Whole-body bioelectrical impedance analysis in patients with chronic heart failure: reproducibility of the method and effects of body side

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Background. **Fluid imbalance and malnutrition have an important role in the clinical setting of chronic heart failure (CHF). Recently, tetrapolar bioelectrical impedance analysis has been suggested as an attractive method which may be used in the clinical assessment of the body composition. The aim of this study was to determine the effects of body side on whole bioelectrical impedance analysis parameters and test-retest reliability, prior to its use in a large cohort of patients.**

Methods. **In 114 consecutive patients with CHF (mean age 65 ± 10 years, left ventricular ejection fraction 31 ± 9%, NYHA functional class 2.6 ± 0.9) we measured the total body resistance, the reactance and the derived angle phase using a single-frequency (50 KHz) tetrapolar plethysmograph device. The evaluations were performed on the left and right sides of the body, in a random order, on two different occasions 30 min apart. The effects of body side were analyzed by the Student's t-test and the test-retest reliability was computed by using the coefficient of variation and intraclass correlation coefficient.**

Results. **In both evaluations, the mean resistance value of the right side was significantly lower (almost 10 ohms) than that of the left side, the reactance was not different, and as a consequence the angle phase was significantly higher (almost 0.1°) in the right than in the left side. The test-retest reliability for all the measurements considered was very high (the intraclass correlation coefficient ranged from 0.95 to 0.99 and the coefficient of variation from 1.7 to 4.3%).**

Conclusions. **In CHF, the body side is important for the whole-body assessment of the resistance and the angle phase, but not for reactance. In addition, all these measurements are characterized by an excellent test-retest reliability and, consequently, do not necessitate a substantial increase in the sample size for the detection of small differences in experimental studies.**

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Patients with heart failure are characterized by alterations in the body fluid content and distribution[1-3] that usually imply adjustments of the dosage of diuretics and sodium intake. In addition, many patients with chronic heart failure (CHF) develop a wasting syndrome, known as cardiac cachexia, that is a strong independent risk factor for a poor prognosis[4]. This syndrome is diagnosed when a history of weight loss is reported[4]; however, the possibility of assessing the nutritional status on the basis of body weight may be misleading if the body fluid content is not taken into consideration. Densitometry, isotope dilution and total body potassium counting are the reference methods for the assessment of body composition, but these techniques are sophisticated, costly, time-consuming and inconvenient, and therefore they are unsuitable for clinical practice[5]. Tetrapolar bioelectrical impedance analysis seems to be an attractive tool for the clinical assessment of human body composition since it is non-invasive, safe, inexpensive, portable, rapid, and easy to use[6]. On the basis of these considerations, the clinical usefulness of whole-body bioelectrical impedance analysis has been tested in a limited number of CHF patients and in particular for the objective measurements of the directional changes in fluid status[7-12].

The aim of the present study was to assess the effects of the body side on the primary impedance parameters and their reproducibility in CHF before its inclusion in clinical trials, and to provide the basic data necessary to determine the appropriate sample size for future studies.

Methods

Patient population. Between September and December 2000, we consecutively enrolled 114 hospitalized patients with CHF in accordance with standard criteria[13]. Patients with amputated limbs or extensive cutaneous diseases were excluded. The clinical characteristics of the patients are given in table I. All patients were receiving standard medical treatment consisting of diuretics (92%), beta-blockers (33%), ACE-inhibitors (76%), angiotensin II receptor blockers (10%), digitalis (58%), aspirin (52%), antiarrhythmics (38%), nitrates (30%), warfarin (44%), calcium antagonists (11%), and statins (27%) in various combinations. In accordance with the criteria of Anker et al.[4], 14.9% of the patients were defined as cachetic. The study was approved by the local Ethics Committee, and written informed consent was obtained from all patients.

Bioelectrical impedance analysis. In the morning, all patients underwent two evaluations separated by a time interval of 30 min. The last meal was eaten at least 2 hours before the first evaluation and consisted of a light breakfast without coffee or tea. Between the two examinations any drug, meal or strong physical activity was not permitted. Bioelectrical measurements were obtained from patients with the arms abducted 45° from the legs, clothed but without shoes or socks, placed on a cot in a supine position using a tetrapolar impedance plethysmograph that emitted an 800 μA alternating sinusoidal current at a frequency of 50 KHz (model STA/BIA, Akern RJL Systems, Florence, Italy). The electrode (Blue Sensor SP-00-S, Medicotest A/S, Ølstykke, Denmark) configuration consisted of two measurement electrodes and two distally positioned (near 5 cm) drive electrodes[14]. The measurement electrodes were positioned ipsilaterally on the dorsal surface of the wrist at the level of the processes of the radial and ulnar bones, and on the anterior surface of the ankle between the protruding portions of the tibial and fibular bones. The drive electrodes were positioned on the dorsal surface of the third metacarpal bone of the hand and the dorsal surface of the third metatarsal bone of the foot. The alternating current was delivered by means of the distal electrodes of the hand and foot, and the voltage drop was detected by the proximal electrodes. The external calibration of the instrument was checked with a calibration circuit of known impedance value (resistance 380 ohms, reactance 47 ohms, error 1%). The mean of three consecutive resistance (ohms), reactance (ohms) and phase angle (obtained using the formula: atan reactance/resistance and expressed in degrees) measurements was used for analysis. This procedure was obtained for the left and right sides, in a random order and repeated fully (i.e., the electrodes were also replaced) by the same investigator (G.P.) after 30 min.

