Original Article

Assessment of bioelectrical impedance analysis for the prediction of total body water in cystic fibrosis

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The aim of this study was to compare the measurement of total body water (TBW) by deuterium ($^2H_20$) dilution and bioelectrical impedance analysis (BIA) in patients with cystic fibrosis (CF) and healthy controls. Thirty-six clinically stable patients with CF (age 25.4 $\pm$ 5.6 yrs) and 42 healthy controls (age 25.4 $\pm$ 4.8) were recruited into this study. TBW was measured by ^2H_2O dilution and predicted by BIA in patients and controls. The TBW predicted from BIA was significantly different from TBW as measured using ^2H_2O in patients (P <0.05) but not in controls. Mean ($\pm$SD) values for predicted and measured TBW differed by 5.6 ($\pm$9.1) L in patients and 0.4 ($\pm$3.6)L in controls. This bias was consistent for all controls but not for patients. In CF, BIA over predicted TBW determined by ^2H_2O dilution to an increasing extent at larger TBW volumes. There was a strong correlation between height^2/impedance and TBW in patients with CF (r = 0.90; y = 0.67x + 2.50) and in controls (r = 0.81; y = 0.57x + 9.60). The slope of the regression lines was similar for both groups, however the y intercepts were significantly different (P < 0.05). BIA overestimates TBW in patients with CF, possibly due to invalid factory installed regression equations within BIA instrumentation. Future studies employing BIA as a measure of TBW or FFM in CF should use alternative predictive equations to those that have been developed for healthy individuals. A large scale study to develop specific regression equations for use in CF is warranted.

Keywords: cystic fibrosis, bioelectrical impedance, total body water, body composition

Introduction

Cystic fibrosis (CF) is a genetic disorder characterised by lung disease, malabsorption and elevated sweat electrolytes. In most large CF populations, chronic under-nutrition, weight reduction and linear growth failure have been reported for many years.[1-5] These symptoms frequently lead to abnormalities in body composition causing a decrease in both fat free mass (FFM) and fat mass (FM).[6] Assessments of body composition, therefore, are necessary to both establish optimal nutritional advice by ensuring appropriate reconstitution of body fat and lean tissue, and to monitor changes in body composition during treatment.

It is well established that the measurement of body composition, and hence FM and FFM, provides a good indication of the nutritional status of patients with CF.[4,6-8] The FM and FFM can be determined when the volume of total body water (TBW) for an individual is known. Body water is the most abundant component of the fat free mass in humans and remains relatively constant once adulthood is reached.[9] In patients with CF, however, fluid transport in epithelia is characterised by an imbalance between sodium and chloride transport which results in localised electrical characteristics which may result in changes in water content.[10] The classic approach for the measurement of TBW has been the use of radioactive or stable isotopes in the form of water (e.g., ^3H_2O, ^2H_2O, $H_2{}^{18}O$) on the basis of a dilution principle.[11] The limitations of isotope techniques are that some of the required isotopes are expensive, the procedures require sophisticated equipment and specialised laboratory personnel and the process of analysis can be complicated and time consuming which eliminates their use for immediate clinical assessment and evaluation.

Currently, there are a number of alternative methods available for the prediction of TBW. One such method is bioelectrical impedance analysis (BIA). BIA is quick, portable, non-invasive and inexpensive in comparison to isotope dilution techniques. It is based on the principle of

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measuring the impedance of the human body, which is the vectorial sum of resistance and reactance.[12] Resistance depends on the volume of the conductor and the frequency of the electrical current applied. Reactance is a function of the capacitive properties of the tissue.[13] In simple terms, an electrical current is transported via the water in the human body. As fat is anhydrous, the impedance to flow of an electrical current when expressed relative to conductor length, i.e. height^2/ impedance, is proportional to the amount of TBW.[13-15] Therefore TBW can be predicted via the use of BIA instrumentation. BIA has been used in several studies in CF, however only a limited number have directly compared BIA with other techniques which measure TBW and body composition.[6-8,16,17] Of these studies, two have compared BIA to measures of body water by deuterium dilution (^2H_2O)[7,17] and one[8] has compared BIA to body water measured using $H_2{}^{18}O$ dilution. These studies are limited by their sample size and therefore lack the power to speculate about the accuracy of BIA. The purpose of this study was to compare the measurement of TBW by ^2H_2O dilution and BIA in a larger group of patients with CF and healthy controls and to determine the intra-individual differences between methods for both groups.

