Bioelectrical Impedance Analysis Estimation of Water Compartments in Elderly Diseased Patients: The Source Study

Patrick Ritz for the Source Study

Centre Hospitalier Universitaire, Angers, France.

**Background.** This study validates, in geriatric patients, bioelectrical impedance analysis (BIA) equations that had been derived to estimate total body water (TBW) and extracellular water (ECW) in healthy elderly subjects.

**Methods.** We performed a multicentric trial in six geriatric wards. We studied 169 patients with varying degrees of hydration: dehydrated, euvoletic, and overhydrated. BIA estimates of TBW and of ECW were compared with the measurement of TBW with 18O dilution and of ECW with bromide (Br) dilution.

**Results.** BIA estimated TBW with a difference of 0.48 ± 2.3 l (mean ± SD) (50 kHz; p = .001) and 0.69 ± 2.2 l (100 kHz; p < .001) compared with 18O dilution. The difference was not affected by the hydration status. Estimates of ECW with BIA were systematically biased compared with Br dilution: 4.6 ± 3.1 l (equation from Segal and colleagues; p < .001) and 3.4 ± 2.9 l (equation from Visser and colleagues; p < .001). We propose a new, cross-validated equation.

**Conclusions.** Body water spaces can be estimated accurately in geriatric patients with BIA.

**FLUID imbalance is common among elderly patients. Dehydration is the most common fluid disorder responsible for increased morbidity and mortality and for substantial hospital expenditure (1). Its prevalence increases with age, from about 1% of hospital admissions in 65-year-old patients to above 5% in patients older than 85 years (2). Many age-related physiological and environmental disturbances are responsible for dehydration (1,3–4). Early diagnosis is sometimes difficult because the classical signs may be absent or misleading in an older patient (1). At the other end of fluid imbalance is overhydration, which can result from the failure of various organs (e.g., heart, kidney, or liver) and from inappropriate fluid replacement therapy (5). As for dehydration, there are numerous reports stressing the serious complications that can result from overhydration, and early diagnosis is also difficult.

Beyond gross fluid imbalance, a progressive cellular dehydration has been shown in critically ill patients (6), whereas between-individual variation in cellular hydration can be quite substantial, even in healthy elderly people (7). For all of these reasons, clinicians require a tool both for a discriminative diagnosis of fluid imbalance and for monitoring changes in water spaces in elderly patients. A quantitative measurement of body water spaces is desirable. Total body water (TBW) increases with body weight and is negatively related to fatness. Therefore, a measured TBW value would be informative about hydration status only if it could be compared with a “standard” value. Time trends in TBW tell about changes in fluid balance. However, a preliminary step in the use of TBW measurements is to check the validity of the estimate. The best probes for water spaces are isotopic tracers of water (2H2O, 3H2O, and 2H18O) for TBW and bromide (Br) for extracellular water (ECW). In many clinical circumstances, however, these methodologies might be impractical. They require expertise and expensive equipment. Furthermore, these dilution techniques impose a delay of 2 to 4 hours for the tracer to equilibrate within the pool before sampling. This delay, plus the necessary time for measurements to be performed, often contradicts the necessity for a swift therapeutic decision. Bioelectrical impedance analysis (BIA) is a quick, safe, noninvasive technique to estimate TBW and ECW that does not require much cooperation from the subject (8). It has been shown that BIA can provide accurate estimates of TBW and ECW in healthy elderly subjects (8–10).

Precisions close to 1 l (i.e., 3.8%) can be obtained for estimates of TBW [8]. This technique is reproducible within subjects over a few hours [mean difference, 0.2 l (8)] and over a period of up to 28 days [the coefficient of variation (CV) is about 3% according to Olde Rikkert and colleagues (11)]. BIA might also reliably depict changes in body water (11–14). Therefore, BIA might be the tool required for the diagnosis and management of fluid imbalance. Apart from the work by Olde Rikkert and colleagues (14) dealing with body fluid changes, no study has attempted to validate BIA in elderly patients with a wide range of hydration status. Therefore, the aim of the present study was to check the validity of equations derived by Vaché and colleagues (8) in healthy elderly subjects and in a large group of elderly patients who were overhydrated, euvoletic, or dehydrated. The comparison between estimates of TBW and ECW with BIA was performed versus “gold standards” (i.e., dilution of H218O and Br).

