New bioelectrical impedance formula for patients with respiratory insufficiency: comparison to dual-energy X-ray absorptiometry


ABSTRACT: Malnutrition in patients with severe respiratory insufficiency can lead to severe complications, justifying the use of objective nutritional assessment techniques, such as bioelectrical impedance analysis (BIA), which is an easy, noninvasive method of measuring body composition. The purpose of this study was to develop, and validate against dual-energy X-ray absorptiometry (DXA), a BIA formula to predict fat-free mass (FFM) specific for patients with chronic severe respiratory insufficiency.

Seventy-five ambulatory patients (15 females and 60 males) with severe chronic respiratory insufficiency (obstructive and restrictive) aged 63.6±19.2 yrs (mean±SD), in a stable pulmonary and cardiac condition for 2 months, were measured simultaneously with BIA and DXA. Patients younger than 45 yrs of age and with a body mass index S32 kg/m² were excluded.

The best-fitting multiple regression equation to predict FFM = -6.06 + (height × 0.283) + (weight × 0.207) - (resistance × 0.024) + (sex (males=1, females=0) × 0.024) + (age × (age - 33) × 0.024), gave a correlation coefficient of r=0.952, slope±SEM 0.902±0.034, standard error of the estimate 1.670, and p<0.0001. The mean difference for FFM was 0.2±2.3 kg (mean±SD) and percentage fat mass was -0.7±3.8%.

These results suggest that the bioelectrical impedance analysis formula specific to patients with severe respiratory insufficiency give a better correlation and smaller mean differences than 12 different bioelectrical impedance analysis formulae described in the medical literature. A prediction equation, validated against dual-energy X-ray absorptiometry and based on subjects with similar clinical characteristics, is more applicable to the patients with respiratory insufficiency than a formula developed for healthy subjects.


Severe respiratory insufficiency causes patients to be intolerant of physical effort and to be frequently limited in their daily activity and results in an imbalance between food intake and nutritional needs. Undernutrition and overnutrition can both affect the quality of life and survival of patients with pulmonary disease. Protein-energy malnutrition can lead to quantitative, qualitative and functional alterations of muscle [1, 2] and this affects muscle function, including respiratory muscle in patients with already limited respiratory reserves. Optimal adaptation of nutrition support through the assessment of fat-free mass (FFM) and fat mass (FM) in patients with chronic respiratory insufficiency can avoid or minimize muscle wasting or obesity. For these reasons, the nutritional assessment should include body composition measurements which are based on objective rather than subjective criteria of nutritional evaluation. Body composition can be measured by a number of techniques, including hydrodensitometry, isotope dilution, and whole-body counting of potassium-40 [3]. However, these methods are not easily applicable in ill subjects.

More recent methods for the determination of the FFM are dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA). DXA has been validated against independent methods, including a gamma neutron-activation model [4, 5], total body potassium and hydrodensitometry [6] and is becoming one of the reference methods for body composition analysis, but requires sophisticated technology. BIA is a method of measuring body composition which is easy, noninvasive and inexpensive [7]. BIA measurements have been validated in healthy adults [8–10]. The relationship between body impedance and body composition is dependent on age and sex [11, 12]. Over 20 different formulae permit the calculation of the FFM and FM based on BIA measurements and have generally been validated in healthy, young adults. SCHOLS et al. [13] proposed a BIA formula validated against deuterium dilution for patients with chronic obstructive pulmonary disease (COPD) (n=24), which included weight and height/resistance (ht/R) as independent variables. Recently, PICHARD et al. [14] were unable to obtain clinically relevant correlations between FFM calculated by 12 BIA formulae [8, 9, 11, 15–21], including SCHOLS et al. [13], and DXA-determined FFM, and suggested that a specific formula should be developed for patients with chronic severe respiratory insufficiency.
The purpose of this study was to develop a specific BIA formula for patients >45 yrs old with chronic severe respiratory insufficiency. A validated specific BIA formula would allow the use of BIA for the sequential evaluation of lean tissue and fat reserves and of evolitional changes in these parameters in these patients.