Methods

Power analysis was performed to determine the sample size required to detect a difference between methods for measuring TBW. Based on our data an effect size of 0.7 was calculated for the CF patient group. Alpha was set at 0.05 and beta was 80%. From the published tables[18] it was evident that a minimum of 18 patients with CF were required. For this study 36 clinically stable adults with CF and 42 healthy volunteers from the community were recruited after providing written informed consent. The study was approved by the Queensland University of Technology Human Research Ethics Committee, The Prince Charles Hospital Ethics Committee and The University of Queensland Human Research Ethics Committee.

Pulmonary function tests were administered by standard spirometry (Vitalograph) for the CF group. Measurements were recorded for forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1). Results were expressed as absolute values in litres and as a percentage of the predicted values.

Measurement of height and weight were made using standard procedures. TBW was measured in all subjects using the stable isotope of hydrogen in the form of water (^2H_2O). A 10-15ml aliquot of urine was collected as a baseline sample, then each subject drank a 10% solution of ^2H_2O based on their body weight (0.5g/kg body weight). The dose consumed was recorded to two decimal places of a gram.

A second urine sample was collected 5 hours later. TBW was determined by analysing the enrichment of the pre-dose urine sample, the post-dose urine sample, local tap water and the dose given using isotope ratio mass spectrometry (Hydra, PDZ Europa Scientific, Crewe, UK). Samples were measured in triplicate and expressed relative to standard mean ocean water (SMOW). The equation used for the calculation of deuterium oxide dilution space *(N)* is as follows.

$$N = \frac{TA}{A} \times \frac{(Ea-Et)}{(Es-Ep)}$$

Where *A* is the amount of isotope given in grams, *a* is the portion of the dose in grams retained for mass spectrometer analysis, *T* is the amount of tap water in which the portion of *a* is diluted before analysis, and *Ea, Et, Ep* and *Es* are the isotopic enrichments in delta units relative to SMOW of the portion of the dose, the tap water used, the pre-dose urine sample and the post-dose urine sample.[19] The equations of Schoeller and colleagues[11] were then used to determine TBW.

The BIA measurement was made with a Bodystat-1500 analyser while subjects were in a supine position, arms rested by their side with legs abducted from the mid-line to avoid lower limb contact. Self-disposable electrodes were placed on the dorsal surfaces of the right hand and foot at the distal metacarpals and metatarsals respectively. The BIA generates an excitation current of 500μA at a signal frequency of 50 kHz. Values recorded were TBW in litres and impedance in Ohms. The impedance index (II), which is defined as height^2/impedance, was then calculated. Fat free mass was calculated as TBW/0.73.[14,15]

Statistical analysis

Differences in physical characteristics, TBW, FFM, impedance and II between the patients with CF and controls were determined by t-test. Pearson correlation coefficients were used to determine significant relationships between variables. Limits of agreement for TBW measured via BIA and deuterium dilution were calculated according to the methods described by Bland and Altman.[20]

The relationship between TBW and height^2/impedance in the adults with cystic fibrosis and the controls was modelled by multiple regression, with TBW as the dependent variable. The difference between the groups was modelled by a dummy variable (0/1) identifying the adults with cystic fibrosis, and an interaction between the TBW in the adults with CF and height^2/impedance was also tested for. In effect, whilst TBW is the dependent variable there are three independent variables. Firstly height^2/impedance, secondly the dummy variable (1 or 0) and finally the interaction term which is the product of the dummy variable and height^2/ impedance for each individual. Once those variables have been created, it is necessary to undertake two multiple regression analysis to provide information about potential differences in slopes and intercepts. In the first analysis, TBW is the dependent variable and height^2/impedance and the dummy variable (1/0) are independent variables. If the t-ratio of the dummy variable is statistically significant the intercepts are significantly different. To test the slopes, the same analysis is undertaken but with the addition of the interaction term as a third independent variable. In this analysis, if the t- ratio of the interaction term is significant then the slopes of the two lines are different.

