Nutrition xxx (2012) 1–6

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Cachexia assessed by bioimpedance vector analysis as a prognostic indicator in chronic stable heart failure patients

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ARTICLE INFO

Article history:
Received 13 April 2011
Accepted 20 November 2011

Keywords:
Cachexia
Heart failure
Bioelectrical impedance vector analysis

ABSTRACT

Background: This study explored whether the cachectic state assessed by bioimpedance vector analysis provides additional prognostic information about mortality from all causes.
Methods: We included 519 consecutive patients with stable chronic heart failure (mean age 62.5 ± 16.4 y; 286 males). Cachexia was identified in those subjects who fell outside the right lower quadrant of the reference curve of 95% on the resistance/reactance graph [bioelectrical impedance vectorial analysis (BIVA)-cachexia]. Clinical, anthropometric, and biochemical data were also evaluated.
Results: Patients with BIVA-cachexia ($n = 196$, 37.8%) were older and had significantly lower ejection fraction, handgrip strength, serum albumin, total cholesterol, and triglycerides. The frequency of patients with body mass index < 20, decreased muscle strength, hypoalbuminemia, anemia, anorexia, New York Heart Association functional classes III/IV and edema, as well as creatinine levels, resistance/height, and impedance index was significantly higher in the cachexia group. During 29 ± 11 mo of follow-up, 39 (19.9%) patients with BIVA-cachexia and 38 (11.7%) patients without BIVA-cachexia ($P < 0.0001$) died.
Conclusions: The cachectic state is an independent risk factor for mortality in chronic heart failure patients. BIVA could represent a valuable tool to assess presence of cachexia as changes in body cell mass in heart failure patients because provide information additional to weight loss.
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Introduction

Cardiac cachexia is a common clinical manifestation and serious complication of chronic heart failure (CHF) and is an important predictor of reduced survival [1]. Cachexia is defined as a complex metabolic syndrome associated with underlying illness and is characterized by loss of muscle with or without loss of fat mass. Its identification has been problematic and causal mechanisms are poorly understood [2]. The Cachexia Society has proposed a clinical definition based on the presence of the following criteria: underlying chronic disease and unintentional weight loss of at least 5% in 12 mo or less or body mass index (BMI) <20 kg/m^2 plus more than three of five criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, abnormal biochemistry tests: increased inflammatory markers (C-reactive protein, interleukin 6), anemia (hemoglobin <12 g/dL), low serum albumin (3.2 g/dL) [2].

The prominent clinical feature of cachexia is loss of body weight in adults. However, in patients with severe heart failure (HF), water retention may occur as a consequence of severe hypoalbuminemia; thus, water retention may the account for an increase in body weight despite severe body wasting and loss of body weight may be obscured by fluid retention. Loss of skeletal muscle mass should be considered the most clinically relevant phenotypic feature of cachexia [3]. Alterative methods that reflect fat-free mass loss with or without fluid retention would be helpful in the clinical setting.

To estimate fat-free mass, single-frequency bioelectrical impedance analysis (BIA) is an easy-to-use, noninvasive, and safe

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doi:10.1016/j.nut.2011.11.024

Please cite this article in press as: Castillo-Martínez L, et al., Cachexia assessed by bioimpedance vector analysis as a prognostic indicator in chronic..., Nutrition (2012), doi:10.1016/j.nut.2011.11.024

method with a high degree of reproducibility [4]. However, clinical use of BIA in subjects at extremes of BMI ranges and in subjects with abnormal hydration cannot be recommended for routine assessment of patients until further validation has proven the BIA algorithm to be accurate in such conditions [5]. Therefore, when tissue hydration is variable, conventional BIA (at single frequency or multiple frequencies) produces inaccurate estimations for body compartments, as do other methods of body composition analysis [6].

The need of assumptions for conventional BIA can be overcome by using bioelectrical impedance vector analysis (BIVA or vector BIVA), which is a method based on the measurement of the complex electrical impedance between the right hand and the right foot. The components of the impedance vector, the resistance (R) and the reactance (Xc), are normalized to the height of the subjects (R/H and Xc/H) and plotted as bivariate random vectors (points) on the R-Xc plane (abscissa R/H, ordinate Xc/H) according to the RXc graph method. The vector measured in an individual is compared against the normal interval of the reference population expressed in percentiles of the normal distribution (Gaussian) bivariate, probabilistic graph [6-8]. From the literature, wasting conditions such as cancer, acquired immune deficiency syndrome (AIDS), and anorexia nervosa have been associated with a displacement downward and to the right along the minor axis in the middle regions of tolerance ellipses [9].

Studies have shown that this method is useful in the evaluation of HF in the emergency department and in differentiating acutely dyspneic patients with non-cardiac etiologies with an elevated diagnostic accuracy [10] or in CHF to stratify the severity of the HF. However, it is not clear whether the method is clinically useful to detect depleted patients, because no studies of this approach in patients with HF patients have been published.

Therefore, the aims of this study are to investigate whether cardiac cachexia can be assessed by bioimpedance vector analysis and whether it is a prognostic indicator in chronic stable heart failure patients.