Subjects and methods

Seventy-five ambulatory patients (15 females and 60 males) with severe chronic respiratory insufficiency in a stable clinical condition, aged 45–86 yrs, were included in this study. Table 1 shows the physical characteristics and diagnoses of the patients. Because pulmonary diseases of young patients with respiratory insufficiency are usually different (e.g. cystic fibrosis and myopathies) and patients have different characteristics (table 1), patients under 45 yrs of age were excluded. Nearly 79% of the present patients suffer from COPD. Reviews of the incidence in COPD young patients with respiratory insufficiency are usually diagnoses of the patients. Because pulmonary diseases of stable clinical condition, aged 45–86 yrs, were included in males) with severe chronic respiratory insufficiency in a study group. Thirty-six per cent of the patients were under maintenance medication included theophylline, inhaled or oral corticosteroids and β-agonists (10% of patients). Patients who chronically received steroids (>20 mg prednisone) or diuretics were excluded. Height, weight, BIA and DXA measurements were obtained during the same clinic visit to ensure that the measurements were comparable.

Anthropometric measurements and bioelectrical impedance

Body height was measured to the nearest 0.5 cm and body weight to the nearest 0.1 kg on a balance beam scale. BIA was used to determine FFM and FM as previously described [8, 10, 15, 25, 26]. Estimates are made of body composition from whole-body bioelectrical impedance, \( V = \rho \times h/t/R \), in which the conductive volume \( V \) is assumed to represent FFM, \( \rho \) is the specific resistivity of the conductor, height \( h/t \) is taken as the length of the conductor, and whole-body resistance \( R \) is measured with four surface electrodes placed on the wrist and ankle. Thus, the volume of FFM is directly proportional to \( h/t/R \). In brief, an electrical current of 50 kHz and 0.8 mA was produced by a generator (Bio-Z®; New Cardiopc, Fribourg, Switzerland) and applied to the skin using adhesive electrodes (Sentry Silver Sircuit®; Sentry Medical Products, Irvine, CA, USA) placed on all right side-limbs with the patient in decubitus dorsalis as described previously [27]. The Bio-Z® generator has been cross-validated against the RJL-109® and 101® analysers (RJL Systems, Clinton, MI, USA) and at 50 kHz against the Xiton® analyser (Xiton Technologies, San Diego, CA, USA). The cross-validation produced results of ±5 \( \Omega \) for the resistance and can therefore be considered equivalent. Short-term and long-term reliability of resistance measurements indicate coefficients of variation of 1.8–2.9% [15, 28]. The skin was cleaned with 70% alcohol. Age, sex, height, weight, resistance and reactance were used as independent variables to predict FFM and FM as compared to DXA-derived FFM and FM.

Dual-energy X-ray absorptiometry

The DXA-based technique for body composition measurement requires: 1) general assumptions inherent in the body compartment approach (i.e. soft tissue = body weight - skeletal mass, and soft tissue = fat + water-equivalent tissue), and 2) specific assumptions (soft tissue overlying bone cannot be sampled and its composition has to be extrapolated from the composition of adjacent tissue). DXA is a scanning technique which measures the differential attenuation of two different energy level X-rays as they pass through the body. These measurements allow the determination of bone mineral content and soft tissue mass on a pixel-per-pixel basis. Then, the soft tissue mass is partitioned into fat and nonfat lean body mass by a calibration procedure based on the attenuation of the soft tissue outside the bone and the attenuation of an external dedicated phantom [29, 30]. The advantage is that the method permits, in a few minutes, the derivation of the total FM directly rather than by subtracting the other body compartments [4]. The reproducibility of the measurements is
excellent: 1.2% for the total FFM and FM [31, 32] and 0.5% for the bone mineral content. The FM derived from DXA measurements correlates well with FM determined by hydrodensitometry and total body K measurements [4, 29, 32, 33]. An advantage of DXA over hydrodensitometry, total body potassium and water dilution is that it can provide information about the composition of body segments and muscle mass and the distribution of fat between trunk and limbs [34]. All measurements were performed using Hologic CDR-2000® (Hologic, Waltham, MA, USA, Enhanced Whole-body 5.54 software version).