Table I. Clinical characteristics of 114 consecutive patients with chronic heart failure.

Age (years)	65 ± 10 (39-86)
Sex (M/F)	77/37
Body mass index (kg/m^2)	29 ± 5 (18-41)
NYHA functional class	
I	17
II	32
III	47
IV	18
Cardiac cachexia (n=)	17
Diabetes (n=)	31
Underlying heart disease (n=)	
Coronary artery disease	48
Cardiomyopathy	32
Valvular disease	22
Systemic hypertension	15
Others	7
Laboratory measurements	
Sodium (mmol/l)	137 ± 4 (120-147)
Potassium (mmol/l)	4.2 ± 0.5 (2.7-5.9)
Creatinine (μmol/l)	113 ± 5 (12-323)
Hemoglobin (g/dl)	1.3 ± 0.2 (0.9-1.84)
Erythrocyte sedimentation rate (mm/hr)	27 ± 26 (2-106)
Left ventricular ejection fraction (%)	31 ± 9 (19-55)

Values are expressed as mean ± SD (ranges given in brackets).

Statistical analysis. Data are reported as mean values ± SD. The Student's t-test for paired data was used to compare the measurements between the left and right side of the body. A p value < 0.05 was considered statistically significant. The reproducibility of data was evaluated by means of the intraclass correlation coefficient (ICC)[15] and the coefficient of variation (CV). Thus:

$$ICC = SD^2_{between}/(SD^2_{between} + SD^2_{within})$$

In particular, the reproducibility was considered good if the ICC was between 0.61 and 0.80, and almost perfect if it was between 0.81 and 1. Besides:

$$CV = SD_{within}/mean_{both\ measurements} * 100\%$$

with low values representing good reproducibility.

Since an unreliable measurement of the response variable increases the sample size necessary to detect an important treatment difference with a specified probability, in accordance with Fleiss[15] we then corrected the sample size required for the value of the ICC:

Sample size corrected = sample size required/ICC

Results

The test was performed in all patients. In both evaluations, the mean resistance value of the right side was significantly lower than that of the left side, the reactance was not different, and as a consequence the angle phase was significantly higher in the right than in the

left side (Table II). The values of the ICC derived from all the measurements obtained at the first and second evaluations for the right and left sides were almost perfect and approximately equal to 1. In particular, the ICC values of resistance, reactance and angle phase were 0.99, 0.97 and 0.95 for the left side and 0.99, 0.98 and 0.98 for the right side respectively. These excellent test-retest reliabilities were confirmed by CVs of resistance, reactance and angle phase that were 1.9, 3.2 and 2.7% for the left side and 1.7, 4.3 and 3.9% for the right side respectively.

The sample size for parallel group studies were designed for resistance, reactance and angle phase and the number of subjects with CHF to be included in clinical trials is given in tables III-V.

Discussion

Bioelectrical impedance analysis has become an important method for the assessment of the nutrition and fluid status in humans. The primary impedance parameters are resistance, reactance and the derived phase angle. The principles of bioelectrical impedance analysis postulate that resistance is the opposition of the total body water and electrolytes to the flow of an alternating current of low amplitude and high frequency, and that reactance is the capacitance produced by the tissue interface and cellular membranes. The phase angle is quantified geometrically as the angular transformation of the ratio between reactance and resistance and was used as a measurement of the electrical cellular membrane effects. These measurements are used to estimate the body composition by means of empirical equations based on their correlation with validated reference methods. These equations are frequently used to predict the total body water, the lean body mass and the total body cell mass[5,6]. A large body of the literature concerning bioelectrical impedance analysis in medical journals during the last decade suggests its utilization in healthy subjects of different ages and in patients with different diseases. Although the body composition could be profoundly altered in CHF, surprisingly few data are available as far as bioelectrical impedance analysis in this syndrome is concerned[7-12]. In 1994, Sergi et al.[7] found that in CHF bioelectrical impedance analysis at 50 KHz explained 89% of the extracellular water variability, and more recently, Steele et al.[11] measured the total body water using stable isotope dilution and single-frequency bioelectrical impedance analysis in 12 men with CHF in NYHA classes II-III and reported a strong correlation between the two methods

Table II. Whole-body bioelectrical impedance parameters.

