Validation of Multi-Frequency Bioelectrical Impedance Analysis in Detecting Changes in Fluid Balance of Geriatric Patients

Marcel G.M. Olde Rikkert, MD, * Paul Deurenberg, PhD, † René W.M.M. Jansen, MD, PhD, * Martin A. van't Hof, PhD, ‡ and Willibrord H.L. Hoefnagels, MD, PhD *

OBJECTIVES: Multi-Frequency Bioelectrical Impedance Analysis (MFBIA) is a quick, simple, and inexpensive method to assess body fluid compartments. This study aimed at determining the validity of MFBIA in detecting clinically relevant changes of fluid balance in geriatric patients.

DESIGN: A prospective, observational study.

SETTING: The 22-bed Geriatric Department of the University Hospital Nijmegen.

PARTICIPANTS: Hospitalized patients were eligible if they did not have a pacemaker, were not suffering from terminal illnesses, and did not have psychogeriatric diseases likely to interfere with capacity to consent or comply. During a 16-months period, 218 patients were admitted, of whom 78 patients were eligible and 53 consented to participate.

MEASUREMENTS: Each subject's fluid balance was diagnosed twice a week as dehydrated, overhydrated, or euvoletic, based on standardized physical examination, laboratory tests, and weight evaluation. Changes in fluid balance were quantified by measuring total body water (TBW) and extracellular fluid (ECF) applying deuterium- and bromide-dilution techniques. Impedance at 1, 5, 50, and 100 kHz and body weight were measured daily. Sensitivity and Guyatt's responsiveness indexes of MFBIA in detecting dehydration and overhydration were determined.

RESULTS: In total, 1071 MFBIA measurements were performed, during which 14 transitions from dehydration to euvoletic and 13 transitions from overhydration to euvoletic were monitored. Rehydration of dehydrated patients caused an increase in TBW and ECF of 3.4 ± 1.8 L and 1.9 ± 1.9 L, respectively, which resulted in significant decreases in impedance of 133 ± 67 Ω at 1 kHz and 93 ± 61 Ω at 100 kHz (P = .001). Treatment of overhydrated patients caused a TBW and ECF loss of 3.8 ± 4.2 L and 3.1 ± 3.8 L, respectively, which resulted in significant increases in impedance of 104 ± 72 Ω at 1 kHz and 81 ± 68 Ω at 100 kHz (P < .001). Sensitivity of a single MFBIA in diagnosing dehydration and overhydration was 14% and 17%, respectively. Responsiveness indexes of weighing and MFBIA for dehydration and overhydration were similar at all frequencies and greater than one.

CONCLUSION: The sensitivity of a single impedance measurement in detecting dehydration and overhydration was low. However, responsiveness of serial measurements to intra-individual changes in fluid balance was good. Therefore, this noninvasive technique may be used in clinical practice to improve monitoring fluid balance in geriatric patients, especially when daily weighing is difficult. J Am Geriatr Soc 45:1345-1351, 1997.

The evaluation of fluid balance in older patients is a major challenge in geriatric medicine. First, because of the instability of fluid balance in frail older patients, overhydration and dehydration are very common problems in geriatric practice. Second, it is very difficult to make a reliable assessment of a patient's fluid balance, especially in mild and moderate disturbances of fluid balance. It has been shown that physical examination is not very sensitive in recognizing early stages of dehydration. From the laboratory perspective, plasma osmolality, serum sodium concentration, and blood urea nitrogen/creatinine ratios are used most frequently to assess dehydration. However, high normal or elevated serum osmolality may be present in geriatric patients without dehydration. Similarly, early stages of overhydration caused by congestive heart failure are difficult to diagnose. Therefore, an accurate and noninvasive diagnostic instrument to assess fluid balance is greatly needed.