Statistical analysis

Results are expressed as mean±s.d. Multiple regressions were calculated to test correlations between DXA and the various independent variables (sex, age, height, weight, resistance, reactance, ht2/R) to predict FFM by BIA. Bland-Altman [35] analysis was used to compare the DXA results generated by DXA to those of BIA. The differences between the values are plotted against the DXA-derived FFM. This analysis allows the calculation of the bias (estimated by the mean differences) and the limits of agreement (two standard deviations of the difference) [35]. Statistical significance was set at p<0.05 for all tests.

Results

Table 1 summarizes the physical characteristics, diagnoses and pulmonary functions of the study group. The patients had a mean age of 65.6±9.1 yrs, weight of 54.6±9.8 kg and BMI of 19.3±3.7 kg·m⁻², which is below the normal range for this age of population.

Table 2 shows the results of the five different multiregression calculations for FFM and FM by BIA compared to DXA in males, females and both groups combined.

| Table 2. – Correlations, slope and standard error of the estimate (see) for fat-free mass (FFM) and fat mass (FM) measured by bioelectrical impedance analysis (BIA) or dual-energy X-ray absorptiometry (DXA) |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| BIA formula variables | FFM | | | FM | |
| | r | slope±SEM | SEE kg | TE kg | r | slope±SEM | SEE kg | TE kg |
| **Both sexes (n=75)** | | | | | | | | |
| Age, sex, ht, wt, R, Xc | 0.95 | 0.91±0.03 | 1.67 | 1.73 | 0.98 | 0.95±0.03 | 1.70 | 1.72 |
| Sex, ht, wt, R | 0.95 | 0.90±0.03 | 1.67 | 1.75 | 0.98 | 0.95±0.03 | 1.72 | 1.76 |
| Sex, ht, wt, Xc | 0.93 | 0.87±0.04 | 1.94 | 2.06 | 0.97 | 0.93±0.03 | 2.02 | 2.06 |
| Sex, ht, R, Xc | 0.90 | 0.81±0.05 | 2.25 | 2.47 | 0.55 | 0.30±0.05 | 3.67 | 6.59 |
| Sex, ht/R, Xc | 0.86 | 0.74±0.05 | 2.53 | 2.88 | 0.55 | 0.30±0.05 | 3.67 | 6.60 |
| **Males (n=60)** | | | | | | | | |
| Age, ht, wt, R, Xc | 0.93 | 0.87±0.04 | 1.41 | 1.50 | 0.98 | 0.95±0.03 | 1.48 | 1.51 |
| Ht, wt, R | 0.93 | 0.86±0.06 | 1.48 | 1.57 | 0.97 | 0.95±0.03 | 1.55 | 1.56 |
| Wt, ht/R | 0.88 | 0.78±0.05 | 1.75 | 1.96 | 0.96 | 0.92±0.04 | 1.91 | 1.96 |
| Ht, R, Xc | 0.88 | 0.78±0.05 | 1.75 | 1.95 | 0.44** | 0.19±0.05 | 2.74 | 6.10 |
| Ht/R, Xc | 0.78 | 0.61±0.06 | 2.05 | 2.60 | 0.39** | 0.15±0.05 | 2.46 | 6.27 |
| **Females (n=15)** | | | | | | | | |
| Age, ht, wt, R, Xc | 0.96 | 0.92±0.08 | 1.49 | 1.49 | 0.99 | 0.97±0.05 | 1.51 | 1.51 |
| Ht, wt, R | 0.95 | 0.91±0.08 | 1.53 | 1.52 | 0.98 | 0.97±0.05 | 1.60 | 1.60 |
| Wt, ht/R | 0.89 | 0.79±0.11 | 2.17 | 2.28 | 0.97 | 0.93±0.07 | 2.36 | 2.28 |
| Ht, R, Xc | 0.65 | 0.42±0.14 | 2.65 | 3.83 | 0.67 | 0.46±0.14 | 4.63 | 6.37 |
| Ht/R, Xc | 0.51 | 1.14±0.54 | 2.71 | 3.75 | 0.45† | 0.20±0.11 | 3.62 | 7.71 |