**METHODS**

**Subjects**

A total of 169 subjects living in six French institutions were recruited. The study was approved by the Auvergne
medical school ethical committee and by the French Ministry of Health. One ward was a step-down unit, and others were long-stay units. All patients aged 60 years and older admitted to these wards were eligible for the study and were included if they had no exclusion criteria and signed written informed consent. Patients entered the hospital for various reasons (e.g., infection, acute organ failure, weight loss, or hydration disorders) and with varying medical conditions (e.g., heart failure, kidney failure, or stroke aftermath). All subjects were in clinically stable condition for at least a week after the start of the treatment. No patient was excluded on the basis of drug treatment. Exclusion criteria were: end of life, patients requiring intensive care (e.g., sepsis, surgery, or acute organ failure), ascites, artificial nutrition, or any limb abnormality preventing BIA measurement. Physical characteristics of the volunteers are given in Table 1. Participants varied in their hydration status, an estimate of which was performed by a senior geriatrician on the basis of the following criteria: Subjects were considered dehydrated if they had a lasting skinfold at the anterior side of the thigh and/or plasma sodium higher than 142 mmol/l, overhydrated if they had edema (ankles, arms, or flanks) and/or plasma sodium lower than 135 mmol/l, and euvoletic in all other cases. Table 2 shows water spaces, plasma sodium concentrations, and osmolarity in the three groups. Wide ranges in plasma sodium (128–146 mmol/l) and in osmolarities (264–338 mmol) could be demonstrated in these patients.

Study Design
The protocol of the study consisted of the measurement of TBW by 18O dilution and of the measurement of ECW by Br dilution, plus the determination of BIA and anthropometrical measurements.

Baseline Samples
After an overnight fast (~12 hours), volunteers gave a plasma and urine sample for natural abundance determinations of 18O enrichments and Br concentrations.

Doses
A weighed amount of 2% 18O-enriched water (~50 g) was given orally to all subjects. A weighed amount of ~20 g potassium bromide syrup (~1 g Br) was given to half of the study subjects. Flasks containing the doses were weighed after the doses were given, and the exact weights of the doses taken were recorded. In the validation experiment on healthy elderly subjects (8), Visser’s and Segal’s equations were accurate. Therefore, we dosed only 84 patients with Br.

Post-Dose Samples
Plasma and urine samples were collected 4 and 5 hours after the dose. In the mean time, the subjects were allowed to have their usual breakfast but were limited to a consumption of 250 ml of water, which is 1 SD for the measurement of TBW with 18O diluted water (8). Plasma and urine samples were immediately frozen and kept at −20°C until analysis.

Anthropometric Measurements
Body weight was measured in light clothing to the nearest 0.1 kg with SECA scales (SECA, Les Mureaux, France). Height was measured (in subjects who could stand, i.e., all but 43 patients) to the nearest 0.2 cm with a height gauge. In all volunteers, the knee-to-heel length was measured to the nearest 0.2 cm with a SECA toise according to the technique described by Chumlea and colleagues (15). Anthropometric measurements were performed during the 5th hour following the dose of tracers.