Results

The characteristics of the patients with CF and the healthy controls are presented in Table 1. There were no significant differences in age or height between the two groups. Patients weighed significantly less than controls (P<0.05) and had a significantly lower BMI (P <0.05). Pulmonary function tests demonstrated mild to moderate lung disease in the CF group with mean values for FEV_1 of 2.4 ± 0.7 litres and FVC 3.5 ± 0.8 litres.

There were no significant differences between patients and controls for measures of height^2/impedance or TBW measured via ^2H_2O dilution (Table 1). Patients had significantly greater scores for resistance, measured in Ohms, and TBW measured via BIA (P <0.05) compared to controls.

There was a significant difference between TBW predicted via BIA and TBW measured via ^2H_2O for the patients with CF (P<0.05) but not for controls. There were no differences in either group between FFM measured by ^2H_2O dilution. The mean bias and limits of agreement for patients and controls are presented in Table 2.

Table 1. Physical characteristics of subjects studied

Variable	Cystic fibrosis patients N=36 females=19; males=17		Normal controls N=42 females =27; males=15	
	Mean	SD	Mean	SD
Age (years)	25.4	5.6	25.4	4.8
Weight (kg)	61.9	12.2	68.7*	16.3
Height (cm)	168.7	8.1	170.8	8.8
BMI (kg/m^2)	21.6	2.9	23.8*	4.4
Impedance (Ω)	615	117	569	91
H^2/I (cm^2/Ω)	48.3	11.4	52.9	11.6
TBW - BIA (L)	42.6	14.7	37.4*	7.5
TBW – ^2H_2O (L)	37.1#	8.0	37.9	8.5
FFM - ^2H_2O (kg)	50.8	10.9	52.0*	11.6

* Significantly different from CF patients (P<0.05); # Significantly different from TBW - BIA (L); CF, cystic fibrosis; BMI, body mass index; H^2/I, height^2/Impedance; TBW, total body water; BIA, bioelectrical impedance analysis ^2H_2O, deuterium oxide

Table 2. Limits of agreement for total body water in patients with CF and controls

	Cystic fibrosis subjects (N=36)		Control subjects (N=42)	
	Bias	Limits	Bias	Limits
^2H_2O TBW (L) vs BIA TBW (L)	5.6	-12.7 to 23.8	-0.4	-7.9 to 6.7

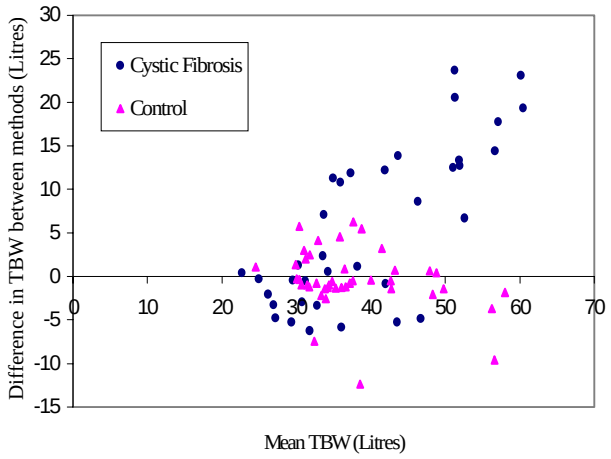

Figure 1. The difference between TBW measured via BIA and deuterium dilution plotted against the average of the two measurements.

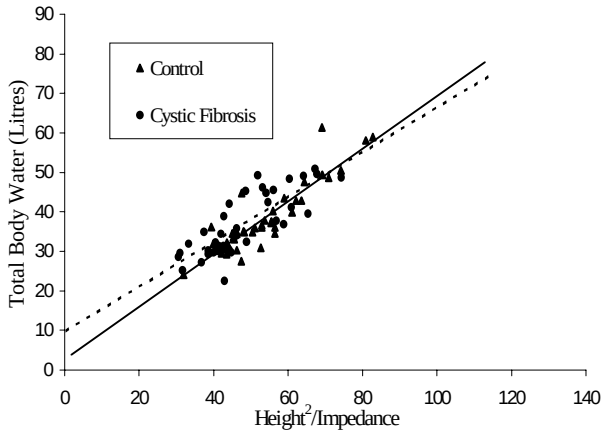

Figure 2. Impedance index versus total body water in CF subjects (circles) and controls (triangles).