ht: height; wt: weight; R: resistance; Xc: reactance. Total error (TE)=[(FFMBIA - FFMDXA)/n]. **: p<0.01; †: p=nonsignificant; all others p<0.0001.
Table 3. – Comparison of fat-free (FFM) and fat (FM) mass as measured by bioelectrical impedance analysis (BIA) and dual-energy X-ray absorptiometry (DXA)

<table>
<thead>
<tr>
<th></th>
<th>Females (n=15)</th>
<th>Males (n=60)</th>
<th>All (n=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance Ω</td>
<td>577.3±88.0</td>
<td>522.8±83.7</td>
<td>533.7±86.7</td>
</tr>
<tr>
<td>Reactance Ω</td>
<td>64.7±16.9</td>
<td>63.3±19.9</td>
<td>63.6±19.2</td>
</tr>
<tr>
<td>FM kg</td>
<td>36.0±4.0</td>
<td>35.8±5.2</td>
<td>36.0±4.0</td>
</tr>
<tr>
<td>FM %</td>
<td>31.1±10.8</td>
<td>31.8±10.4</td>
<td>31.0±10.2</td>
</tr>
<tr>
<td>Difference FFM (BIA-DXA) kg</td>
<td>0.2±2.3</td>
<td>0.2±1.6</td>
<td>0.2±1.8</td>
</tr>
<tr>
<td>Difference % FM (BIA-DXA)</td>
<td>-0.7±3.8</td>
<td>-0.3±3.0</td>
<td>-0.4±3.1</td>
</tr>
</tbody>
</table>

Values are shown as mean±SD.

Discussion

With the availability of portable BIA machines, the clinical use of BIA has markedly increased in recent years and has facilitated the assessment of nutritional status of healthy and ill individuals. A progressive change in body composition is anticipated in patients with chronic respiratory diseases with increasing age, progression of the disease, severe disability and lack of mobility. The precision of formulae published in the literature, however, depends on a number of factors, including age and state of hydration. The purpose of this study was to determine the best regression equation for the prediction of FFM determined by BIA in comparison to DXA-derived FFM in patients with severe chronic respiratory insufficiency.

Patient population

Patients had a severe chronic ventilatory insufficiency (mean forced expiratory volume in one second (FEV1) = 36.2±13.0% of predicted) and suffered from obstructive or restrictive pulmonary diseases, with various consequences on their nutritional status. Nutritional assessment by BIA or DXA is desirable because it permits the detection of low FFM in patients who may not be significantly below ideal body weight, but who have an excess of FM that may mask protein malnutrition. Given that a large portion of the population studied was underweight, this validation is limited. Indeed, most of the subjects in this study had a low BMI and could be reasonably well detected as being undernourished by height, weight, age and sex alone. Severely obese patients (BMI >32 kg·m⁻²) were excluded from the study to eliminate a possible methodological bias introduced by excessive FM in obese patients [21, 23]. Half of the subjects included in this study were underweight, with a BMI of 018.5 kg·m⁻², and a few of the subjects were overweight (BMI 27–32 kg·m⁻²). Such a distribution reflects the usual body weight in a population of respiratory insufficiency and adds further value to the study results.

Fewer females were included in the study, because fewer females subjects with respiratory insufficiency presented themselves to the outpatient clinic and it has been shown that the incidence of COPD has a male predominance of up to 10:1 [22].

