Multifrequency bioelectrical impedance estimates the distribution of body water

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Cha, Kichul, Glenn M. Chertow, Jorge Gonzalez, J. Michael Lazarus, and Douglas W. Wilmore. Multifrequency bioelectrical impedance estimates the distribution of body water. *J. Appl. Physiol.* 79(4): 1316–1319, 1995.—Multifrequency bioelectrical impedance analysis was used to estimate the ratio of extracellular water (ECW) to total body water in subjects with end-stage renal disease. The body's resistance was measured at frequencies ranging from 1 kHz to 1 MHz. The impedance index (height^2/resistance) determined at low frequency (5 kHz) correlated most closely with ECW ($r = 0.886$) using sodium bromide dilution as the standard of comparison. In contrast, the ratio of height squared to resistance determined at high frequency (500 kHz) correlated most closely with total body water ($r = 0.974$) using deuterium oxide dilution as the standard of comparison. The ratio of resistance at 500 kHz to resistance at 5 kHz was directly correlated ($r = 0.767$) with the ratio of ECW to total body water. Multifrequency bioelectrical impedance analysis may assist in the evaluation of body water distribution in end-stage renal disease and other clinical disorders of fluid volume and/or distribution.

sodium bromide; deuterium oxide; end-stage renal disease; correlation

BIOELECTRICAL IMPEDANCE ANALYSIS (BIA) is a widely studied and valid method of body composition analysis (11–13, 15, 16). BIA is based on the bioelectrical principle of impedance, the vector sum of resistance and reactance. Resistance (R) is the opposition to electrical current related to the length and diameter of a cylinder. The human body resembles a set of serially connected cylinders (e.g., arms, legs, and trunk) with known height and relatively constant diameter. If length and diameter are known, R reflects the volume of the cylinders and the composition of their fluids that carry an electrical charge. Reactance reflects the component of impedance due to the presence of capacitive elements, such as cell membranes.

To utilize this technique, electrocardiograph (ECG)-like surface electrodes are placed on the skin, through which electrical connections are created between the body and an impedance meter. The meter determines the body's R to an imperceptible alternating current passed through the body by measuring the voltage drop between the wrist and ankle. At a given frequency (typically 50 kHz), the measured R is a function of the length and cross-sectional area of conductive mass within the body. The volume of conductive mass can be predicted as a function of the impedance index (ht^2/R) (11–13, 15, 16).

Multifrequency BIA (MFBIA) operates on the principle that the body's R is dependent on the frequency of the alternating current applied. Total body water (TBW) is distributed between the intracellular (ICW) and extracellular water (ECW) spaces and is separated by cell membranes. Cell membranes separating these compartments act as capacitors that insulate the ICW at low frequencies so that predominantly ECW is measured. At higher frequencies, however, the membranes are permeable to the current so that ICW and ECW (TBW) are measured.

Estimates of body water distribution by MFBIA have been shown to correlate with fluid compartments in normal animals (8) and in healthy human adults (19). MFBIA has not been previously employed in body composition analyses in humans with acute or chronic illness or in individuals with potentially variable hydration status. We therefore performed MFBIA in 28 chronic hemodialysis patients, a group in whom abnormal states of body water distribution and tissue hydration are common and of paramount clinical importance.

METHODOLOGY

Principles. Assuming the body is a cylindrical conductor with a uniform cross-sectional area, the R of the body is a function of the resistivity (ρ), the length (L), and the cross-sectional area of the conductor (A)

$$R = \rho \times (L/A)$$

Multiplying the numerator and denominator by L yields

$$R = \rho \times (L \times L)/(A \times L)$$

$A \times L$ is the volume of the conductor (V). Rearranging the equation yields

$$V = \rho \times (L^2/R)$$

When R at low frequency (R_{low}) is included in the above equation, V approximates ECW; when R at high frequency (R_{high}) is included, V approximates TBW. Because the specific resistivity is different between ECW and TBW (ρ_1 and ρ_2, respectively), as expressed

$$ECW = \rho_1 \times (L^2/R_{low})$$

$$TBW = \rho_2 \times (L^2/R_{high})$$

The ratio ECW/TBW can be expressed as the ratio of two equations above

$$ECW/TBW = \rho_1 \times (L^2/R_{low})/\rho_2 \times (L^2/R_{high})$$

$$= (\rho_1 \times R_{high})/(\rho_2 \times R_{low})$$

Assuming that ρ_1 and ρ_2 are constant

$$ECW/TBW \propto R_{high}/R_{low}$$

Therefore, the water compartment ratio can be expressed as a function of the ratio of R_{low} to R_{high} only, excluding the length of the conductor.

