Body-water compartments measured by bio-electrical impedance spectroscopy in patients with chronic obstructive pulmonary disease.

Clinical Nutrition (1998) **17**: 15–22

Body-water compartments measured by bio-electrical impedance spectroscopy in patients with chronic obstructive pulmonary disease

E. M. BAARENDS*, W. D. VAN MARKEN LICHTENBELT†, E. F. M. WOUTERS*, A. M. W. J. SCHOLS*‡

**Department of Pulmonology and †Department of Human Biology, Maastricht University, ‡Asthma Center Hornerheide, Horn, The Netherlands (Correspondence to E. B. University Hospital Maastricht, Department of Pulmonology, PO Box 5800, 6202 AZ Maastricht, The Netherlands)*

Abstract—It was previously demonstrated that single frequency bio-electrical impedance (BIA) measurement at 50 kHz is a useful method to assess total body water (TBW) in patients with chronic obstructive pulmonary disease (COPD). In the present study it was examined whether bio-electrical impedance spectroscopy (BIS) could predict extracellular water (ECW) and improve the prediction of TBW in these patients.

TBW and ECW (corrected bromide space) were measured by deuterium and bromide dilution. In 37 COPD patients prediction equations were obtained using BIS (5–500 kHz) measurements, and these were cross validated in a second group of 40 COPD patients. All patients were in a clinically stable condition.

TBW predicted by BIS was not significantly different from actual TBW and demonstrated a comparable standard error of estimate (SEE) as found previously in healthy subjects (♂ correlation coefficient: r = 0.88, SEE: 2.3 L, ♀ r = 0.85, SEE: 2.9 L). Predicted ECW using BIS-measurements was not significantly different from measured ECW (♂ r = 0.75, SEE: 1.4 L, ♀ r = 0.73, SEE: 1.2 L), but the error in the prediction was relatively large and the correlation between predicted and actual ECW relatively low compared to most studies in healthy subjects.

Predicted TBW using BIS was comparable to actual TBW, but presented no improvement of the prediction of TBW using BIA at 50 kHz and a patient specific regression equation. The error of the prediction of ECW by BIS limits the ability to predict fluid shifts in individual patients with clinically stable COPD.

Key words: Chronic obstructive pulmonary disease; Total body-water; Extracellular body-water; Body composition; Bioelectrical impedance spectroscopy

Introduction

Several chronic and acute disease states are accompanied by marked changes in body compartments. The estimation of the body compartments is not only of importance in research, but also in the clinical situation. Numerous body composition methods are presently available, but most of these are either too sophisticated, too inconvenient (especially for bed-ridden subjects), time consuming or require large and stationary equipment, often at high cost, which make these methods unsuitable for clinical practice.

Therefore, the estimation of body composition by bio-electrical impedance (BIA) represents a simple, practical and convenient method. Since the 1980s numerous studies have been performed to predict total body water (TBW) using BIA at 50 kHz, but it appears that this technique involves several drawbacks. The standard error of estimate of BIA is usually 1–3 l (1), which limits the ability to measure small effects of intervention on body composition (2, 3). Furthermore, the use of BIA at 50 kHz to measure the resistance of TBW has been questioned (4, 5), since the frequency at which the current flows through both extracellular water (ECW) and intracellular water (ICW) may differ between individuals, and is probably higher than 50 kHz. Finally, TBW measurements may be misleading in case of a deviating ECW/ICW distribution following disease or severe starvation (6–8).

Theoretically, the resistance of intracellular and extracellular water can be obtained by bio-electrical impedance spectroscopy (BIS). Using BIS the resistance of the body can be measured at a spectrum of frequencies. At low frequencies the current flows primarily through ECW because the capacity of cell membranes is minimized, whereas at high frequencies the current passes also through ICW (9, 10). It is hypothesized that, in order to predict TBW, it is more accurate to use the resistance of TBW obtained by BIS than the resistance at 50 kHz, because theoretically the latter is a suboptimal representative of the resistance of TBW. Until now, the BIS has been predominantly evaluated in healthy subjects (10–15), but the accuracy to measure body-water compartments should particularly be tested in wasting conditions associated with subtle to marked fluid shifts such as in patients with chronic obstructive pulmonary disease (COPD).

The purpose of this study was to examine whether body-water compartments using BIS-measurements (ranging from 5 to 500 kHz) are accurately predicted in patients

with severe COPD, using (isotope) dilution methods as a reference. In a first patient group, prediction equations based on BIS measurements were built, and these were subsequently cross validated in a second COPD study group.

Methods

Patients

Firstly, 37 patients (23♂) with moderate to severe COPD (16) were studied. The body mass index (BMI: weight/height^2) ranged widely from 13.6 to 31.0 kg/m^2 (Table 1A). Prediction equations derived from this study population were tested in a second group of 40 (32♂) COPD patients (Table 1B).

All patients were referred by a pulmonary physician to the rehabilitation center for pulmonary rehabilitation, in a stable clinical condition. None of the patients had a respiratory tract infection or clinically visible signs of oedema at the time of the study. When the measurements were performed the patients did not receive any diuretic medication. Patients exhibiting an increase in forced expiratory volume in 1 s (FEV_1) > 10% of baseline after inhalation of a β_2-agonist or those suffering from cancer, unstable pulmonary or cardiac conditions, active gastrointestinal abnormalities, recent surgery, or severe endocrine disorders were excluded from the study. The study was approved by the local ethical committee. Procedures followed were in accord with the Helsinki declaration from 1977 as revised in 1983.