Comparison of two methods of body composition

The rationale was to compare two different methods for measuring body composition that measure independent parameters, *i.e.* electrical variation (BIA) versus photon absorption (DXA). BIA has been cross-validated with hydrodensitometry [9], skinfold measurements [36, 37] and deuterium dilution in healthy subjects [38, 39]. Disease and body composition compartments that deviate from normal may result in changes that invalidate the prediction equations derived from healthy adults with normal weight [40]. Therefore, prediction equations for this subgroup of respiratory patients should be validated.

Pichard et al. [14] tested 12 different prediction equations [8, 9, 11, 13, 15–21] from the medical literature in a group of patients with respiratory insufficiency and found that correlation coefficients varied from r=0.66 to 0.94 with variations in mean FFM of -1.9–+8.0 kg [14]. Such variations preclude clinical utilization. The COPD-specific formula by Sökel et al. [13], which included 24 males and 8 females, correlated height to deuterium-determined total body water. Their formula overestimated the FFM by 5.1±3.1 kg in females and by 3.8±3.1 kg in males, with similar pathologies to the patients in the study by Pichard et al. [14]. Their patient sample may have been too small to control adequately for patient variability. Segal et al. [9] and Van Loan and Mayclin [17] noted sex differences in FFM and FM. Sex-based formulae appear to improve the prediction of BIA [41]. The lack of concordance noted between the results of Sökel et al. [13] and those of Pichard et al. [14] is also likely to be due to the different validation criteria (deuterium dilution versus DXA).
The best-fit prediction equation for this group of respiratory insufficiency patients was: FFM = -6.06 + (height × 0.283) + (weight × 0.207) - (resistance × 0.024) + (sex (males = 1, females = 0) × 4.036), with r=0.952. The prediction equation developed in this study has an SE of 1.67 kg and can be considered ideal as rated according to the system reported by HOUTKOOPER et al. [42]. Patients with BMI >32 kg·m⁻² were excluded because the degree of variation in FM is greater in more obese individuals and leads to greater prediction errors [21, 23].

Variables influencing prediction accuracy of bioelectrical impedance analysis equations

HOUTKOOPER et al. [42] noted ht/R to be the best single predictor of body composition. The addition of other independent variables such as age and sex was thought to adjust for the geometric complexity of the human body and helped to improve the fit of the prediction model. Because sex has been shown to be a factor that influences FFM and FM, the males and females were examined separately [9]. However, the goal was to combine the males and females if this was justified by the results of the analysis. For practical application of the BIA in the clinical setting, it would be an advantage to have only one equation, as long as the prediction ability of the equation is not compromised.

In the present subjects the best prediction equation for FFM was obtained when height, weight, age, resistance, reactance and sex (if males and females were combined) were included. Age and reactance, however, did not significantly influence the prediction equation (p=0.44 and 0.32, respectively). Therefore the prediction equation chosen was the one that included height, weight, resistance and sex as independent variables. Resistance by itself was not a good predictor of body composition (r=0.52, SEE=4.9 kg), because it is not an indicator of body size or volume. However, when resistance was combined with height (r=0.88, SEE=2.7 kg), it predicted FFM better than height and weight (r=0.81, SEE=3.4 kg) and ht/R (r=0.82, SEE=3.3 kg) (data not shown). SJALPARTZ et al. [21] found that prediction equations which included weight as well as height and resistance as independent variables improved the prediction accuracy of BIA. This was confirmed in the present study (r=0.93 and 0.95, SEE=1.67 and 1.94 kg, respectively). Prediction formulae that included ht/R with or without weight and resistance and reactance without weight decreased the prediction accuracy of BIA in all three groups (males, females and both sexes combined).

The predictive capacity of BIA using height, weight, resistance and sex for FM was excellent in males and females, separately or combined, in this study; however, the use of BIA to predict FM is not recommended. BIA measures body conductivity based on water and electrolyte content, appears to be quantitatively related to lean mass and measures FM neither quantitatively (kg of fat) nor qualitatively (fat as a percentage of total body weight) [9]. Since arms and legs contribute approximately 80% of resistance and reactance, it is possible that the FM could be underestimated in older subjects with primarily truncal fat accumulation.