Study subjects. Twenty-eight patients with end-stage renal disease (ESRD) on chronic hemodialysis were studied; these individuals were part of a larger study examining the role of single frequency BIA in nutritional assessment (6). Individuals aged below 35 or above 75 yr, amputees, and individuals hospitalized within 60 days for a nonvascular access complication were ineligible. Efforts were made to sample a broad cross-section with regard to age, sex, primary renal diagnosis, diabetic status, and body habitus. Each participant was evaluated on a nondialysis Thursday or Friday at the outpatient Clinical Research Center (CRC) at the Brigham and Women's Hospital. The study protocol was approved by the Human Research Committee, and each participant gave written informed consent.

D_2O and NaBr dilution. The D_2O was pyrogen free 99.9% pure (Cambridge Isotope Laboratory, Woburn, MA). A 3% solution of NaBr was prepared the day before the CRC evaluation by a research pharmacist using NaBr powder (99.6% pure NaBr, Spectrum, Gardena, CA) and standard cold sterilization techniques (Millex-GS 0.22-mm filter, Millipore, Bedford, MA). Venous blood samples were obtained to determine background concentrations of D_2O and NaBr. D_2O (9 ml) and NaBr (50 ml) were then injected through an intravenous line. Four hours after the injection, venous blood samples were drawn from distinct sites to determine the concentrations of D_2O and NaBr at equilibrium. The participants were instructed to refrain from oral intake during the equilibrium period.

Whole blood samples were centrifuged at 3,000 rpm for 15 min, and the plasma was stored in sealed plastic tubes at $-20°C$ until analysis. Concentrations of D_2O were determined by using mass spectroscopy (model 3-60, Nuclide, Bellefonte, PA) (20). The coefficient of variation for the analysis of D_2O by this method is <2% and typically is <0.75% (Metabolic Solutions, Merrimack, NH). NaBr concentration was determined by using high-performance liquid chromatography (model 338, Beckman Instruments, Ramon, CA) using a modification of a method previously described (14).

The D_2O space was calculated from the administered dose of the tracer and the concentration at equilibrium, corrected for the background concentration (17). The TBW was derived from the D_2O space by using a correction factor of 1.04 to account for nonaqueous hydrogen exchange (9, 18). The ECW was calculated in a similar manner from NaBr dilution and was corrected for nonextracellular bromide distribution and the Donnan equilibrium (2, 5). The TBW and ECW volumes were converted to mass by multiplying by the density of water at 37°C (0.994 g/ml).

MFBIA. Subjects were positioned supine. Four prepackaged ECG electrodes (Medtronics, Haverhill, MA) were applied to the skin as previously described (12). The impedance electrodes were secured on the side contralateral to the arteriovenous hemodialysis fistula or graft. Alternating current was applied with an amplitude of 100 mA at 26 frequencies distributed from 1 kHz to 1 MHz. Whole body R was measured by the voltage drop detected at the wrist and ankle. Standing height was measured to the nearest 5 mm. Body weight was measured on a calibrated scale to the nearest 0.1 kg.

Statistical analyses. The impedance index (ht²/R) was determined at each frequency and compared with standards for ECW and TBW. The Pearson correlation coefficients (r) and standard errors of estimation were determined. All P values are two tailed. Statistical analyses and graphical representation were performed with SPSS+/PC (SPSS, Chicago, IL).

TABLE 1. *Subject characteristics*

	Men ($n = 13$)	Women ($n = 15$)
Age, yr	49.9±10.9	57.9±10.4
Height, cm	175.3±8.4	159.1±7.2
Weight, kg	84.2±16.6	62.1±10.3
Body mass index, kg/m²	27.3±4.42	24.6±4.1
TBW, liters	49.2±9.0	33.1±4.1
ECW, liters	15.5±2.9	12.0±1.7
ECW/TBW	0.32±0.03	0.36±0.04
$R_{5 kHz}$, Ω	572.7±69.5	717.0±72.8
$R_{50 kHz}$, Ω	501.8±61.0	650.3±71.1
$R_{500 kHz}$, Ω	439.7±59.0	584.3±70.5

Values are means ± SD; n, no. of subjects. TBW, total body water; ECW, extracellular water; $R_{5 kHz}$, $R_{50 kHz}$, and $R_{500 kHz}$, resistance at 5, 50, and 500 kHz, respectively.

RESULTS

Subject characteristics are outlined in Table 1. Mean body weight was 72.4 kg (range 44.6–117.5 kg). TBW accounted for an average of 60.3% of body weight; ECW was 34.1% of TBW (range 26.7–41.3%). Table 2 shows the correlation coefficients between ht²/R determined at varying frequencies along with body water compartments by the aforementioned standard methods. The correlation between ht²/R and ECW decreased gradually ($r = 0.886–0.828$) as the frequency of the alternating current applied was increased from 1 kHz to 1 MHz. In contrast, the correlation between ht²/R and TBW increased only slightly ($r = 0.964–0.974$ at 500 kHz, $r = 0.965$ at 1 MHz) with increasing alternative current. To determine whether results from MFBIA could be used to approximate the distribution of body water, the ratio of R at 500 kHz to R at 5 kHz ($R_{500 kHz}/R_{5 kHz}$) by MFBIA was compared with the ECW/TBW estimated by D_2O and NaBr dilution. There was a significant correlation between these two variables ($R = 0.767, P < 0.001$) as shown in Fig. 1. A linear regression equation describing this relationship was developed

$$ECW/TBW = 0.757 \times (R_{500 kHz}/R_{5 kHz}) - 0.258$$

DISCUSSION

MFBIA was conceived as a method to quantify fluid compartments based on the principle that the body's