Table 1A Characteristics of the first patient group

	Total	Males	Females	*P* value*
n =	37	23	14	
FEV_1 (%pred)	37.6 ± 13.8	36.0 ± 15.0	40.0 ± 11.6	ns
FVC (%pred)	82.0 ± 15.8	79.4 ± 17.6	86.3 ± 11.5	ns
Age (yr)	65 ± 9	65 ± 8	65 ± 10	ns
BMI (kg/m^2)	22.4 ± 4.2	22.6 ± 3.7	22.1 ± 5.1	ns
TBW (L)	30.8 ± 5.1	33.4 ± 3.9	26.4 ± 3.8	$P < 0.001$
ECW (L)	13.2 ± 2.1	13.9 ± 2.2	12.2 ± 1.6	$P = 0.05$
ECW (% TBW)	43.5 ± 5.3	41.6 ± 5.4	46.5 ± 3.7	$P < 0.05$

*difference between males/females.
FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; TBW: total body water; ECW: extracellular water.

Body composition

Body height was determined to the nearest 0.5 cm (Lameris, WM 715, Breukelen, The Netherlands) with subjects standing barefoot. Body weight was measured with a beam scale to the nearest 0.1 kg (SECA, FRG) with subjects barefoot and in light clothing.

To measure total body water each patient received a weighted 1 gram/L estimated TBW (17) oral dose of deuterium labelled water (D_2O: 99.84 atom percentage excess) mixed into ≈ 50 ml water. For the estimation of extracellular water 60 mg sodium bromide (NaBr) per litre estimated TBW was added to the deuterium dose. Patients received this 'cocktail' in the late evening around 10 pm. Just before and approximately 10 h later a venous blood sample and an urine sample (from second voiding) were obtained (18, 19). Urine was analyzed for deuterium with an isotope ratio mass spectrometer according to the standard Maastricht protocol (19). Deuterium dilution space was calculated from the quantity of administered D_2O the urine D_2O concentrations following complete distribution. TBW was calculated from these values by applying a conversion factor of 1.04. This correction accounts for exchange of labile hydrogen that occurs in humans during the equilibrium period (20).

Bromide concentration in serum ultrafiltrate was determined with HPLC, and ECW was estimated by the corrected bromide space (CBS) that was calculated from the quantity of administered bromide and the concentration of bromide in the background blood sample and the blood sample after complete equilibrium as described by Lichtenbelt et al (18). CBS was calculated correcting for the bromide in the non-extracellular sites (0.90), and the Donnan equilibrium (0.95).

Bio-electrical impedance spectroscopy measurements (BIS)

Bio-electrical measurements were taken using a four-surface-electrode technique in the early morning at a standardized time, the same day isotope dilution was performed. Measurements were made while the patients were lying comfortably on a polystyrene mattress, with the legs separated, and the arms relaxed aside, not touching

Table 1B Characteristics of the second patient group

	Total	Males	Females	*P* value*	*P* value#
n =	40	32	8		
FEV_1 (%pred)	40.3 ± 16.8	37.9 ± 15.6	49.9 ± 17.8	$P = 0.05$	ns
FVC (%pred)	87.9 ± 16.2	86.7 ± 16.2	87.9 ± 16.2	ns	ns
Age (yr)	65 ± 9	67 ± 8	60 ± 9	$P = 0.05$	ns
BMI (kg/m^2)	23.9 ± 4.4	24.0 ± 3.9	23.6 ± 6.3	ns	ns
TBW (L)	34.3 ± 5.1	35.6 ± 4.6	29.3 ± 4.2	$P < 0.001$	$P < 0.01$
ECW (L)	15.1 ± 2.3	15.8 ± 1.9	12.6 ± 1.6	$P < 0.001$	$P < 0.01$
ECW (%TBW)	44.2 ± 4.1	44.5 ± 4.0	43.2 ± 4.6	ns	ns

*difference between males/females.
#difference between groups 1 and 2.
FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; TBW: total body water; ECW: extracellular water.

the trunk. The electrodes (Tracets MP3000, LecTec Corporation, Minnetonka MN) were placed at the right side on the hand and the foot as described by Lukaski et al (21). Impedance was measured using a bio-electrical impedance spectrometer (Xitron 4000b, Xitron technologies, San Diego, California) at a spectrum of 48 frequencies ranging from 5 to 500 kHz.

Pulmonary function tests

Lung function tests consisted of flow volume measurements (forced expiratory volume in 1 s: FEV_1, forced vital capacity: FVC). The highest value of at least three measurements was used and expressed as a percentage of the reference value (22).