Bioelectrical impedance analysis has recently become a popular method of assessing body composition because it is a quick, safe, and noninvasive technique that requires little help from the patient. It has been shown that the resistance or impedance to a weak electrical current at a frequency of 50 kHz is inversely proportional to the amount of total body water and the lean body mass. Multi-Frequency Bioelectrical Impedance Analysis (MFBIA) instruments have been developed because low and high frequency measurements may distinguish between ExtraCellular Fluid (ECF) and Total Body Water (TBW). This can be explained by the fact that...
the alternating current is unable to penetrate the cell membrane at low frequencies because of the capacitive properties of the membrane. At present, the validity of MFBIA as a tool in measuring body composition has been established in extensive epidemiological studies showing that fat free mass, ECF, and TBW in healthy older populations can be estimated adequately with MFBIA.11-13

In the diagnosis and treatment of fluid balance, MFBIA can be used as a discriminative or as an evaluative measurement of disturbances of fluid balance. As a discriminative tool, MFBIA needs to provide reliable data about the actual hydration state of unknown patients. However, even in euvolemic older subjects, the individual errors in estimating ECF and TBW by means of population-based regression equations using impedance and height as independent variables are too large to be useful in clinical practice. Furthermore, prediction formulas determined in healthy older populations cannot be applied to patients with disturbances in water and/or electrolyte metabolism. Moreover, there is probably a large between-subjects variability in euvolemic fluid volumes in older subjects. Therefore, the first question to be asked is whether a single MFBIA, judged by means of population-based reference values for euvolemia, is useful as a discriminative assessment of fluid balance in geriatric patients.

In a previous study, we showed that within-subject variability of MFBIA was small in very healthy older subjects with stable fluid balance and that the responsiveness of MFBIA to 9% decline in ECF was excellent. Therefore, we examined whether MFBIA can be used in detecting changes of fluid balance in individual geriatric patients. Apart from changes in body fluid compartments, MFBIA is influenced by changes in body temperature, lean body mass, hematocrit, and serum electrolyte concentrations as well. Such changes occur frequently in geriatric patients. To assess the usefulness of MFBIA in monitoring fluid balance in geriatric patients, we tested whether serial MFBIA correlates well with changes in weight and body fluid compartments in patients who are treated for fluid balance disturbances. Finally, we studied whether MFBIA is sufficiently responsive to changes in fluid balance, compared with the within-subject variability in subjects with a stable fluid balance, to be useful in monitoring fluid balance.

METHODS

Subject Selection

This study was part of a larger nontherapeutic research project aimed at the validation of diagnostic measures in monitoring fluid balance in geriatric patients. The research protocol for this project was approved by the local Committee on Human Experimentation. Only subjects judged as capable of giving written informed consent were allowed to be included in this nontherapeutic study (Clinical Dementia Rating scale ≤ 1). Subjects were selected from the 22-bed Department of Geriatric Medicine of the University Hospital Nijmegen during the period September 1, 1994, to December 31, 1995. To be eligible for this study, subjects did not have a pacemaker, were not terminally ill, and did not have psychogeriatric diseases likely to interfere with compliance and capacity to consent. Patients (n = 218) were screened for eligibility during the first days of admission. Written informed consent was obtained from 53 (68%) of the 78 eligible subjects. All subjects were characterized by measures of independence in activities of daily living (Barthel-index), mobility (Tinetti Balance and Gait Evaluation-score), life satisfaction (Philadelphia Geriatric Center Morale Scale), and cognition (Mini-Mental State Examination).

Fluid Balance Evaluation

During hospitalization each patient's fluid balance was assessed twice a week by two geriatricians who were unaware of the MFBIA results. Each clinical assessment was based on standardized physical examination, weight measurement, laboratory tests (hematocrit, serum sodium, urea, and creatinine), relevant data from medical history, and nursing observations. Physical examination consisted of determining the so-called Boston heart failure score and the assessment of those indicators of dehydration that have proved to correlate with dehydration regardless of age: tongue dryness, longitudinal tongue furrows, dryness of the mucous membranes of the mouth, upper body muscle weakness, confusion, sunkenness of eyes, and axillary moisture. By this rigorous clinical assessment, patients were judged twice a week as dehydrated, overhydrated, or euvolemic. After monitoring the effects of therapy, each assessment was reconsidered. Dehydration and overhydration were defined as conditions characterized by a clinically significant shortage or overload of TBW that necessitated therapy.