BIA
BIA measurements were performed with an Analyocor-3 analyzer (Spengler, Cachan, France). All the investigators had been equipped with analyzers from the same series and had attended a course where the complete procedure was taught. Measurements were performed after a rest of at least 30 minutes and during the 5th hour post-dose in a temperature-controlled room. Four surface electrodes (Sentry Silver EKG electrodes; Spengler, Cachan, France) were placed on clean, degreased skin at the limb ends in a standardized manner. The current injecting electrodes were located in the distal end of the third metacarpal bone and of the second metatarsal bone. The current detector electrodes were located between the styloid processes of the radius and ulna and between the two maleoli of the ankle. Measurements were performed both on the left and on the right side of the body. Three frequencies were used 5 kHz, 50 kHz, and 100 kHz, at a current of 400 μAmp. Electronic precision of the instrument is better than 1 Ω, and the response is linear be-

### Table 1. Physical Characteristics of the Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Men (n = 60)</th>
<th>Women (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>79.9 ± 9.3</td>
<td>82.9 ± 7.4*</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>65.9 ± 12.5</td>
<td>58.3 ± 13.6*</td>
</tr>
<tr>
<td>Height, cm</td>
<td>165.9 ± 7.5</td>
<td>152.6 ± 6.7*</td>
</tr>
<tr>
<td>Knee height, cm</td>
<td>52.4 ± 2.9</td>
<td>48.1 ± 2.6*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.9 ± 4.0</td>
<td>24.9 ± 4.8</td>
</tr>
<tr>
<td>TBW, l</td>
<td>34.0 ± 5.5</td>
<td>26.3 ± 4.6*</td>
</tr>
<tr>
<td>ECW, l</td>
<td>19.9 ± 4.3</td>
<td>14.9 ± 2.9*</td>
</tr>
</tbody>
</table>

*Significantly different between men and women.
†Data obtained by 18O dilution.
‡Data are limited to 84 values (47 women and 37 men) and were obtained by bromide dilution.

### Table 2. Hydration Parameters in the Study Groups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dehydrated (n = 44)</th>
<th>Euvolemic (n = 67)</th>
<th>Overhydrated (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBW, l</td>
<td>29.7 ± 6.6</td>
<td>28.6 ± 5.8</td>
<td>29.6 ± 6.3</td>
</tr>
<tr>
<td>ECW, l</td>
<td>17.3 ± 4.6</td>
<td>16.2 ± 4.0</td>
<td>17.7 ± 4.5</td>
</tr>
<tr>
<td>ICW, l</td>
<td>12.2 ± 4.3</td>
<td>13.6 ± 4.3</td>
<td>11.8 ± 3.8</td>
</tr>
<tr>
<td>Na, mmol/l</td>
<td>141.1 ± 3.6*</td>
<td>138.7 ± 1.7*</td>
<td>137.0 ± 4.8*</td>
</tr>
<tr>
<td>Osmolarity, mmol</td>
<td>294.2 ± 10**</td>
<td>296.0 ± 13**</td>
<td>288.4 ± 10.4**</td>
</tr>
</tbody>
</table>

Notes: TBW = total body water; ECW = extracellular water; ICW = intracellular water. See Methods for the description of the hydration categories.
**p < .001; ***p < .01 by ANOVA. Osmolarity was calculated as [2(Na + K) + urea + glycemia].
†Number of patients limited to 84.
tween 100 and 2500 Ω. Reproducibility with Sentry electrodes is better than 2 Ω.

**Analytical Methods**

$^{18}$O enrichments were measured with the CO$_2$-H$_2$O equilibration technique, adapted for use with vacutainers on a continuous-flow gas chromatography-isotope ratio mass spectrometer (μgas, Micromass, Manchester, UK) as already described (8). Plasma Br concentrations were measured by means of high-performance liquid chromatography as described by Miller and Cappon (16), using a diode array detector (Partisil 10 SAX column, Whatman International Ltd., Maidstone, UK). Protein-free plasma samples were obtained after centrifugation using an MPS1 micropartition system (Amicon, Lyon, France).