A Bland Altman plot of the difference between TBW measurements and the average of the TBW measurements is shown in Figure 1. There is a significant positive correlation for the patients with CF between the means and the differences (r =0.76; P<0.05). No such correlation was found in the controls.

There was a significant correlation between the II and TBW measured via deuterium dilution in patients (r =0.81; $y = 0.57x + 9.6$; P<0.05) and also in controls (r = 0.90; $y= 0.67x + 2.5$; P<0.05). We found no significant differences between groups when examining the slope of the regression line (Fig. 2.) but the y intercept was significantly different between groups (P <0.05).

Discussion

The ability to define and quantify body composition in health and disease is a useful tool that can be used to document changes in growth and predict abnormal ratios of body

compartments that can provide evidence of malnutrition. It is important that the techniques available for this measurement in patients with CF are accurate and suitable for bedside assessment. In this study, two techniques that measure TBW and hence, FFM, (BIA and ^2H_2O dilution) have been compared in patients and in healthy controls.

When comparing the mean values, this study did not demonstrate any significant differences between patients with CF and controls for TBW or FFM as measured by ^2H_2O dilution. We reported a significant difference in weight and BMI between patients and controls, however the contribution of FFM to total body weight did not differ. This indicates that patients in this study had significantly reduced proportions of body fat compared to the controls. The controls did not differ from our patients in age or height.

When comparing TBW measurement techniques within each group a significant difference between BIA and ^2H_2O dilution was found in patients with CF. The BIA method tended to overestimate the true TBW by 5.6 litres in our group of patients. In body composition terms, this is equivalent to approximately 7.6 kg of fat free mass. This is in contrast to the results previously[7] where it was found that BIA underestimates TBW in CF compared to ^2H_2O dilution. Azcue and colleagues[8] showed no difference between TBW measured by BIA and $H_2{}^{18}O$. The difference between methods did not exist for the controls in the present study.

In general, linear regression plots or correlation coefficients have been used compare different techniques for assessing body composition in CF.[7,8,16,21] Whilst this form of analysis provides an indication of the relationship between variables, it is misleading when used to directly compare two methods of measurement. Alternatively the method of Bland and Altman[20] may be used to calculate the limits of agreement (mean ± 2SD) which then highlights within-subject variability between two techniques. The current study has demonstrated that the limits of agreement for patients with CF are much wider than for controls when determining TBW using both ^2H_2O dilution and BIA. In patients the total spread of the limits for the determination of TBW was 36.5 litres and in controls the spread was 14.2 litres. These limits of agreement are too wide for BIA predictions of TBW to be accepted for clinical or research purposes in patients with CF. In addition the fact that Figure 1 shows a significant positive correlation in the patients with CF between the mean TBW and the difference in TBW between methods indicates that the bias is not consistent across the range of body water measured. This suggests that BIA technology overestimates TBW determined by ^2H_2O dilution to an increasing extent at larger volumes. Error of this type may be due to the algorithm used to predict TBW from impedance within the software of the apparatus.

Previous authors[8,17] have examined the relationship between II and TBW in patients with CF and have speculated that the II is the best single predictor of TBW in patients.[8] These studies demonstrated significant correlations between the II and TBW for both patients with CF and healthy controls. These correlations showed the same degree of accuracy between groups, but the relationship between these parameters was different between patients and controls. Azcue and colleagues[8] found a steeper slope in patients with CF whereas Borowitz and Conboy[17] demonstrated a steeper slope in their control subjects. The present study found no differences between patients and controls in the slope of the regression line, but the y intercept differed significantly between groups (Fig 2.).

In summary, this paper indicates that the use of BIA in patients with cystic fibrosis is controversial. We have demonstrated a significant difference in patients between BIA and ^2H_2O dilution for determining TBW with very wide limits of agreement between techniques. Also, we found BIA over-predicted TBW in CF to an increasing extent as the TBW volume increased. The fact that similar observations were not found in our controls indicates that predictive equations developed for healthy individuals may not be valid in patients with CF. The reason for this however is not clear. Disturbed water balance is unlikely to be the reason, as bioelectrical impedance measures both intracellular and extracellular components simultaneously.