Body composition analysis (BCA) was performed twice in each patient using deuteriumoxide- and potassium bromide-dilution techniques to quantify clinically relevant changes in TBW and ECF. First BCA was carried out 1 day after obtaining informed consent. BCA was repeated each time a patient's fluid balance changed from euvolemia to dehydration or overhydration, or vice versa. In patients without changes in fluid balance during the entire admission period, BCA was carried out for the second time just before discharge from the hospital.

BCA consisted of administering a cocktail of 10.0 g deuterium oxide and 900 mg potassium bromide orally before MFBIA measurements. After 3.5 hours dilution time, a venous blood sample was drawn. After sublimation of the plasma, the deuterium concentration was determined in the sublimate by infrared spectroscopy analysis. TBW was calculated from the given dose and the tracer concentration determined in plasma using a correction of 5% for non-aqueous dilution. Bromide in plasma was determined after ultra-filtration by high pressure liquid chromatography. A correction of 5% was used for the Donnan effect and a correction of 10% for non-extracellular dilution. Analytical measurement errors in bromide and deuterium dilution methods, as measured by within-run and between-run variability in two pairs of identical blood samples, were 2.2% and 2.5%, respectively. Validity of these dilution methods in measuring body fluid compartments is similar to that of other dilution methods.

Impedance and Weight Measurements

MFBIA and weight measurements were performed daily (provided that this did not interfere with diagnostic or therapeutic procedures). All measurements were performed in the morning, just after awakening, while the patients were still lying in bed. Four-electrode MFBIA was performed on the nondominant side, following the methodology for total body measurements. Impedance was measured at four frequen
The study sample of 53 patients showed eight different patterns in the order of disturbances of fluid balance during the observation period (Table 1). The sample consisted of 17 men and 36 women with a mean age of 80.1 (5.6) years. In total, 26 patients suffered from a disturbance of fluid balance, which was frequently caused by more than one factor (Table 2). Two patients suffered from iatrogenic dehydration and overhydration, caused by an overshoot of diuretic therapy and intravenous rehydration, respectively. Overall, ADL performance, mobility, morale, and cognition in the group were in the 95% reference range of MFBIA in euvolemic patients. Sensitivity of a single MFBIA judged by comparing it with the reference range of MFBIA in euvolemic patients was tested with paired t-tests. Pearson's correlation coefficients were calculated to relate changes in impedance to changes in body fluid compartments and weight. The usefulness of MFBIA as a discriminative instrument was analyzed by calculating the sensitivity of a single MFBIA judged by comparing it with the 95% reference range of MFBIA in euvolemic patients. Significance of changes in weight, TBW, ECF, and impedance values were tested with paired t-tests. Pearson's correlation coefficients were calculated to relate changes in impedance to changes in body fluid compartments and weight. The usefulness of MFBIA as an evaluative instrument for fluid balance was determined by calculating Guyatt's responsiveness index (RI) for MFBIA at all four frequencies. RI is defined as the clinically relevant change (Δ) relative to the standard deviation of changes among stable subjects. This was calculated in analysis of variance examining repeated test observations, in which the variability in within-subject changes is represented by the square root of twice the mean square error (MSE). An RI greater than one means that clinically relevant changes are larger than the noise-level. The RI of MFBIA was compared with the responsiveness for changes in body weight.

All episodes of dehydration and overhydration necessitated therapeutic adjustments. Therefore, the differences between the first observation in case of dehydration or overhydration and the mean of a subject's observations in the state of euvoolemia were considered to be clinically relevant changes. The within-subject variability was calculated by analysis of variance as the standard deviation (SD) of the observations during euvoolemia, pooled over all patients. The clinical relevant changes and within-subject SD were calculated both absolutely (in Ohm, kg) and relatively to the euvolemic level as coefficients of variation (CV in %). An RI was calculated for each clinically relevant change in fluid balance using individual changes in MFBIA and weight and overall within-subject SD. For the entire group, mean RIs in detecting dehydration and overhydration were calculated for MFBIA and weight. Significance of the differences between RIs for the subsequent four frequencies and for daily weighing were tested by repeated measures analysis of variance.