No attempt was made to predict total body water, since isotope dilution studies were not used in the subjects of this study. Variations in hydration could affect the predictive capacity of BIA formulae. In haemodialysis and intensive care patients, it has been noted that excess intracellular or extracellular fluid causes an overestimation of the total body water. When the hydration level of the FFM is >73%, BIA overestimates the FFM and underestimates the FM. In these patients, BIA no longer permits accurate estimation of FFM with prediction equations that were developed for healthy subjects with normal hydration levels. Patients with visible oedema and fluid retention were excluded to minimize errors as a result of hydration status. All patients were in a clinically stable state (no decompensation for >2 months). While it is possible that the subjects in this study differed in hydration state and therefore in body density from the normal population, an attempt was made to have excluded patients with excess fluid of >1 L and error due to abnormal hydration levels was minimized.

**Dual-energy X-ray absorptiometry**

Although DXA is not yet considered to be the “gold standard” for measuring body composition, it is one of the best reference methods [43]. DXA estimates the FM without making assumptions related to lean mass, potassium concentration or density, which are the basis of traditional methods, such as underwater weight, total body potassium and total body water techniques [44]. DXA measures the soft tissue and bone mass independently and then separates the soft tissue into lean mass and FM. There remains, however, some discussion about comparability of different hardware and software, and previous studies have noted that caution must be exercised when making comparisons between studies if different hardware and software versions have been used [45–47]. TOTHILL et al. [46] found that percentage FM measured by Hologic DXA was not significantly different from that obtained by underwater weighing. They also noted that Hologic instruments re-reported lower FM than Lunar and Norland DXA. SNEAD et al. [47] suggested that DXA underestimates the percentage FM in older and obese subjects, owing to an underestimation of truncal fat [47]. Hologic Enhanced Version 5.54 software was used in this study. In a number of measurements it was found that the percentage FM was 2.2±3.6% greater with this software version than with a previous version (whole-body 5.35). Therefore the problem of underestimation of FM appears to have been corrected with newer versions of the Hologic software.

A limitation of DXA is that it does not measure total body water separately from the FFM. Therefore excess body hydration would result in overestimation of the FFM, as is noted with BIA. Further validation studies in ill subjects using DXA as a criterion measure should simultaneously measure water compartments (i.e. deuterium oxide dilution) to determine abnormalities in hydration state.

Sixty-eight per cent of patients in this study with respiratory insufficiency walked <1,000 m·day⁻¹, as assessed by a pedometer (unpublished data). Subjects with similar heights and weights have different quantities of FFM and FM depending on the amount of physical activity tolerated...
by individual patients. Pichard et al. [48] found that BIA formulae that resulted in excellent correlations in normal controls resulted in poor correlations in elite runners and vice versa. It is, therefore, possible that the validity of BIA formulae depends on the degree of activity rather than on pathology. Further research into the validation of BIA should, therefore, look at ambulatory capacity in ill subjects and investigate whether physical activity must be considered as a factor in choosing the prediction equation for estimating the FFM and FM in subjects, regardless of primary diagnosis.

**Study limitations**

A limitation of this study was the relatively small subject pool. In addition, the statistical analysis used population-based concepts which are not directly applicable to individual subjects. Further validation is necessary to confirm the robustness of the proposed equation.

**Conclusions**

The present results suggest that bioelectrical impedance analysis, a simple and noninvasive procedure, is relevant in the clinical assessment of body composition of patients with severe respiratory insufficiency when using a prediction equation based on subjects with similar characteristics. The best-fitting multiple regression equation to predict fat-free mass included height, weight, resistance and sex. The present prediction equation should be used with caution in individuals younger than 45 yrs of age and with a body mass index $532 \text{ kg} \cdot \text{m}^{-2}$.

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**References**