**Calculations and Statistical Methods**

$^{18}$O dilution spaces were calculated from increases between mean enrichment 4 and 5 hours post-dose and baseline values. TBW was considered 1% smaller than the $^{18}$O dilution space to account for exchanges with nonaqueous compounds (17). ECW was calculated from the mean concentration in plasma Br 4 and 5 hours post-dose, according to Miller and Cappon (16). The equation that gives ECW is

\[ \text{ECW} = 0.90 \times 0.95 \times (\text{Br dose})/[(\text{delta} \text{Br plasma})], \]

where Br dose is the dose given, delta (Br plasma) is the difference between the mean plasma concentration after dose and the baseline concentration. The correction factor 0.95 is for Donnan equilibrium, and 0.90 corrects for the distribution of Br in nonextracellular sites.

TBW was calculated from impedances measured at 50 and 100 kHz with equations derived by Vaché (8):

TBW (l) = \( 2.896 + 0.366 \text{ Ht}^2 / \text{R100} + 0.137 \text{ wt} + 2.485 \text{G} \)

TBW (l) = \( 3.026 + 0.358 \text{ Ht}^2 / \text{R50} + 0.149 \text{ wt} + 2.924 \text{G} \)

ECW was calculated from the impedance measured at 5 kHz with equations derived by Segal and colleagues (18) and Visser and colleagues (9). These equations were used because they were accurate in healthy elderly subjects, with the same BIA analyser and the same tracer method.

\[ \text{ECW (Segal, l)} = -6.1 + 0.284 \text{ Ht}^2 / \text{R5} + 0.112 \text{ wt} \]

\[ \text{ECW (Visser, men, l)} = 4.8 + 0.225 \text{ Ht}^2 / \text{R5} \]

\[ \text{ECW (Visser, women, l)} = 1.7 + 0.2 \text{ Ht}^2 / \text{R5} + 0.057 \text{ wt} \]

In all of these equations, Ht is height in cm, R is impedance, wt is weight in kg, and G is gender (0 for women and 1 for men).

Results are expressed as mean ± SD unless stated otherwise. Comparisons of means were performed by ANOVA or Student’s t test where applicable. Agreement between measurements was assessed with the technique described by Bland and Altman (19). Multiple regression models were calculated with stepwise backward regressions (F to enter = 4; F to exit = 3.96). Statistical computations were performed on a Statview 4.0 statistical package (Abacus Concept, La Jolla, CA). Significance was accepted at the 5% level.

**RESULTS**

**Physical Characteristics**

Physical characteristics for the patients are given in Table 1. Forty-four patients were dehydrated, 58 were overhydrated, and 67 had a normal hydration status.

**Bioelectrical Impedance Analysis**

Impedance did not differ significantly between the right and the left side of the body at current frequencies of 5 kHz, 50 kHz, and 100 kHz (data not shown). Therefore, the impedances measured on both sides were averaged for each individual.

TBW calculated with the equation using impedance at 50 kHz differed from TBW measured by $^{18}$O dilution by 0.48 ± 2.3 l (p = .01). This difference was not affected by the hydration status or by the gender of the patients. It was 0.25 ± 2.4 l in dehydrated patients, 0.42 ± 2.41 l in overhydrated patients, and 0.69 ± 2.2 l in euvolemic patients (ANOVA; F = .47, p = .63).

TBW calculated with the equation using the impedance at 100 kHz differed from TBW measured by $^{18}$O dilution by 0.62 ± 2.4 l (p = .001). This difference was not affected by the hydration status of the patients (0.39 ± 2.5 l in dehydrated patients, 0.57 ± 2.41 l in overhydrated patients, and 0.82 ± 2.4 l in euvolemic patients) (ANOVA: F = .41, p = .66). Figure 1 displays the Bland and Altman plot for TBW measurements ($^{18}$O dilution) and estimates (50 and 100 kHz). For the 126 patients in whom both height and knee height were available, TBW was calculated from the impedance at 50 kHz, and either measured height or height derived from knee height. TBW estimates only differed by 0.21 l (p = .04).