RESULTS

Participation

The study sample of 53 patients showed eight different patterns in the order of disturbances of fluid balance during...
overhydration, and 71 measurements had to be excluded because fluid balance could not be assessed. The individual number of days during which MFBIA was performed ranged from 4 to 66. Individual means of MFBIA in euvolemic patients (Table 1: Pattern: A) showed a between-subject variability of 12 to 13%. An euvolemic reference range was constructed as the overall mean impedance plus or minus twice the between-subjects SD of the euvolemic patients (Figure 1). The sensitivities of a single 100-kHz MFBIA in detecting dehydration and overhydration, when compared with this reference range, were 14% and 17%, respectively. All frequencies proved to be equally insensitive.

**Serial MFBIA Versus Changes in Body Fluid Compartments and Weight**

At all frequencies absolute changes in MFBIA correlated with changes in TBW and ECF caused by the diuretic treatment of overhydration (Table 3). The increases of TBW, ECF or weight during treatment of dehydration did not correlate significantly with increases in MFBIA.

**Responsiveness of MFBIA and Weighing**

The numerator of the Responsiveness Index is determined by the changes of MFBIA measured during clinically relevant changes in fluid balance. These changes were variable, but overall the individual increases in dehydration and decreases in overhydration were highly significant at all frequencies (Table 4). Initial impedance values in dehydration were outside the individual euvolemic range at all frequencies (Figure 2). In the case of overhydration, only two patients had values inside the individual euvolemic impedance ranges (Figure 3).

Responsiveness Indexes were calculated based on these above-mentioned changes in weight and MFBIA and the within-subject variability of the euvolemic episodes in the same subjects (n = 25; Table 1: B-G) as the denominator. Responsiveness indexes for dehydration and overhydration were greater than 1, and there were no significant differences between RIs at the four frequencies (P = .475). RIs for overhydration and dehydration did not differ significantly (P = .200). Initial dehydration weight was 3.0 ± 1.9 kg lower than euvolemic weight (P < .001). Initial overhydration weight was 3.7 ± 4.0 kg higher than euvolemic weight (P < .001). The responsiveness index of weight changes in detecting dehydration and overhydration, which were 2.9 ± 1.9 and 3.7 ± 4.1, respectively, did not differ significantly from the RIs of MFBIA (P = .489).

**DISCUSSION**

This study demonstrates that changes in serial impedance measurements in geriatric patients during clinically relevant changes in fluid balance are large enough to be distinguished from within-subject variability in MFBIA during euvolemia. However, detection of dehydration or overhydration based on a single MFBIA was not possible. Responsiveness of MFBIA was similar at all frequencies. Therefore,
Table 4. Mean Differences (Δ) Between Initial Total Body Impedance (Z) During Dehydration and Overhydration Episodes and the Responsiveness Indexes (RI) of MFBIA for These Disturbances of Fluid Balance (means ± SD)

<table>
<thead>
<tr>
<th>Frequency (kHz)</th>
<th>Δ_{dehydr-euvol} (Ω; n = 14)</th>
<th>P*</th>
<th>Δ_{overhydr-euvol} (Ω; n = 13)</th>
<th>P*</th>
<th>RI_{dehydr-euvol} (Ω; n = 14)</th>
<th>RI_{overhydr-euvol} (Ω; n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>133 ± 67</td>
<td>&lt;.001</td>
<td>-104 ± 72</td>
<td>&lt;.001</td>
<td>2.6 ± 1.8</td>
<td>2.0 ± 1.3</td>
</tr>
<tr>
<td>5</td>
<td>123 ± 75</td>
<td>&lt;.001</td>
<td>-97 ± 71</td>
<td>&lt;.001</td>
<td>2.6 ± 2.3</td>
<td>2.1 ± 1.4</td>
</tr>
<tr>
<td>50</td>
<td>113 ± 75</td>
<td>.003</td>
<td>-85 ± 70</td>
<td>.001</td>
<td>2.9 ± 2.6</td>
<td>2.1 ± 1.7</td>
</tr>
<tr>
<td>100</td>
<td>93 ± 63</td>
<td>&lt;.001</td>
<td>-81 ± 68</td>
<td>.001</td>
<td>2.4 ± 2.1</td>
<td>2.1 ± 1.7</td>
</tr>
</tbody>
</table>

* By paired t tests.