TABLE 2. *Correlation coefficients between impedance index and TBW and ECW at frequencies ranging from 1 kHz to 1 MHz.*

	ht²/R at:	
	TBW	ECW
1 kHz	0.964	0.885
5 kHz	0.966	0.886
10 kHz	0.968	0.884
15 kHz	0.970	0.881
30 kHz	0.973	0.874
50 kHz	0.974	0.868
100 kHz	0.974	0.859
150 kHz	0.974	0.855
300 kHz	0.974	0.849
500 kHz	0.974	0.843
1 MHz	0.965	0.828

ht²/R, impedance index.
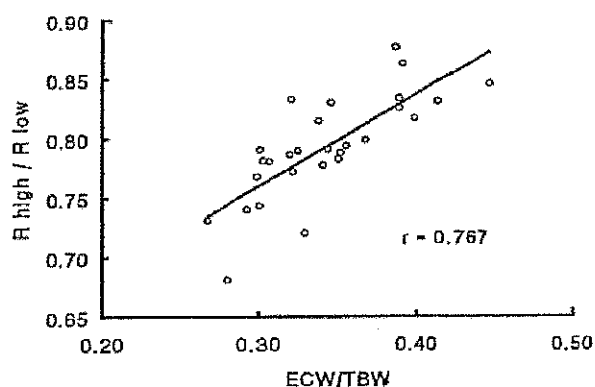
R_{high} reflects TBW (i.e., the sum of ECW and ICW), whereas R_{low} reflects ECW. Ideally, high-frequency alternating currents should penetrate cell membranes completely while low currents should be fully excluded. Practically, there are technical difficulties in the delivery of extreme frequencies because of safety, electrode polarization impedance, and stray capacitance (1). The results in Table 2 might reflect some of these difficulties, showing a marginally reduced correlation of MFBIA with standards of comparison at the high extreme (1 MHz) for TBW and the low extreme (1 kHz) for ECW. It has been suggested that the impedance at true extreme frequencies (zero and infinite) can be predicted from resistive and reactive components measured within a limited frequency range by employing the Cole-Cole function (7, 10). We have previously observed that the reactive components are measured less reliably than the resistive component, adversely affecting the prediction of R (0 Hz) and R (∞Hz).

Figure 1 shows a strong correlation between ECW/TBW and $R_{500 kHz}/R_{5 kHz}$ ($r = 0.767$). Although the correlation between ECW/TBW and the resistance ratio was lower than that between ht^2/R and TBW, it should be noted that the distribution was more narrow for ECW/TBW (0.34 ± 0.04) than for TBW (40.6 ± 10.5 liters). This reduction in variability attenuates the magnitude of the correlation coefficient and highlights some of the difficulties in using the correlation coefficient alone to compare the strength of association of two methods of clinical measurement (3).

Although this method offers potential for body water distribution analysis, further improvements in technique may be required. It appears as if the predictive power of MFBIA is attenuated by its estimation of ECW rather than TBW. This may be related in part to previous findings that MFBIA fails to compartmentalize ECW in the trunk segment. In the limbs, muscle and fat planes are uniformly oriented so that low-frequency alternating current passes through most of the ECW space. In contrast, the trunk contains nonuniformly oriented visceral organs and loops of bowel so that a considerable proportion of the low frequency conduction pathway is detoured. In a recent study from

this laboratory, ~50% of peritoneal fluid (ECW) was undetected using a low-frequency current applied by MFBIA (4).

Regardless, the ability to detect change on repeated examinations may prove to be a more clinically meaningful feature of MFBIA than its capacity to precisely estimate the actual ECW/TBW. Although we did not have the opportunity to evaluate our subjects longitudinally, experimental results performed in this laboratory suggest that MFBIA is highly reproducible (coefficient of variation <1.8) so that a biologically important change in the ECW/TBW ratio, as occurs in many acute and chronic illnesses, could be detected with this technique at the bedside (H. Suzuki, J. D. Rounds, and D. W. Wilmore, unpublished data).

In summary, the R_{high}/R_{low} ($R_{500 kHz}/R_{5 kHz}$) estimated by MFBIA was shown to be strongly correlated with the ECW/TBW as-determined by NaBr and D_2O dilution methods in 28 persons with ESRD of diverse age, sex, race, baseline renal disease, and body size, and composition. Serial tests to assess sensitivity to change, and association of R_{high}/R_{low} with relevant clinical outcomes, such as pulmonary function, and nutritional and functional status, will be required to better define the role of this technology.

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