Digestive Diseases and Sciences, Vol. 43, No. 3 (March 1998), pp. 663–667

Intra- and Extracellular Water Dynamics on Rehydration in Cholera and Noncholera Patients

MOHAMMED I. HOSSAIN, MBBS, DCH, IQBAL KABIR, MD, PhD, GEORGE J. FUCHS, MD, MARTIN J. McCUTCHEON, PhD, JOSE O. ALVAREZ, PhD, and MOHAMMED A. KHALED, PhD

To estimate the intra- and extracellular body water compartments during rehydration of patients with cholera and noncholera diarrhea by bioimpedance analyzer, we studied 30 patients with acute watery diarrhea. Total body water (TBW), intracellular water (ICW), and extracellular water (ECW) of severely dehydrated adult patients were measured with a dual frequency bioimpedance analyzer at different phases of rehydration. Fluid compartments between cholera and noncholera patients were compared. Cholera patients gained more TBW than noncholera patients during recovery. Unlike patients with noncholera diarrhea, the gain in cholera patients was mainly contributed by the ICW (1.5 ± 1.6 vs 3.0 ± 1.2 liters, respectively, $P < 0.01$). It was also observed that the recovery of the ICW compartment in cholera patients occurred rapidly within the first 2 hr after infusion. Differential dynamics of body water compartments in cholera compared to noncholera patients as observed in this study may contribute further to understanding the mechanism of dehydration in diarrheal disease, which might help in improving case management.

KEY WORDS: intracellular water; extracellular water; bioimpedance; cholera; water dynamics.

Cholera is a major cause of acute dehydrating diarrhea. In severe dehydration, intravenous fluid therapy is life-saving. Current methods to assess dehydration clinically in patients with acute watery diarrhea are cumbersome and sometimes inaccurate. Laboratory methods, including hematocrit (Hct), total protein, and/or specific gravity of blood require skilled labor, and are costly and invasive. Bioimpedance analysis (BIA) is a rapid, noninvasive, and inexpensive method previously found to assess human body composition relatively accurately (1). This method has also recently been demonstrated to be suitable for monitoring the hydration status of cholera patients during rehydration (2). The basic principle of BIA is that an imperceptible current, at a safe level, can be conducted through the human body composed of body water containing electrolytes. Body water is further divided into two main subcompartments, extracellular water (ECW) and intracellular water (ICW). It has also been predicted theoretically, that a low frequency current can only be conducted extracellularly whereas a high frequency current can pass through both extra- and intracellular spaces (3). Thus it would be possible to measure total body water (TBW), ECW, and ICW, since TBW = ECW + ICW. Based on these assumptions, several investigators

Manuscript received April 8, 1997; revised manuscript received August 26, 1997; accepted December 3, 1997.

From the International Centre for Diarrheal Disease Research, Bangladesh (ICDDR,B), GPO Box 128, Dhaka 1000, Bangladesh; Department of Pediatrics, Louisiana State University, New Orleans, Louisiana; and Departments of Biomedical Engineering, International Health and Nutrition Sciences, University of Alabama at Birmingham, Alabama 35294.

The study was done at the Clinical Research and Service Centre, ICDDR,B, Dhaka, Bangladesh.

Address for reprint requests: Dr. Iqbal Kabir, Scientist, ICDDR,B, GPO Box 128, Dhaka 1000, Bangladesh.

0163-2116/98/0300-0663$15.00/0

have used dual or multifrequency BIA methods to estimate human body composition (4–6).

Although BIA methods could assess body composition relatively accurately, the accuracy is highly dependent on the homeostasis of body water compartments (7). In this respect, therefore, the use of BIA to estimate body water compartments accurately might be compromised in the dehydrated patients with fluctuating body fluid. However, we hypothesized that changes in the body water compartments can be monitored effectively even if these compartments are perturbed as in dehydrated patients. BIA has been used previously in different disease conditions (8–10). Moreover, we have used BIA to monitor changes in body fluid in the same patients; therefore, we speculate that it would not affect the fluid homeostasis in the same individual. The BIA method was, therefore, used in this study to characterize changes in water compartments of patients with severe acute dehydrating diarrhea.