Theoretical considerations

The electrical impedance of the body is measured by introducing a small alternating current through the body and measuring the difference in potential. An alternating electrical current flows through the body by different physical mechanisms. The current flows through physiological fluids by the movement of ions. This movement is opposed by viscosity and other effects, which can be modelled electrically as a resistance. In addition, the applied current will charge cell membranes and other interfaces, which can be modelled electrically as capacitors. Thus, the impedance (Z) of the body can be modelled by an equivalent electrical circuit with a parallel combination of capacitive (resulting in the reactance: X) and resistive elements (resistance: R), where the absolute value of $Z = (X^2 + R^2)^{0.5}$ and arctan (X/R) is its phase angle (23). The impedance is strongly dependent on the frequency of the alternating current. At low frequencies, the bio-electrical current flows primarily through extracellular fluids and reactance is minimized since the capacitant aspects of body cells (cell membranes, tissue interfaces) are thought to be bypassed. As frequency increases the capacitant properties start to retard the current, producing an increase in reactance. The capacitant effects reach a peak with a maximum reactance value, but as the frequency of the current increases the current penetrates all body tissues completely, since at high frequency the rate of charge and discharge becomes such, that the effect of the capacitance is diminished to insignificant properties (23, 24). With increasing frequency, the resistance will decrease, because the amount of conducting volume is increasing. A plot of the resistance versus the reactance of tissue, as a function of frequency, characteristically forms a semicircular arc, the center of which is depressed below the real axis. This frequency dependence of the complex Z can be modelled empirically by the Cole-Cole equation. From this equation the resistance of ECW (Recw) and of TBW (Rtbw) at respectively zero and infinity frequency can be obtained. Considering that in the electrical model used, the Recw and Ricw are linked parallel, the Ricw can be calculated from the Recw and Rtbw (Rtbw = (Ricw*Recw)/(Ricw + Recw)) (23). In the present study Recw and Ricw were obtained using the software provided by the manufacturer previously described in detail (24) which models the impedance and phase angle spectra data into the Cole-Cole model, using nonlinear curve-fitting, and adjusting for the time delay caused by the speed at which electrical information is transferred through a conductor.

The prediction of ECW and TBW using Recw and Ricw depends on the underlying theory. The theory most frequently used is based on the principle that the complex impedance (reactance and resistance) of a conducting cylinder is related to its length (L), cross-sectional area (A), the frequency of the signal and the resistivity of the material (ρ). At a specific fixed frequency therefore: $Z = \rho*(L/A)$, by multiplying this equation by L/L, the equation of the volume of a conducting cylinder becomes $\rho*(L^2/Z)$ (23). If the contribution of the reactance is neglected (because it is usually small) the volume of a conducting cylinder is related to $\rho*(L^2/R)$ (1, 23), where L is estimated by height. The ratio height^2/resistance is usually referred to as the resistivity index (RI).

In the second theory, based on emulsion sciences, the apparent resistivity of a conducting material is also thought to be dependent on the restricting concentration of non-conductive material in the suspension: $\rho = \rho_0/(1-C)^{3/2}$, where ρ is the apparent resistivity of the conductive material; ρ_0 is the actual resistivity of a conductive material; and C is the volumetric concentration of the nonconductive marterial contained in the mixture (24). An extensive explanation of this theory is described by Hanai as well as by Lorenzo et al (24, 25). Until now there has been no uniformity concerning the theory used to obtain the prediction of body water compartments, we tested both the theory using the RI and the theory based on emulsion sciences.

Based on the above mentioned theories the following equations were tested:

1. The relationship between height^2/Rtbw and TBW, height^2/Recw and ECW were determined from the first group of patients and subsequently used to predict TBW and ECW in the second group of patients.
2. The prediction formulas for TBW and ECW based on the theory of Hanai. The equations have been described in detail previously (24). There are several constants used in these equations, which are based on assumptions, as described by Lorenzo et al (24). These equations are built on an assumption concerning the volumetric concentration of non-conductive elements in the body at low and high frequencies, an assumption concerning the calculation of total body volume, the assumption that the constants used in the equation are not variable, and that the Hanai equation can be applied at high and low frequencies to mixtures found in the human body. The constants involved in the prediction equation are a correction factor (K_B) for a whole body measurement between wrist and ankle and a constant for body density. Furthermore, the equations are built on the assumption that the total volume of a body fluid can be described as: $K_B*\rho_F*(L^2/R)$, where ρ_F represents the resistivity of the water. Therefore, in these formulae ECW and ICW

resistivity constants are used. However, these coefficients were derived by the manufacturer using other reference methods than our own. Therefore, the standard resistivity coefficients were replaced by resistivity coefficients calculated from our first patient group. TBW and ECW were subsequently predicted from the formulae provided by the manufacturer and the patient-specific resistivity coefficients.

Data analysis

Results are given as mean ± SD. Correlation coefficient analysis was performed to test the linear relationship between variables. Multiple regression analysis was performed in order to obtain partial correlations and prediction equations. Differences between groups 1 and 2, or men and women were tested with a Mann-Whitney U test. Differences between actual and predicted body-water compartments were analyzed with a paired *t*-test and following the procedures suggested by Altmann & Bland (26). To compare two methods, the mean difference or the mean underestimation or overestimation from 0 (=bias) was calculated. In addition, the SD of the mean difference between actual and predicted body-water compartment was calculated, which indicates the error of an individual prediction (= "error"). Level of significance was determined as a P value < 0.05.

Results

There was no significant difference in pulmonary function between the first group in which the prediction equations were built (group 1) and the group in which cross-validation was performed (group 2), but body composition was different between the groups. TBW and ECW were significantly higher in group 2, but ratio ECW/TBW was comparable between the groups (Table 1).

The regression equations for the prediction of TBW and ECW using the RI are demonstrated in Table 2. With respect to the prediction of TBW, the regression equations were significantly different for men and women, but this was not the case for the prediction of ECW. The partial correlation between the RI (height^2/Rtbw) and TBW (adjusted for the correlation with ECW) was still statistically significant in men, but not in women. The partial correlation between the RI (height^2/Recw) and ECW (adjusted for the correlation with TBW) was not statistically significant.