Figure 2. Means and ranges for repeated impedance measurements at 100 kHz during euvolemic condition in 14 geriatric patients and their initial impedance values in dehydrated condition (*).

Figure 3. Means and ranges for repeated impedance measurements at 100 kHz during euvolemic condition in 13 geriatric patients and their initial impedance values in overhydrated condition (+).

Single frequency impedance analysis can be a valuable instrument in monitoring fluid balance in geriatric patients because it is sensitive to clinically relevant changes, within-subject variability in stable fluid balance is low, and the measurements are easy to perform.

Body Composition Analysis

Body composition analysis was used to characterize the subjects and the changes in their fluid balance. TBW of euvolemic geriatric patients was 52.3(7.3)% of their body weight. This is in agreement with the general decline of TBW with age. The within-subject variability found in TBW (6.0%) and ECF (7.6%) was caused partly by analytical errors in the measurement of body water compartments by bromide- and deuterium-dilution. However, variability could also be attributable to nonanalytical errors caused by spilling some drops of the tracer doses and biological within-subject variability in fluid balance. Tremor, dependency in ADL, and swallowing difficulties made a complete oral intake of the tracer doses difficult for most geriatric patients. Therefore, true within-subject variability in body composition for a period of nearly 1 month appeared to be rather small in these patients. To our knowledge, there are no other data to estimate this biological variability. The clinical assessment of fluid balance in this study is quantified by body composition analysis. Results of the two BCAs in dehydrated and overhydrated subjects differed significantly, which confirmed the clinical assessments of fluid balance.

Impedance Measurements

In this study we have chosen to analyze the observed changes in repeated impedance measurements of individual patients without translating measurements expressed in Ohms to estimates of TBW or ECF. First, the prediction formulas developed in older populations, based on height, sex, and total body impedance, are validated only in healthy older subjects. Standard errors of the estimates, even in these healthy older individuals, reached 8.5% for TBW and 12.3% for ECF. By definition, the chance that errors are even larger in individual cases is 31.7%. Moreover, these prediction errors will be substantially larger if formulas are applied in patients with deviations from the normal distribution of body water in extra- and intracellular space and changes in electrolyte concentrations. Hence, from a clinical point of view these prediction formulas are not valuable at all. Depending on the specific causes of changes in total body water, other clinical studies have indeed demonstrated that predicted changes were systematically too small or too large.

Single impedance measurements proved to be of little help in the discriminative diagnosis of dehydration and overhydration. Considerable between-subject variability in the euvolemic size of body fluid compartments, in body fluid composition, and in body build probably caused the wide euvolemic reference ranges. MFBIA correlated well with changes in weight and body fluid compartments in patients going from overhydration to euvoeemia. However, MFBIA did not correlate with these changes in patients going from dehydration to euvoeemia. This provides even more evidence why the MFBIA cannot accurately quantify the magnitudes of fluid volumes. Moreover, no single frequency was superior...
in tracking changes in fluid balance over time. The observed changes in impedances during transitions from disturbed fluid balance to euvalemia may be influenced by the frequent occurrence of hypo-osmotic dehydration and leg edema in overhydration. Seven of the 14 episodes of dehydration were characterized by hyponatremia, with a minimum sodium concentration of 118 mmol/L. The observed loss of electrolytes was caused by diuretics, diarrhea, vomiting, and salt-losing nephritis. During rehydration serum sodium concentration gradually normalized. This implies that both the amount of conducting body fluids, as well as their conductivity, increased. The effect of increasing conductivity on net total body impedance may be substantial because both variables are related linearly. The expected correlation of changes in impedance after rehydration with changes in TBW and fluid balance to euvolemia may be influenced by the frequent tracking changes in fluid balance over time. The observed within-subject variability in MFBIA of 4 to 5% in euvolemic subjects of this study is greater than the 2,3 and 2.7% day-to-day variability of 50-kHz impedances found in healthy older subjects. In younger subjects, day-to-day variability ranged from 8.7% at 1 kHz to 2.0% at 100 kHz, and week-to-week variability ranged from 6.7% at 1 kHz to 2.4% at 100 kHz. However, these latter studies are less comparable because we used better electrodes with larger surface areas (± 4 cm²). Day-to-day variability can result from biological variability and analytical errors. Analytical errors and biological variability in body fluid compartments during euvalemia proved to be small in this study. However, the day-to-day changes in MFBIA may also be (partly) caused by changes in body or skin temperature, in hematocrit, and in serum electrolyte concentrations. Hence, the larger within-subject variability may be explained by intercurrent illnesses not related directly to fluid balance but still influencing the conductivity of the body. In all euvolemic episodes studied, there were eight episodes of fever (maximum temperature 39°C), six episodes of anemia (minimum hematocrit 0.26 L/L), and five episodes of hyponatremia (minimum sodium concentration 132 mmol/L). It has been demonstrated that fever and anemia lower body impedance and that hyponatremia raises it. Because of the observed comorbidity, the true day-to-day variability in MFBIA could not be determined.