MATERIALS AND METHODS

Thirty patients (15 male), ages 18–45 years, were recruited from the patients attending the Clinical Research & Service Centre of International Centre for Diarrheal Disease Research, Bangladesh, from mid-1995 to early 1996. On admission, the history of illness was taken and a clinical examination was performed. All patients had acute watery diarrhea (AWD), either due to cholera or not, with severe dehydration as assessed according to the WHO guidelines (11). For the BIA measurement we used a dual-frequency BIA analyzer, which operates at 5 kHz to measure the ECW and at 180 kHz to measure the TBW (constructed at the University of Alabama at Birmingham). It gives value for impedance (Z), and Z is determined by the formula $Z = (R^2 + Xc^2)^{1/2}$ where R is resistance and Xc is reactance. In addition to the Z value, the instrument also gives the volume (in liters) of TBW, ECW, and ICW (by computing TBW − ECW) utilizing the built-in formula of Deurenburg et al (4). Each subject was lying supine with limbs slightly away from the trunk (with clothes on, but no shoes or socks). After cleaning the skin with alcohol, electrocardiographic electrodes were placed on the wrist and ankle on the same side of the body while the intravenous line was placed on the other side of the body. The tetrapolar electrode system of the dual-frequency BIA machine was connected to the electrodes in the following manner. The wrist electrode pair was placed on the third metacarpophalangeal joint in the middle of the dorsal side of the hand and 1 in. proximal to the first electrode, between the styloid process of the radius and ulna. Similarly, the electrode pair for the ankle was placed at the third metatarsophalangeal joint on the dorsal side of the foot and 1 in. above the first electrode, between the medial and lateral malleolus of the ankle. The BIA measurements were made at 0 hr (admission), 2 hr (ie, at partial correction of dehydration), at 6 hr (approximately after full hydration), and at 24 hr (when body fluid compartments were assumed to be stable). All patients were initially managed with intravenous cholera saline (containing Na^+ 133 mmol/liter, K^+ 13 mmol/liter, Cl^- 98 mmol/liter, and acetate 48 mmol/liter of water) 100–120 ml/kg given over 3–4 hr followed by rice-ORS (containing 50 g rice powder boiled for 7 min in 1100 ml of water with 3.5 g NaCl, 2.5 g $NHCO_3$, and 1.5 g KCl) (12) orally to replace any ongoing fluid loss. Cholera was diagnosed immediately by dark-field microscopic examination and treated with an appropriate antibiotic. Cholera infection was confirmed by rectal swab culture. Hct was determined on admission and at 24 hr to examine the adequacy of hydration. Intake and output charts were maintained. Means and standard deviations were calculated and were compared by using Student's t test.

RESULTS

Seventeen cholera (nine men, eight women) and 13 noncholera (six men, seven women) patients were studied. Their age (mean ± SD) was 31.8 ± 9 years. The duration (mean ± SD) of diarrhea before hospitalization in cholera and noncholera patients was 14 ± 9.8 and 19.5 ± 16.5 hr, respectively ($P = 0.26$). Table 1 shows the changes in body weight, body water compartments, and impedance values from 0 to 24 hr. The significant gain in body weight (4.3 kg) and TBW (4.8 liters) over 24 hr as well as the reduction of mean Hct from 52% to 38% indicates that all patients had severe dehydration. ECW and ICW were also affected concordantly. The changes in body weight, body water compartments, and impedance values were further stratified for cholera and noncholera patients (Table 2). Mean changes in TBW and particularly ICW in cholera patients were greater than in noncholera patients 5.6 vs 4.3 liters ($P = 0.11$) and 3.0 vs 1.5 liters ($P = 0.01$), respectively. The changes in ECW compartments in both groups, however, were comparable and consistent with the changes in Hct values. Impedance values both at high and low frequencies were significantly higher at 0 and 24 hr and in female than male patients (Table 3). Impedance values were positively related with Hct values ($P < 0.05$) and inversely related to improvement of hydration status and body weight ($P < 0.05$). Comparison of the changes in ECW and ICW values in cholera and noncholera patients, over time from 0 to 2, 0 to 6, and 0 to 24 hr were also examined (Figure 1). In cholera patients, the ICW was preferentially repleted relative to ECW early during rehydration. Furthermore, compared to noncholera patients, ICW in patients with cholera was repleted faster and earlier during rehydration. Recovery of ICW in the noncholera patients, on the other hand, was initially slow; however, it stabilized after 6 hr, concomitant with changes in the