The patient specific resistivity coefficients based on emulsion sciences calculated in group 1 (ρECW: ♂ 169, ♀ 166, ρICW: ♂ 1067, ♀ 1256) deviated considerably from the resistivity coefficients provided in the software by the manufacturer (ρECW: ♂ 215, ♀ 206, ρICW: ♂ 824, ♀ 797).

The predicted TBW using both the RI or the software of the BIS was not statistically significant from actual in men (Table 3). Also there was no significant difference between predicted TBW using the RI and actual TBW in women.

ECW in men was best predicted by the software of the BIS, since there was a greater bias in the prediction of ECW using the RI, as shown in Table 3. Predicted ECW in women was not statistically different from actual ECW using both the RI or the software of the BIS and resulted in a comparable bias.

Statistical analysis revealed that the prediction of TBW or ECW using the RI involved a systematic fault (Fig. 1). TBW minus predicted TBW correlated significantly to mean TBW in both males (r = 0.68, $P < 0.001$) and females (r = 0.88, $P < 0.01$). Also ECW minus predicted ECW correlated significantly to mean ECW in both males (r = 0.76, $P < 0.001$) and females (r = 0.78 $P < 0.05$). In the

Table 2 Prediction equations using the resistivity index (Height^2/resistance) in BIS

	RI with	intercept	slope	r	SEE	*P*-value	partial r*	*P*-value
♂	Rtbw	10.7882	0.3653	0.82	2.21	<0.001	0.72	<0.001
♀	Rtbw	12.1960	0.2910	0.73	2.69	<0.01	0.38	0.19
♂ + ♀	Recw	6.8641	0.1668	0.65	1.60	<0.001	0.22	0.21

RI: resistivity index (height^2/resistance); r: correlation; SEE: standard error of estimate.
*partial r = the correlation adjusting for the correlation between TBW and ECW.

Table 3 Mean actual and predicted body water compartments for men and women separately

	Men				Women			
		r	B	E		r	B	E
Actual TBW	35.6 ± 4.6				29.3 ± 4.2			
RI	36.2 ± 2.8	0.85**	0.68	2.6	28.9 ± 1.8	0.85*	0.30	2.9
Emulsion	36.1 ± 4.8	0.88**	0.49	2.3	34.0 ± 4.2**	0.91*	4.79	1.8
Actual ECW	15.8 ± 1.9				12.6 ± 1.6			
RI	13.8 ± 0.8**	0.63**	1.93	1.6	12.2 ± 0.8	0.73#	0.34	1.2
Emulsion	15.8 ± 1.9	0.75**	0.08	1.4	12.9 ± 1.8	0.66[1]	0.33	1.4

#$P < 0.05$, *$P < 0.01$, **$P < 0.001$, [1]ns: $P = 0.08$.
r: correlation between actual and predicted body water compartment; B: bias = mean difference between actual and predicted body water compartment; E: error = SD of mean difference;
TBW: total body water; ECW: extracellular water; RI: predicted volume using the resistivity index (height^2/res); Emulsion: predicted volume based on emulsion sciences.

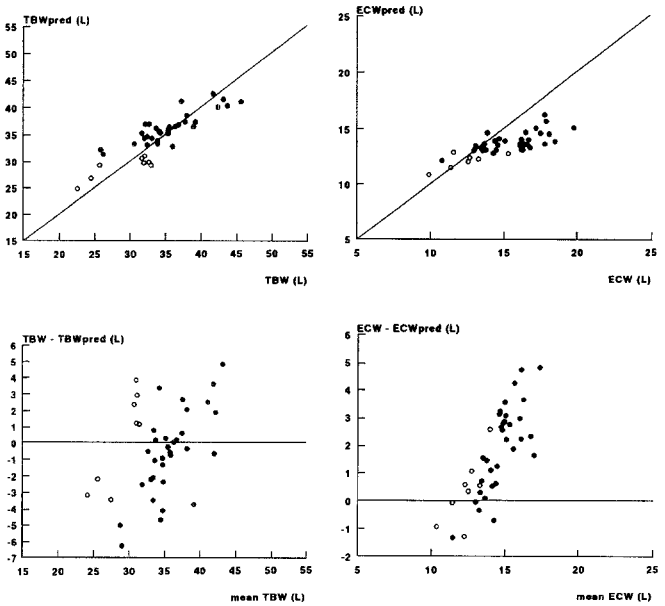

Fig. 1 Results of cross-validation based on the resistivity index, (O) = women.

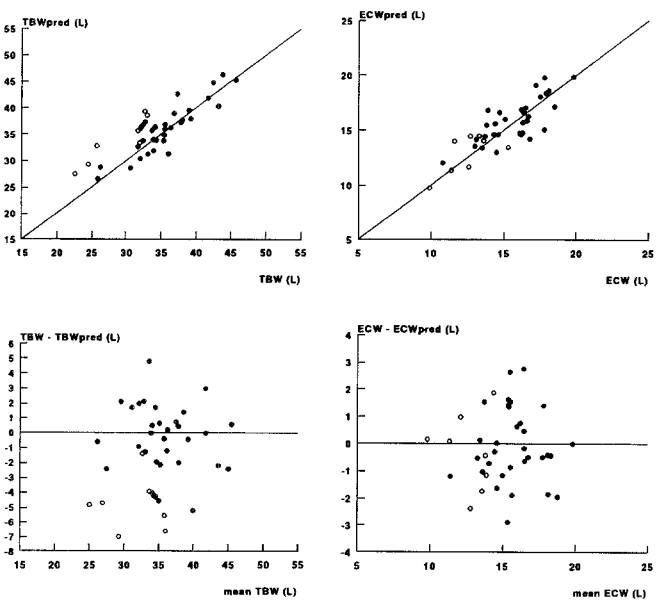

Fig. 2 Results of cross-validation based on emulsion sciences; (O) = women.

prediction of TBW and ECW based on emulsion sciences there were no such systematic faults (Fig. 2).