Extracellular water calculated with equations using impedance at 5 kHz differed from ECW measured by Br dilution. The difference was 4.6 ± 3.1 l with Segal and col-
leagues’ (18) equation ($p < .001$) and $3.4 \pm 2.9$ l with Visser and colleagues’ (9) equation ($p < .001$) and was not affected by gender. The subjects having had ECW measured with Br were split into two groups by randomization. A model specific for the first group (Table 3) was set by multiple linear regression of variables that were correlated to ECW in this group. Only $Ht^2/R5$ turned out to be an independent variable. When applied to the second group, this model created no bias (Table 2). The reverse procedure was applied (model established on the second group and applied to the first group) and produced a very similar equation without bias. Therefore, data from the two groups were pooled and subjected to the multiple regression analysis procedure. Only $Ht^2/R5$ came out as a significant and independent variable (Table 3).

**DISCUSSION**

The present study tested, in geriatric patients, the validity of BIA equations that were derived in healthy elderly subjects. The main result of this multicentric trial is that, regardless of the hydration status of the patients, BIA can be used as a bedside technique for estimating TBW.

BIA relies on a very simple principle. Cells are envisaged as floating in a water and electrolyte milieu (TBW) contained in a cylinder (the body). The reciprocal of the impedance opposed to a light alternating current is proportional to TBW (for a current frequency higher than or equal to 50 kHz) or to ECW [for frequencies below 5 kHz (20)]. This impedance then needs to be converted into TBW or ECW by means of equations that are said to be age, disease, and population specific (8).

Very few equations relate to TBW estimates in healthy elderly subjects (8,21,22), and even fewer are pertinent to geriatric patients (14). We chose Vaché and colleagues’ (8) equations because they were acquired with the same bioelectrical impedance analyzer (Analyzedor 3) and because the reference method ($^{18}$O dilution) was the same. $^{18}$O dilution has several advantages over $^3$H dilution to measure TBW (8,23). The net result is that TBW estimates with $^{18}$O are very precise, with a between-day, within-subject CV of 0.7% for repeated measurements (8) and are very accurate.

Because not all BIA users have machines delivering a 100-kHz current, we investigated equations derived for 50 kHz and 100 kHz frequencies. For our group of patients, estimated TBW differed from reference measurements by $0.48$ l (50 kHz) and $0.62$ l (100 kHz). Although these differences are statistically significant (probably as the result of the large number of degrees of freedom) we believe that they are acceptable in clinical practice. The 95% confidence limits were 0.11 to 0.84 l (50 kHz) and 0.24 to 1.00 l (100 kHz). We also consider that height calculated from knee height (15) can be used because the difference it induces in comparison to measured height is minimal (0.2 l). Therefore, BIA can be used as a discriminative tool for TBW measurement. It is also important that this applies to situations with varying degrees of hydration, precisely when clinicians require an estimate of TBW. The present study involved subjects with a mild degree of dehydration. This is because written informed consent was required for participating in the study. Although dehydrated patients are numerous, dehydration impairs cognitive functions and prevents an informed consent. The high prevalence of fluid imbalance makes BIA an attractive tool. Even for those patients in whom the estimated TBW was different from the measured TBW, it could be hypothesized that BIA is a good tool for monitoring changes in fluid balance. Support for this comes from a study by Olde Rikkert and colleagues (11). In their study on healthy elderly subjects, it was shown that over 28 days the within-subject, between-day CV for repeated measurements was 3%, 5 times smaller than the between-subject variation. This means that repeated measurements were within 1 l for those subjects. Furthermore, Olde Rikkert and colleagues (14) showed that the weight and water loss induced by a furosemide administration were correctly monitored by BIA. Individual differences shown in Figure 1 might appear to be large. However, the reproducibility of BIA estimates in the short term (8) and over longer periods [28 days (11)] suggests that a subject with a large residual in Figure 1 might remain so on later assessments. BIA could therefore be useful in monitoring changes in TBW.