TABLE 1. BODY COMPARTMENT PARAMETERS OF PATIENTS AT ADMISSION (SEVERE DEHYDRATION) AND 24 HOUR (AFTER REHYDRATION)*

	Cholera (N = 17)			*Noncholera (N = 13)*		
	0 hr	*24 hr*	P	*0 hr*	*24 hr*	P
Age (yr)	30.4 ± 6.8			33.6 ± 11.0		
Height (cm)	156.6 ± 7.5			157.5 ± 9.2		
Body mass index	17.5 ± 2.0			18.6 ± 2.5		
Body weight (kg)	38.7 ± 6.0	43.2 ± 6.7	<0.05	41.8 ± 6.4	46.1 ± 6.9	0.1
TBW (liters)	25.7 ± 3.4	31.1 ± 4.7	<0.001	27.5 ± 3.7	31.8 ± 4.5	<0.02
ICW (liters)	17.0 ± 2.5	19.9 ± 2.8	<0.001	18.2 ± 2.5	19.7 ± 2.8	0.155
ECW (liters)	8.7 ± 1.2	11.2 ± 2.2	<0.001	9.3 ± 1.3	12.1 ± 1.8	<0.001
Hct (%)	51.1 ± 7.0	39.4 ± 7.1	<0.001	50.4 ± 5.5	37.3 ± 4.0	<0.001
ZH (ohms)	789 ± 135	589 ± 98	<0.001	726 ± 132	554 ± 69	0.056
ZL (ohms)	1236 ± 196	857 ± 174	<0.001	1127 ± 171	755 ± 82	<0.001

* ZH, impedance at high frequency; ZL, impedance at low frequency. Values are mean ± SD. Age, height, and body mass index were comparable (*P* value not significant) between cholera and noncholera patients.

ECW compartment. As the distribution of male and female patients in the cholera and noncholera groups were similar and stratified analyses between male and female patients also showed similar results as above, the stratified analyses results are not shown in the text.

TABLE 2. ESTIMATED CHANGES IN BODY WEIGHT AND WATER COMPARTMENTS FROM 0 TO 24 HOURS IN CHOLERA AND NONCHOLERA PATIENTS*

	Cholera (N = 17)	*Noncholera (N = 13)*
Body wt (kg)	4.4 ± 1.3	4.3 ± 1.2
Body wt (%)	11.5 ± 3.2	10.3 ± 2.6
TBW (liters)	5.6 ± 1.8	4.3 ± 2.4
ECW (liters)	2.6 ± 1.4	2.8 ± 1.0
ICW (liters)†	3.0 ± 1.2	1.5 ± 1.6
Hct (%)	14.5 ± 2.2	14.3 ± 2.1
ZH (ohms)	206.8 ± 64.9	171.6 ± 86.6
ZL (ohms)	383.0 ± 134.8	371.2 ± 106.2

* ZH, impedance at high frequency; ZL, impedance at low frequency. Values are mean ± SD.
† $P < 0.01$.

TABLE 3. IMPEDANCE (*Z*) AT 0 AND 24 HOUR*

Impedance (ohms)	*Male (N = 15)*	*Female (N = 15)*
High frequency		
0 hr (a)	677 ± 63	851 ± 135
24 hr (b)	515 ± 36	633 ± 83
Low frequency		
0 hr (c)	1064 ± 102	1319 ± 175
24 hr (d)	760 ± 56	921 ± 133

* Values are mean ± SD. $P < 0.05$ (male vs female, a vs b, and c vs d).