Actual ECW/TBW was compared to the four ratios predicted ECW/predicted TBW. This is shown in Figure 3. In men, the predicted ratio ECW/TBW based on the RI (ECW_{RI}/TBW_{RI}: 0.38 ± 0.01) was significantly different from actual ECW/TBW (0.45 ± 0.04, $P < 0.001$). In fact, the best estimation of ECW/TBW was obtained by ECW_{EM}/TBW_{EM} (predicted ECW/TBW based on emulsion sciences: 0.44 ± 0.03, bias: –0.004, error: 0.04), but the correlation between actual and predicted ECW/TBW was not strong (r = 0.44, $P < 0.05$). ECW_{EM}/TBW_{RI} was also not significantly different from actual (0.44 ± 0.03), however, it did not correlate to actual ECW/TBW (r = 0.11, ns). ECW_{RI}/TBW_{EM} (0.39 ± 0.04) was significantly different from actual ECW/TBW in men.

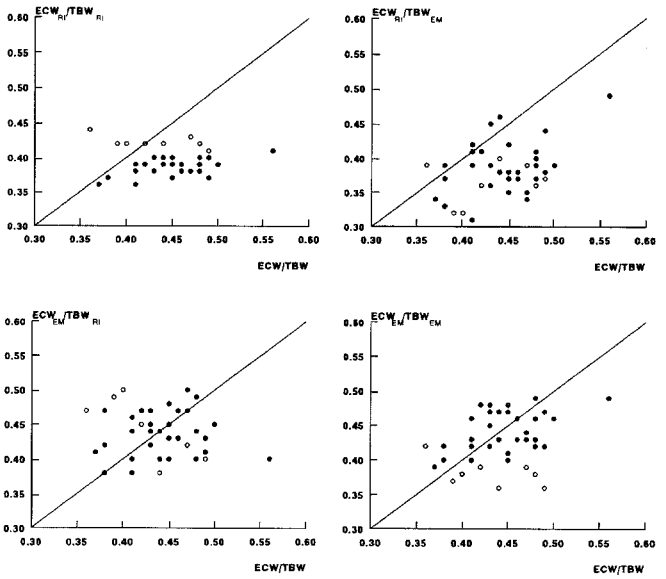

Fig. 3 Correlation between actual ECW/TBW and predicted ECW/TBW; (O) = women; RI = predicted body water compartment based on the resistivity index; EM = predicted body water compartment based on emulsion sciences.

In women, both ECW_{RI}/TBW_{EM} (0.36 ± 0.03, $P < 0.01$) and ECW_{EM}/TBW_{EM} (0.38 ± 0.02, $P < 0.05$) were significantly different from actual ECW/TBW (0.43 ± 0.05). ECW_{RI}/TBW_{RI} (0.42 ± 0.01) was not significantly different from actual, but did not correlate significantly with actual ECW/TBW (r = –0.48, ns). Also ECW_{EM}/TBW_{RI} (0.44 ± 0.04, bias: 0.01, error: 0.08) was not significantly different from actual ECW/TBW; however, this predicted ratio only tended to correlate (r = –0.69, $P = 0.06$) with the actual ratio ECW/TBW. Moreover, as can be seen in Figure 3, this relationship was reversed.

Discussion

This study shows that in stable COPD patients, predicted TBW using bio-electrical impedance spectroscopy is not significantly different from actual TBW. The bias and error in the prediction are, however, comparable to that of the prediction of TBW by bio-electrical impedance measurement at 50 kHz. Predicted ECW using BIS-measurements was not significantly different from measured ECW, but the error in the prediction was relatively large and the correlation between predicted and actual ECW relatively low compared to most studies in healthy subjects. Therefore, predicted ECW/TBW by BIS was only weakly correlated to actual ECW/TBW. In men ECW and TBW were best predicted (the least bias, error and/or systematic fault) using equations built on emulsion sciences and patient specific resistivity coefficients (24, 25), which incorporate the influence of conductive as well as non-conductive elements in the body. TBW predicted using the formulae based on

the emulsion sciences in women resulted in a significant bias, but we recognize that conclusions concerning the female COPD patients in this study must be handled carefully, since the number of women in the cross-validation was small.

Single frequency measurement studies using the resistance at 50 kHz in health and disease

Several validation studies in the late 1980s and early 1990s in healthy adults have shown that bio-electrical impedance at 50 kHz, using similar measurement conditions as in the present study, generally results in a good correlation with TBW with standard errors of estimates (SEE) ranging from 1.4 to 3.5 L (1). In a previous study (27) it was shown that BIA at 50 kHz was a useful measurement to predict TBW in clinically stable COPD patients with a SEE of only 1.8 L.