In contrast, BIA with published equations leads to systematic biases in estimating ECW when applied to the geriatric patients of the present study. Visser and colleagues’ equations (9), derived from healthy elderly subjects, has proven accurate in our group of healthy subjects (mean difference 0.0 $\pm$ 2.5 l). The same was true for Segal and colleagues’ equation (18), although it was derived from adults (mean difference 0.0 $\pm$ 3.0 l). The bias observed in the present geriatric patients could come from an inaccurate measurement of ECW with Br, from altered electrical properties of cell membranes, or from changes in fluid repartition. It is unlikely that the Br measurements are erroneous. Indeed, the same technique was used for healthy subjects (8), and in the present study, the mean CV for plateau concentration in Br was 1.5% (data not shown). Furthermore, Finn and colleagues (6), in a study of critically ill patients, and Kim and colleagues (24), in a study of AIDS patients, have shown that intracellular penetration of the Br tracer is not changed appreciably. Br distribution is therefore confined to ECW, provided that a 10% correction is made (16). It could also be the case that the repartition between intracellular and extracellular water is altered by age and/or disease. Steen (25) showed that the ratio of ECW to TBW increased with age. If the ex-

<table>
<thead>
<tr>
<th>Model Established on</th>
<th>Equation</th>
<th>$R^2$</th>
<th>SEE</th>
<th>Mean Difference on the Other Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 ($n = 42$)</td>
<td>$2.82 \pm 0.36$ Ht$^2$/R5</td>
<td>.61</td>
<td>2.6</td>
<td>$-0.18 \pm 2.44$ ($p = .70$)</td>
</tr>
<tr>
<td>Group 2 ($n = 42$)</td>
<td>$5.74 \pm 0.27$ Ht$^2$/R5</td>
<td>.43</td>
<td>2.4</td>
<td>$0.4 \pm 2.69$ ($p = .44$)</td>
</tr>
<tr>
<td>Group 1 + Group 2 ($n = 84$)</td>
<td>$3.66 \pm 0.33$ Ht$^2$/R5</td>
<td>.55</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>
tracellular fluid expansion was mostly in the limbs, impedance at 5 kHz would be underestimated and ECW artificially increased. Furthermore, limbs represent the largest component of the impedance of the body.

ECW was not correlated to plasma sodium, osmolality, or classical protein markers of malnutrition (data not shown). We have derived an equation to calculate ECW in geriatric patients. This equation remains to be evaluated in other diseased patients.

In conclusion, BIA with specific equations for elderly subjects could be used as a bed-site tool for discriminative diagnosis and for monitoring changes in fluid balance in geriatric patients. This validity applies to TBW across the range of hydration disorders.

Acknowledgments
This work was supported by the Perrier Vittel Water Institute.

The Source Study is a French multicentric study coordinated by Dr. P. Ritz (Human Nutrition Research Centre-Auvergne). Investigators were (by alphabetical order): Dr. S. Acher (Paris, Bichat), Pr. B. Beaufrière (Clermont-Ferrand), F. Blondé-Cynober (Paris, Hôtel-Dieu), Dr. A. Boulier (Paris, Bichat), Dr. F. Bouthier, Dr. F. Bouthier-Quintard (Limoges), Pr. T. Constans, Dr. V. Dardaine (Tours), Dr. J.C. Desport (Limoges), Dr. A. Ghisolfi-Marque (Toulouse), Dr. R. Hermet (Clermont-Ferrand), Dr. C. Lambert (Paris, E. Roux), Pr. B. Vellas (Toulouse), Dr. J.P. Vincent (Paris, E. Roux), and Dr. M.J. Arnaud (Perrier Vittel Water Institute).

We thank Line Godiveau for secretarial assistance and Miriam Ryan for correcting the English.

Address correspondence to Patrick Ritz, MD, PhD, Service de Médecine B, Centre Hospitalier Universitaire, F-49033 ANGERS CEDEX 01, France. E-mail: patrick.ritz@wanadoo.fr

References

Received June 16, 2000
Accepted September 20, 2000
Decision Editor: John E. Morley, MB, BCH