DISCUSSION

The changes in body weight and TBW in our patients were quite comparable, as predicted, since any gain in body weight on rehydration would be expected to be due to the restoration of body water compartments. Packed cell volume or hematocrit, as an index of dehydration and rehydration, also agrees well with the changes in TBW and body weight. Changes in ECW and ICW compartments together are complementary and constitute the total change of TBW. The absolute values of TBW of the study patients as assessed by BIA on admission indicate that this compartment was more than 65% of body weight, which exceeds the normal limit (60%) (13). This is in contrast to what should be expected in dehydrated patients. As mentioned earlier, the mathematical algorithm developed for normal subjects might not be valid for the patients having significant alterations in the body water compartment (7). However, when these parameters were stratified for cholera and noncholera groups, differences were observed that reflect intriguing dynamic behaviors of the water compartments.

The increase in TBW of severely dehydrated patients with cholera was higher than in the severely dehydrated noncholera patients but not significantly different, which may be due to small sample size. There were also no significant differences in the ECW compartment between the two groups and therefore this difference in cholera patients was primarily contributed by the ICW compartment. The changes in the ECW compartments in both the groups were comparable and in agreement with Hct measure-

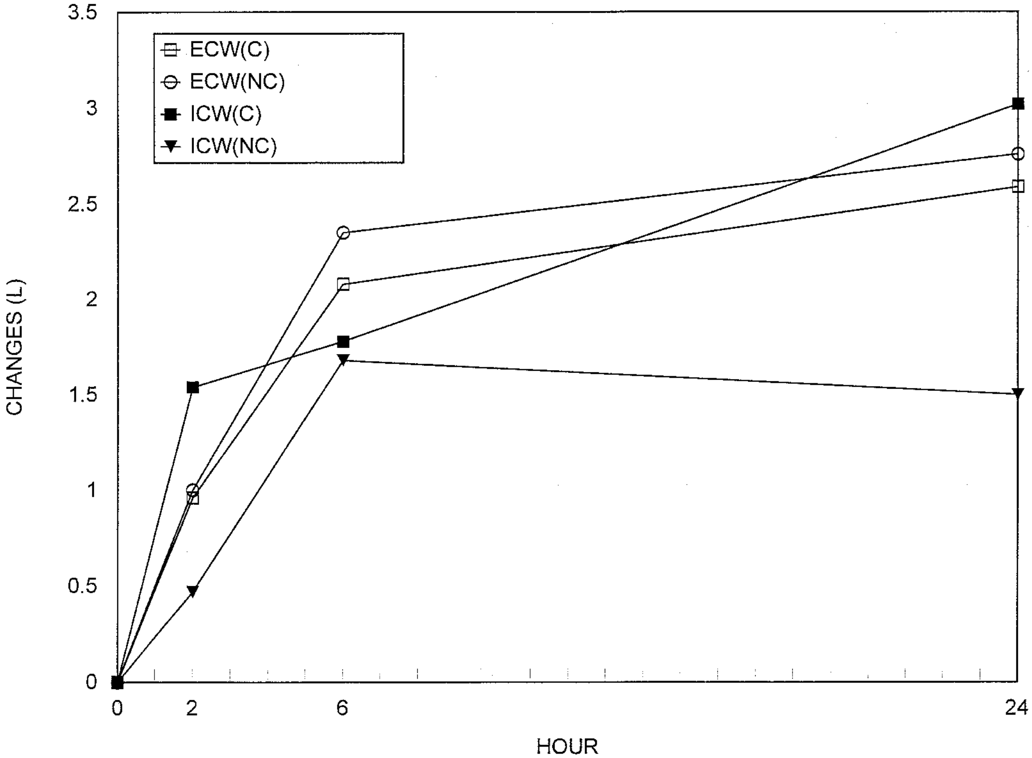

Fig 1. Estimated changes of ECW and ICW compartments in cholera (C) and noncholera (NC) patients.

ments. Changes in Hct indirectly reflect extracellular fluid status, which was affected equally in both cholera and noncholera patients.

The percent change of body weight confirmed that all patients were appropriately categorized as severely dehydrated as assessed initially by following the WHO guidelines (11). However, the differences in the pattern of repletion of ICW and ECW indicate a greater depletion and involvement of the ICW compartment in cholera patients compared to noncholera patients. We believe that this difference might be a reflection of the more rapid fluid loss that typically occurs in cholera, although other mechanisms cannot be excluded. It has been observed that the volume of stool and stool electrolyte concentrations are different in cholera and noncholera diarrhea (14). Although the mechanism of diarrhea in cholera and enterotoxigenic *E. coli* (noncholera) may be similar, ie, cAMP-mediated, the magnitude of fluid loss is much higher in cholera than that in noncholera patients (15). Women have less lean body mass than men and thus less total body water. The higher impedance value observed in women might be because impedance is inversely related to total body water.

