished data from (10).

believed. This example shows that calculations of fluid distribution between physiological body compartments after intravascular fluid administration cannot be performed on the assumption that Ringer's solution will remain solely in the ECF volume. Although an infusion fluid is isotonic in the test tube, its net effect on a human may be modified by the kidney. Measurements of the sodium balance could be an important adjunct to a more complete understanding of how crystalloid fluid affects the body.

It should be noted that the present study was undertaken in healthy volunteers. The results may not be relevant to fluid administration during anesthesia and surgery. Other studies are needed to confirm the findings under such circumstances. Additional information regarding the difficulties for the kidney to excrete the sodium contained in an isotonic crystalloid solution may then be obtained by assessing urine osmolality. Such data were not collected in the present series of experiments, but urinary electrolytes and osmolality were measured in one of our other studies in which male volunteers received isotonic, nearly isotonic, and hypertonic fluid (10). Exploratory analyses of these data suggest that the expected urinary sodium concentration is only 60–80 mmol/L when isotonic urine is passed. For the urinary sodium concentration to be close to the sodium concentration of Ringer's solution, it seems to be necessary that the kidney concentrates the urine to approximately 500 mosmol/kg, which involves increasing its sodium content (Fig. 4, unpublished observations). Increasing the U-Na concentration requires some time for the kidney (8), whereas excretion of fluid in response to intravascular fluid administration apparently operates much faster, thereby inducing the fluid shift described in the present report.

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