Equally, fundamental deviations from the electrical theory that underpins the bioelectrical impedance method are also unlikely. The assumptions in the electrical theory relate primarily to the shape and configuration of the conductor and whilst the patients with cystic fibrosis were lighter and shorter than the controls fundamentally their shape and configuration is no different. Therefore, there is a need to develop regression equations that can be used to predict TBW, and hence FFM, from impedance values obtained from BIA in patients with CF.

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References

1. Schwachman H, Kulczycki L. Long term study of 105 patients with cystic fibrosis. Am J Dis Child 1958; 96: 6-15.
2. Sproul A, Huang N. Growth patterns in children with cystic fibrosis. J Pediatr 1964; 65: 664-676.
3. Wells A, Bond GM, Fon PJ, Marshall DJ, Shepherd RW. A cross-sectional study of pulmonary function and nutritional status of children with cystic fibrosis. J Food Nutr 1984; 41: 65-71.
4. Soutter V, Kristidis P, Gruca MA, Gaskin KJ. Chronic undernutrition/growth retardation in cystic fibrosis. Clinics Gastroenterol 1986; 15 (1): 137-155.
5. Lai H, Kosorok MR, Sondel SA, Chen ST, FitzSimmons SC, Green CG, Shen G, Walker S, Farrell PM. Growth Status of children with cystic fibrosis based on the National Cystic Fibrosis Registry data: evaluation of various criteria used to identify malnutrition. J Pediatr 1998; 132: 478-485.
6. Lands L, Gordon C, Bar-Or O, Blimkie CJ, Hanning RM, Jones NI, Moss LA, Webber CE, Wilson WM, Heigenhause JF. Comparison of three techniques for body composition analysis in cystic fibrosis. J Appl. Physiol 1993; 75 (1): 162-166.

7. Newby M, Keim NL, Brown DL. Body composition of adult cystic fibrosis patients and control subjects as determined by densiometry, bioelectrical impedance, total-body electrical conductivity, skinfold measurements, and deuterium oxide dilution. Am J Clin Nutr 1990; 52: 209-213.
8. Azcue M, Fried M, Penchartz PB. Use of bioelectrical impedance analysis to measure total body water in patients with cystic fibrosis. J Pediatr Gastroenterol Nutr 1993; 16: 440-445.
9. Cheek DB. Human Growth: Body Composition, Cell Growth, Energy, and Intelligence. Philadelphia: Lean & Febiger, 1968.
10. Quinton PM, Bijman J. Higher bioelectrical potentials due to decreased chloride absorption in the sweat glands of patients with cystic fibrosis. N Engl J Med 1983; 308: 1185-1189.
11. Schoeller D, Van Santen E, Peterson DW, Dietz W, Jaspan J and Klein PD. Total body water measurement in humans with ^{18}O and ^{2}H labelled water. Am J Clin Nutr 1980; 33: 2686-2692.
12. Cha K, Chertow GM, Gonzalez J, Lazarus M, Wilmore DW. Multifrequency bioelectrical impedance estimates the distribution of body water. J Appl Physiol 1995; 79 (4): 1316-1319.
13. Hoffer E, Meador CK, Simpson DC. Correlation of whole body impedance with total body water content. J App Physiol 1969; 27: 531-535.
14. Forbes G. Methods for determining composition of the human body. Pediatrics 1962; 29: 477-494.
15. Behnke A, Wilmoe JH. Evaluation and regulation of body build and composition. New Jersey: Prentice Hall, 1974.
16. Spicher V, Roulet M, Schaffner C, Schultz Y. Bioelectrical impedance analysis for estimation of fat-free mass and muscle mass in cystic fibrosis patients. Eur J Pediatr 1993; 152: 222-225.
17. Borowitz D, Conboy K. Are bioelectrical impedance measurements valid in patients with cystic fibrosis? J Pediatr Gastroenterol Nutr 1994; 18: 453-456.
18. Kraemer H, Thiemann S. How Many Subjects? California: Sage Publications Inc, 1987.
19. Halliday D, Miller AG. Precise measurement of total body water using trace quantities of deuterium oxide. Biomedical Mass Spectrometry 1977; 4: 82-89.
20. Bland J, Altman D. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 8: 307-310.
21. Johnston J, Leong MS, Checkland EG, Zuberbuhler PC, Conger PR, Quinney HA. Body fat assessed from body density and predicted from skinfold thickness in normal children and children with cystic fibrosis. Am J Clin Nutr 1988; 48: 1362-1366.