In general, also in other clinical situations, BIA at 50 kHz was found to produce valid estimates of TBW. In some studies involving patients on dialysis, fluid loss could be reasonably well estimated with BIA (28, 29), although sometimes TBW was poorly predicted (30). Studies in patients with growth hormone deficiency (31), patients with cystic fibrosis (32, 33), malnourished or obese subjects (34), patients with acromegaly (35) or anorexia nervosa (36) showed that the estimation of body composition with BIA was valid. In contrast, in Crohn's disease BIA was found to overestimate TBW significantly by 5.9 (± 1.1)% (37). In cancer patients Simons et al (38) found that height^2/resistance at 50 kHz was a good predictor of TBW (r^2 = 0.85, SEE 2.2 L), but that TBW was overestimated in malnourished lung cancer patients. In a recent editorial (39) it was discussed that BIA at 50 kHz seems able to predict TBW in a wide range of conditions.

The use of the resistance or impedance at 50 kHz to measure the resistance of TBW is derived from the work of Nyboer (40) who determined that this was the critical frequency (= frequency when the reactance reaches the maximum value) of muscle tissue. With respect to the fact that probably only at frequencies higher than 100 kHz the current flows through all body tissues, the resistance at 50 kHz seems to be suboptimal to measure the resistance of TBW (4, 5). Furthermore although, as summarized above, single frequency BIA measurements at 50 kHz seem to estimate TBW reasonably, information concerning the distribution of water in intra- and extracellular compartments is not provided.

Multifrequency BIA and BIS studies in health and disease: prediction of TBW

Studies from the 1990s until now, investigating the prediction of ECW and TBW using multifrequency BIA or BIS in healthy subjects, in general using similar measurement conditions as the present study, demonstrated promising results (10–15, 24). Using prediction equations including multifrequency BIA (resistance > 100 kHz) or BIS (Rtbw) measurements: height^2/resistance (or impedance), and/or other variables in the regression equation, the variance in TBW ranged from 83% to 98%, with a SEE between 1.2 L and 3.6 L (10–15, 24). In one study (15), double sided and proximal measurements were used, but these different measurement conditions did not improve the prediction. Furthermore, Rtbw was used instead of a fixed (high) frequency in the latter study (15), but this also did not result in a significant improvement of the prediction of body-water compartments by BIS. In contrast, in a study by Cornish et al (41) in rats it was found that the impedance at the critical frequency resulted in a better prediction of TBW with a lower variation coefficient (5.9%) compared to the variation coefficient in studies with a fixed frequency. It can be concluded from the results of all these studies, however, that the SEE of the predicted TBW obtained by multifrequency BIA or BIS is comparable or only a slight improvement of the prediction of TBW resulting from the measurement at 50 kHz as summarized earlier above.

In the present study, performed in clinically stable COPD patients cross-validation showed that the best predicted TBW (with the least bias, error and/or systematic fault) was obtained by the prediction equations based on emulsion theories in men, and the equation based on height^2/Rtbw in women. Predicted TBW correlated significantly to actual TBW (♂: r = 0.88, ♀: r = 0.73), and there was no significant difference. The error could amount to 2.3 L in men and 2.9 L in women. In addition, the prediction of TBW in women and men using the resistivity index involved a systematic error: with a higher TBW the difference between actual and predicted TBW became larger. Compared to the prediction of TBW using the BIS, the correlation coefficient between actual and predicted TBW using BIA at 50 kHz (and a COPD-specific regression equation from Schols et al [27]) was even better (r = 0.91) however, and the error amounted to 2.2 L, with no systematic error. It can therefore be concluded that BIS did not improve the prediction of TBW by BIA at 50 kHz in this study. This is difficult to explain from a theoretical viewpoint, but could be due to the fact that Rtbw is not actually measured, but obtained by calculations (based on a model). As mentioned above, there are no studies clearly demonstrating a lower SEE in the prediction of TBW using Rtbw or the resistance at high frequency compared to SEE of the prediction of TBW at 50 kHz reported in numerous studies.

Multifrequency BIA and BIS studies in health and disease: prediction of ECW

In studies performed in healthy subjects, using general comparable measurement conditions as in the present study, the prediction equations of ECW including either multifrequency BIA (resistance at 1 or 5 kHz) or BIS (Recw) measurements resulted in an r^2 ranging from 0.74 to 0.96 (10–15, 24) with an SEE between 0.6–1.75 L. Validation studies of multifrequency BIA or BIS in disease are limited, which is surprising since the accuracy of the prediction

of ECW and TBW should particularly be studied in populations in which fluid shifts can occur. In surgical patients Hannan et al (42) found that predicted ECW was not derived from the resistance measurement at 5 kHz, but in stepwise regression analysis the reactance at 50 kHz was chosen as a better predictor of ECW. It was also found in these surgical patients (after cross-validation) that predicted ECW declared 86% of the explained variation in actual ECW, but that SEE was 1.7 L. A study of Sergi et al (43) showed that in patients with fluid retention states ECW was correlated (r^2 of 0.74) with height^2/resistance at 1 kHz, whereas in healthy persons r^2 was 0.85. Sergi et al (43) found a difference between healthy and sick subjects in the intercept of the regression line and suggested that there is a difference in body conductivity when water disorders occur.

In the present study the best prediction of ECW resulted in a relatively great error of 1.4 L in both males and females, and there was a low correlation (range r: 0.63–0.77) between actual and predicted ECW compared with the previously described studies. Particularly in men, ECW seemed better predicted (less bias, error and systematic fault) using the equations based on emulsion sciences (including patient-specific resistivity coefficients). Again, prediction of ECW using the resistivity index resulted in a significant systematic error (with increasing ECW, the difference between actual and predicted ECW became larger).