	First evaluation		Second evaluation	
	Left side	Right side	Left side	Right side
Resistance (ohms)	540 ± 102	530 ± 103*	546 ± 104	535 ± 103*
Reactance (ohms)	59 ± 13	59 ± 13	60 ± 14	60 ± 14
Phase angle (degrees)	6.3 ± 1.1	6.4 ± 1.1*	6.3 ± 1.2	6.4 ± 1.1*

Values are expressed as mean ± SD. * $p < 0.05$ vs left side.

Table III. Sample size table when resistance is under investigation ($\alpha = 0.05$).

Difference (ohms)	Power of 0.80		Power of 0.90		Power of 0.95	
	N	NC	N	NC	N	NC
10	1648	1665	2206	2229	2728	2756
20	412	417	552	558	682	689
30	184	186	246	249	304	308
40	103	105	138	140	171	173
50	66	67	89	90	110	112
60	46	47	62	63	76	77
70	34	35	46	47	56	57
80	26	27	35	36	43	44
90	21	22	28	29	34	35
100	17	18	23	24	28	29

N = number of subjects to be included; NC = number of subjects corrected for intraclass correlation coefficient.

Table IV. Sample size table when reactance is under investigation ($\alpha = 0.05$).

Difference (ohms)	Power of 0.80		Power of 0.90		Power of 0.95	
	N	NC	N	NC	N	NC
1	2943	3004	3940	4021	4872	4972
2	736	752	985	1006	1218	1243
3	327	334	438	447	542	554
4	184	188	247	253	305	312
5	118	121	158	162	195	199
6	82	84	110	113	136	139
7	61	63	81	83	100	103
8	46	47	62	64	77	79
9	37	38	49	51	61	63
10	30	31	40	41	49	51
11	25	26	33	34	41	42
12	21	22	28	29	34	35
13	18	19	24	25	29	30

Abbreviations as in table III.

Table V. Sample size table when phase angle is under investigation ($\alpha = 0.05$).

Difference (degrees)	Power of 0.80		Power of 0.90		Power of 0.95	
	N	NC	N	NC	N	NC
0.1	2041	2083	2732	2788	3378	3447
0.2	511	522	683	697	845	863
0.3	227	232	304	311	376	384
0.4	128	131	171	175	212	217
0.5	82	84	110	113	136	139
0.6	57	59	76	78	94	96
0.7	42	43	56	58	69	71
0.8	32	33	43	44	53	55
0.9	26	27	34	35	42	43
1.0	21	22	28	29	34	35
1.1	17	18	23	24	28	29

Abbreviations as in table III.

($r = 0.83$). Furthermore, bioelectrical impedance analysis seems to be able to monitor diuretic therapy in CHF as well as to assess serial changes in body fluids[8,10,12]. In 1980, Subramanyan et al.[12] reported a significant increase in the resistance, reactance and phase angle in CHF patients after decongestive therapy and for the first time showed that the total body impedance technique appears to be useful for the objective monitoring of the fluid status in patients with CHF and in guiding the therapy. It has also been reported that the improvement in the mechanical cardiac status was associated with a significant decrease in reactance[9]. These data suggest that bioelectrical impedance analysis may play a significant role in the management of CHF patients, but that at present it is underutilized. Prior to its use in a large cohort of patients with CHF, we investigated the effects of body side on bioelectrical impedance analysis parameters, and assessed the test-retest reliability of the measurements that is important in sample size calculations.

We have found different values of the resistance and angle phase, but not of the reactance between the two body sides. Such an asymmetry in the resistance value is in agreement with the results of two previous studies[16,17]. In healthy subjects, Robert et al.[16] found mean values of resistance on the right body side which were 10 ohms lower than those on the left and explained this effect as the result of a greater lean body mass on the dominant side of the body that promotes lower resistance values and therefore increased conduction of the current. But this hypothesis does not explain the absence of this phenomenon when the reactance is being evaluated, and in our opinion the presence of the liver on the right side could contribute to these effects. On the basis of these results, we can state that when the resistance and angle phase are under evaluation in CHF, it is recommendable to always use the same side of the body; on the other hand, this is not mandatory when the reactance is being analyzed.

In order to analyze drug effects, the measurement error should be known in order to distinguish changes due to interventions from testing variations. The same can be applied for patient follow-up. Knowledge of the measurement error would allow one to detect impairments in parameters that are actually disease-induced and not due to a testing error. If a variable value changes outside the CV, then the change can be considered to be an effect of therapy or of disease progression. On the contrary, any amount of change within the range of error should be considered within the experimental error. Our findings show the high test-retest reliability of the primary bioelectrical impedance parameters obtained both on the left and right side of the body, as shown by the low CV values (all < 5%) and by the high ICC values (almost 1). These ICC values allow the calculation of the sample size which would be necessary in future studies.

In conclusion, our findings suggest for the first time that in CHF the body side in bioelectrical impedance analysis is very important when the resistance and angle phase are being considered, and that such asymmetry is not evident for the reactance. The excellent test-retest reliabilities of the measurements on the same body side are helpful for the determination of the sample size required in future studies. These results should assist investigators in planning studies aimed at evaluating the effectiveness of interventions on primary whole-body bioimpedance parameters.

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