The dynamics of body water compartments as described above are, to our knowledge, the first observation to show differential changes of ICW and ECW compartments in patients with cholera and noncholera dehydrating diarrheas as monitored by bioimpedance. BIA is a simple, rapid, and noninvasive method that provides a better assessment of hydration status and a more precise characterization of water compartments, which may further help in understanding the mechanisms of dehydration in diarrheal diseases.

ACKNOWLEDGMENTS

This research was supported by ICDDR,B. The ICDDR,B is supported by agencies and countries which share its concern for the health problems of developing countries.

REFERENCES

1. Lukaski H, Johnson P, Bolonchuk W, Lykken G: Assessment of fat free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr 41:810–817, 1985
2. McDonald J, Chanduvi B, Velarde G, Cama R, Diaz F, Carrillo L, Torre V, Watanabe J, Villarreal J, Ramirez-Ramos A, Mantle R, Gilman R: Bioimpedance monitoring of rehydration in cholera. Lancet 341:1049–1051, 1993
3. Cole K, Cole R: Dispersion and absorption in dielectrics. I. Alternating current characteristics. J Chem Phys 9:341–346, 1941
4. Deurenberg P, Schouten FJM: Loss of total body water and

extracellular water assessed by multi frequency impedance. Eur J Clin Nutr 46:247–255, 1992
5. Segal K, Burastero S, Chun A, Coronel P, Pierson R, Wang J: Estimation of extracellular and total body water by multi frequency bioelectrical impedance measurement. Am J Clin Nutr 54:26–29, 1991
6. Chumlea W, Guo S: Bioelectrical impedance and body composition: Present status and future directions. Nutr Rev 42:123–131, 1994
7. Khaled M, McCutcheon M, Reddy S, Pearman P, Hunter G, Weinsier R: Electrical impedance in assessing human body composition: The BIA method. Am J Clin Nutr 47:789–792, 1988
8. Royall D, Greenberg GR, Allard JP, Baker JP, Harisson JE, Jujeebhoy KN: Critical assessment of body composition measurements in malnourished subjects with Crohn's disease: The role of bioimpedance analysis. Am J Clin Nutr 59:325–350, 1994
9. Zillikens MC, van den Berg JWO, Wilson JHP, Swart GR: Whole-body and segmental bioelectrical-impedance analysis in patients with cirrhosis of the liver: Changes after treatment of ascites. Am J Clin Nutr 55:621–625, 1992
10. Fredrix EWHM, Saris WHM, Socters PB, Wouters EFM, Kester ADM, von Meyenfeldt MF, Westertrep KR: Estimation of body composition by bioelectrical impedance in cancer patients. Eur J Clin Nutr 44:749–752, 1990
11. World Health Organization: Programme for Control of Diarrheal Diseases. A manual for the treatment of diarrhea: for use by physicians and other senior health workers. WHO/CDD/SER/82.2-Rev.2/1990
12. Gore SM, Fontaine O, Pierce NF: Impact of rice-based oral rehydration solution on stool output and duration of diarrhea: Meta-analysis of 13 clinical trials. Br Med J 304:287–292, 1992
13. Pace N, Rathburn E: Studies on body composition. III. The body water and chemically combined nitrogen content in relation to fat content. J Biol Chem 158:685–691, 1945
14. Molla AM, Rahman M, Sarker SA, Sack DA, Molla A: Stool electrolyte content and purging rates in diarrhea caused by rotavirus, enterotoxigenic *E. coli*, and *V. cholerae* in children. J Pediatr 98:835–838, 1981
15. Glass RI. Cholera and non-cholera vibrios. *In* Enteric Infection: Mechanism, Manifestation and Management. MJG Farthing, GT Keusch (eds). New York, Raven Press, 1988, pp 317–325