It appears that ECW in this study was not predicted very accurately, which is not surprising since the partial correlation (correlation between ECW and RI, when the intercorrelation between TBW and ECW is accounted for) was not statistically significant in the group of patients used to derive the prediction equations. In the few other studies in healthy subjects in which the partial correlation between ECW and prediction variables was calculated, significant correlations could be found (10, 12).

Prediction of fluid shifts

The ratio ECW/TBW ranged from 36% to 56% in the studied COPD patients, which is comparable to the study by Hannan in the surgical patients (42), whereas in the healthy subjects of the study of Marken Lichtenbelt et al (15) ratio ECW/TBW ranged from 39% to 48%. The error in the prediction of TBW, accompanied by the error in the prediction of ECW, and the relatively low correlation between actual and predicted ECW, probably caused the poor prediction of the ratio ECW/TBW. Mean predicted ECW/TBW based on emulsion sciences in the studied male COPD patients was not significantly different from actual ECW/TBW, but only a weak correlation between actual ECW/TBW and predicted ECW/TBW was found. To our knowledge no other clinical study has yet tested whether the errors in predicting ECW and TBW are small enough to predict the ratio ECW/TBW.

The reason for the inaccuracies in the prediction of TBW and especially ECW are probably partly due to the underlying assumptions and problems inherent to bioelectrical impedance. These are the errors incorporated in the prediction formulae caused by inaccuracies of the reference methods to calculate ECW and TBW (5) and the not entirely correct assumption that the body is an isotropic conductor with a uniform length and cross-sectional area, as explained in the review by Kushner (1). Also, possibly the assumptions and constants incorporated in the equations based on the theory of Hanai need reconsideration in order to improve the prediction accuracy. Furthermore, in diseases such as in COPD, physiological processes (variations of ionic concentrations, osmotic pressure, membrane function) may influence resistivity, which are not accounted for by BIS in the presently used theories and/or equations.

In summary, TBW predicted by BIS in COPD patients is comparable to, but not an improvement of, the previously published prediction of TBW using BIA at 50 kHz. In general, ECW and TBW were best predicted using the theory of Hanai (25) based on emulsion sciences, which corrects for non-conductive material in the body, but individual differences between actual and predicted ECW could still amount up to 3 L. Because of these errors, the correlation between actual and predicted ratio ECW/TBW was weak, and the prediction demonstrated a relatively large error. It can therefore be concluded that the analysis of BIS needs to be improved in order to predict fluid shifts in COPD patients.

Acknowledgements

This study was supported by a grant from the Dutch Asthma Foundation (project number 91.38).

References

1. Kushner R F. Bioelectrical impedance analysis: a review of principles and applications. J Am Col Nutr 1992; 11: 199–209
2. Forbes G B, Simon W, Amatruda J M. Is bioimpedance a good predictor of body composition change? Am J Clin Nutr 1992; 56: 4–6
3. Tagliabue A, Cena H, Trentani C, Lanzola E, Silva S. How reliable is bio-electrical impedance analysis for individual patients? International Journal of Obesity 1992; 16: 649–652
4. National Institutes of Health Technology assessment conference statement. Bioelectrical impedance analysis in body composition measurement. Am J Clin Nutr 1994; 64(suppl): 524s–532s
5. Heitmann B L. Impedance: a valid method in assessment of body composition? Eur J Clin Nutr 1994; 48: 228–240
6. Keys A, Brozek J, Henschel A, Mickelsen O, Taylor H L. The biology of human starvation. Volume 1. Minneapolis: University of Minnesota Press 1950: 63–78
7. Moore F D, Olesen K H, Mcmurrey J D, Parker H V, Ball M R, Boyden C M. The body cell mass and its supporting environment. Philadelphia, London: WB Saunders, 1963
8. Schizgal H M. Body composition. In: Fischer J E (ed). Surgical nutrition. Boston, Toronto: Little, Brown and Company 1983: 3–17
9. Jenin P, Lenoir J, Roullet C, Thomasset A L, Ducrot H. Determination of body fluid compartments by electrical impedance measurements. Aviat Space Enviro Med 1975; 46(2): 152–155
10. Segal K R, Burastero S, Chung A, Coronel P, Pierson R N, Wang J. Estimation of extracellular and total body water by multiple frequency bioelectrical-impedance measurement. Am J Clin Nutr 1991; 54: 26–29
11. Deurenberg P, Schouten F J M. Loss of total body water and extracellular water assessed by multifrequency impedance. Eur J Clin Nutr 1992; 46: 247–255