In summary, the changes in MFBIA measured in geriatric patients with a high rate of comorbidity and their within-subject variability resulted in an acceptable responsiveness for dehydration as well as overhydration (Rs all >1). Responsiveness to minimal relevant changes in fluid balance could not be determined in all patients although this validation procedure has been recommended by Guyatt. We found an overall responsiveness in detecting a loss or increase of 11% of TBW and 10 to 18% of ECF. However, these relatively large changes may well be the minimally detectable changes and may reflect the difficult clinical assessment of fluid balance in older people. Overhydration, merely resulting from changes in ECF, and dehydration, in which more intracellular water was lost, did not result in a different frequency with the best responsiveness. Therefore, our data do not provide good evidence that MFBIA can detect changes in the distribution or movement of fluid between extracellular and intracellular spaces.

Limitations of this study

Only 25% of the total number of patients admitted during this study period could be included. The presence of a moderate or severe degree of dementia was the main reason for exclusion, and it seems unlikely that this is related to the variables measured in this study. Therefore, the external validity of this study was probably not jeopardized by the high exclusion rate.

Body composition analysis resulted in very valuable information in this study, but it was not completely independent of the clinical assessments. Dehydration or overhydration were defined in this study as disturbances of fluid balance necessitating therapy adjustments. These adjustments caused changes in body composition, which were measured by BCA. Moreover, the retrospective evaluation of changes in weight and subject's symptoms after therapy adjustments, the most sensitive indicator of fluid balance, was taken into account in the final conclusions on the subject's fluid balance. Hence, changes measured in BCA during transitions in fluid balance depended indirectly on clinical assessment of fluid balance.

CONCLUSIONS

The responsiveness of bioelectrical impedance analysis in detecting a heterogeneous group of dehydration and overhydration episodes in geriatric patients was good enough to warrant application in clinical practice. However, our data do not support the suggestion that MFBIA is superior to the conventional single frequency (50 kHz) impedance analyzers in monitoring fluid balance in geriatric patients. The responsiveness of impedance analysis was similar to daily weighing, which was performed under strict standardization. Therefore, repeated impedance measurements might improve monitoring fluid balance, especially when daily unclothed weighing is hard to perform, which is the case in many geriatric patients. It might be cost-effective to replace the cumbersome weighing procedure partly with the nonexpensive and simple MFBIA. In monitoring fluid balance of individual patients by serial MFBIA, subject-specific reference ranges should be used. The day-to-day within-subject variability of 5% found in this study and a patient's euvolemic mean impedance can be used to establish such reference ranges. As was found previously for repeated laboratory test results, this study demonstrates for MFBIA that indices of dehydration and overhydration are highly variable among geriatric patients but stable over time. Future studies are needed to show whether monitoring fluid balance by MFBIA can improve clinical diagnoses of earlier stages of dehydration and overhydration.

ACKNOWLEDGMENTS

The authors would like to thank F.J.M. Schouten of the Department of Human Nutrition of the Wageningen Agricultural University for measuring the plasma concentrations of deuterium and bromide. The authors thank the staff of the Department of Geriatric Medicine of the University Hospital of Nijmegen for their help with this study.
REFERENCES