12. Deurenberg P, Schouten F J M, Andreoli A, Delorenzo A. Assessment of changes in extracellular water and total body water using multifrequency bioelectrical impedance. Basic Life Sci 1993; 60: 129–132
13. Van loan M D, Mayclin P L. Use of multi-frequency bioelectrical impedance analysis for the estimation of extracellular fluid. Eur J Clin Nutr 1992; 46: 117–124
14. Van loan M D, Withers P, Matthie J, Mayclin P L. Use of multifrequency spectroscopy to determine extracellular fluid, intracellular fluid, total body water, and fat-free mass. Basic Life Sci 1993; 60: 67–132
15. Van Marken Lichtenbelt W, Westerterp K R, Wouters L, Luijendijk S C M. Validation of bioelectrical-impedance measurements as a method to estimate body-water compartments. Am J Clin Nutr 1994; 60: 159–166
16. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (copd) and asthma. American Review of Respiratory Diseases 1987; 137: 225–228
17. Deurenberg P, Westrate J A, Seidell J C. Body mass index as a measure of body fatness: age and sex specific prediction formulas. Br J Nutr 1991; 65: 105–114
18. Van Marken Lichtenbelt W D, Kester A, Baarends E M, Westerterp K R. Bromide dilution in adults: optimal equilibration time after oral administration. J Appl Physiol 1996; 81: 653–656
19. Westerterp K R, Wouters L, Marken Lichtenbelt W D. The Maastricht protocol for the measurement of body composition and energy expenditure with labeled water. Obesity Research 1995; 3(Suppl 1): 49–57
20. Schoeller D A. Isotope dilution methods. In: Björntröp P, Brodoff B N (eds). Obesity. Philadelphia: JB Lippencott 1992: 80–88
21. Lukaski H C, Johnson P E, Bolonchuk W W, Lykken G I. Assessment of fat-free mass using bio-electrical impedance measurements of the human body. Am J Clin Nutr 1985; 41: 810–817
22. Quanjer P H, Tammeling G J, Cotes J E, Pedersen O F, Peslin R, Yernault J-C. Standardized lung function testing. Eur Respir J 1983; 6(Suppl 16): 5–40
23. Foster K R, Lukaski H C. Whole body impedance – what does it measure? Am J Clin Nutr 1996; 64(suppl): 388s–396s
24. Lorenzo de A, Andreoli A, Matthie J, Withers P. Predicting body cell mass with bioimpedance by using theoretical methods: a technological review. J Appl Physiol 1997; 82: 1542–1558
25. Hanai T. Electrical properties of emulsions. In: Sherman P H (ed). Emulsion Science. London: Academic Press 1968: 354–477
26. Altmann D G, Bland J M. Measurement in medicine: the analysis of comparison studies. The Statistican 1983; 32: 207–217
27. Schols A M W J, Wouters E F M, Soeters P B, Westerterp K R. Body composition by bioelectrical-impedance analysis compared with deuterium dilution and skinfold anthropometry in patients with chronic obstructive pulmonary disease. Am J Clin Nutr 1991; 53: 421–424
28. Biasoli S, Petrosino Z, Cavallli L, Zambello A, Cesaro A, Fazion S. Bioelectrical impedance for the assessment of body composition of dialyzed patients. Clin Nephrol 1989; 31: 274–275
29. Böhm D, Odaischi M, Beyerlein C, Overbeck W. Total body water: changes during dialysis estimated by bio-electrical impedance analysis. Infusiontherapie 1990; 17(Suppl 3): 75–78
30. Thompson C M, Kong C H, Lewis C A, Hill P D, Thompson F D. Can bio-electrical impedance be used to measure total body water in dialysis patients? Physiol Meas 1993; 14: 455–461
31. Snel Y E M, Brummer R J M, Bol E, Doerga M E, Zelissen P M J. Direct assessment of extracellular water volume by the bromide-dilution method in growth hormone-deficient adults. Eur J Clin Invest 1995; 25: 708–714
32. Lands L C, Gordon C, Bar-Or O et al. Comparison of three techniques for body composition analysis in cystic fybrosis. J Appl Physiol 1993; 75: 162–166
33. Newby M J, Keim N L, Brown D L. Body composition of adult cystic fibrosis patients and control subjects as determined by densitometry, bioelectrical impedance, total-body electrical conductivity, skinfold measurements, and deuterium oxide dilution. Am J Clin Nutr 1990; 52: 209–213
34. Schizgal H M. Validation of the measurement of body composition from whole body bio-electrical impedance. Infusiontherapie 1990; 17(Suppl 3): 67–74
35. Brummer R J M, Bengtsson B A, Bosaeus I. Validation of body composition determination by bio-electrical impedance analysis in acromegaly. Eur J Clin Nutr 1992; 46: 47–52
36. Hannan J, Cowen S, Freeman C, Mackie A, Shapiro C M. Assessment of body composition in anorexic patients. Basic Life Sci 1990; 55: 149–154
37. Royall D, Greenberg G R, Allard J P, Baker J P, Harrison J E, Jeejeebhoy K N. Critical assessment of body composition measurements in malnourished subjects with crohn's disease: the role of bioelectric impedance analysis. Am J Clin Nutr 1994; 59: 325–330
38. Simons J P F H A, Schols A M W J, Westerterp K R, Velde ten G P M, Wouters E F M. The use of bioelectrical impedance analysis to predict total body water in patients with cancer cachexia. Am J Clin Nutr 1995; 61: 741–745
39. Editorial. Bioelectrical impedance and body composition. Lancet 1992; 340 (8834–8835): 1511.
40. Nyboer J. Electrical impedance plethysmography. Springfield, II: Charles C Thomas, 1959
41. Cornish B H, Thomas B J, Ward L C. Improved prediction of extracellular and total body water using impedance loci generated by multiple frequency bioelectrical impedance analysis. Phys Med Biol 1993; 38: 337–346
42. Hannan W J, Cowen S J, Fearon, K C H, Plester C E, Falconer J S, Richardson R A. Evaluation of multifrequency bioimpedance analysis for the assessment of extracellular and total body water in surgical patients. Clin Sci 1994; 86: 479–485
43. Sergi G, Bussolotto M, Perini P et al. Accuracy of bioelectrical impedance analysis in estimation of extracellular space in healthy subjects and in fluid retention states. Ann Nutr Metab 1994; 38: 158–165

Submission date: 13 March 1997 *Accepted:* 7 November 1997