Patients and methods

A total of 519 (233 male and 286 female) stable outpatients in New York Heart Association (NYHA) functional classes I-IV, consecutively admitted to the Heart Failure Clinic at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ), were entered into the study. Patients were considered eligible if they were over 18 y of age with confirmed diagnosis of HF based on European Society of Cardiology criteria [1] and not admitted to intensive care units at the time of basal evaluation.

Exclusion criteria were end-stage renal disease, uncontrolled dysthyroidism, hepatic insufficiency, unstable ischemic heart disease (unstable angina and/or myocardial infarction, myocardial revascularization procedure, coronary angioplasty, and/or surgical revascularization within the past 3 mo), acute arrhythmias, and HF secondary to chemotherapy or suspicious of tumor activity, AIDS, or limb amputations.

After the recruitment visit, patients were included in a prospective cohort study. The established follow-up period was 36 mo, and outcome was defined as death from any cause. Follow-up was made by outpatient attendance to our HF clinic, through the hospital information system, or by telephone contact.

The present study was approved by the institutional ethics committee of biomedical research in humans of the INCMNSZ, and all patients were informed regarding the purpose of the study and signed informed consent forms.

Anthropometry

Weight and height were measured in accordance with the manual reference of anthropometric standardization [11]; all subjects wore light clothing and were barefoot. BMI was calculated by dividing the total body weight (kilograms) by the squared height (meters). Also, handgrip strength was measured using the Smedley Hand Dynamometer (Stoelting, Wood Dale, UK). Patients were instructed to apply as much handgrip pressure as possible with their right and left hands. The measurements were repeated twice by each hand, and the highest score was recorded in kilograms [12]. Patients with decreased muscle strength were defined as those subjects who had handgrip strength <25 percentile (male <21.7 kg and women <10 kg).

Body weight at baseline and during follow-up was assessed during all visits. Weight loss was defined as loss of body weight >6% over a period of at least 6 mo. We did not adjust for the development of edema during follow-up.

Bioelectrical impedance analysis

Whole-body bioelectrical impedance was measured in the morning using tetrapolar and multiple-frequency equipment (BodyStat QuadScan 4000; Bodystat Ltd., Isle of Man, UK). All measurements were made according to the tetrapolar method reported in the existing literature [13]. The area where the observation was being conducted was comfortable and free of drafts and portable electric heaters. The subject was fasting and should not have exercised 8 h or consumed alcohol 12 h before the study. During the entire test, the subject placed his legs and arms in a 300 abduction position.

The impedance values were obtained at frequencies of 5, 50, 100, and 200 kHz. Using 50-kHz frequency resistance (R50), reactance (Xc50) and phase angle were obtained by Phase Angle Software 1.0 (Bodystat Ltd.). This frequency was selected because this is the standard frequency used for BIVA.

Bioelectrical impedance vector analysis

The R50 and Xc50 were standardized for height (H) to obtain the impedance vector Z/H, which is represented in the RXc graph (abscissa R/H, ordinate Xc/H) [6,7]. For the evaluation of the vector within groups, mean vector components (R/H and Xc/H) were plotted on the gender-specific 50%, 75%, and 95% tolerance ellipses calculated in the Mexican reference healthy population as an RXc graph [14].

The gender-specific RXc graph was divided into four sectors. Patients with vectors out of the 95% tolerance ellipse of the reference population at the lower right quadrant were classified as cachectic (BIVA-cachexia) [8].

Table 1
Clinical characteristics of patients included in the study

Variable	All patients ($n = 519$)	CHF with BIVA-cachexia ($n = 196$)	CHF without BIVA-cachexia ($n = 323$)	*P* value*
Males, *n* (%)	286 (55.1)	129 (65.8)	157 (48.6)	<0.0001
Age (y)	62.5 ± 16.4	67.2 ± 16.4	59.6 ± 15.8	<0.0001
Ischemic etiology, *n* (%)	254 (49)	98 (50)	156 (48.4)	0.8
Ejection fraction (%)	44.8 ± 16.7	40.8 ± 16.9	47.3 ± 16.1	<0.0001
Creatinine (mg/dL)	1.06 ± 0.39	1.12 ± 0.43	1.02 ± 0.35	0.006
Sodium (mEq/L)	137.0 ± 5.4	136.5 ± 7.4	137.3 ± 3.4	0.18
Medications				
Beta-blockers, *n* (%)	427 (82.3)	163 (83.0)	265 (82.0)	0.76
ACE inhibitor, *n* (%)	183 (35.3)	68 (34.6)	116 (35.9)	0.78
ARB, *n* (%)	320 (61.7)	119 (60.8)	201 (62.2)	0.76
Thiazide diuretics, *n* (%)	231 (44.6)	86 (43.9)	146 (45.1)	0.8
Loop diuretics, *n* (%)	167 (30.2)	66 (33.9)	90 (27.9)	0.16
Oral nitrate, *n* (%)	160 (30.8)	66 (33.7)	93 (28.9)	0.24
ARA, *n* (%)	345 (66.4)	138 (70.2)	207 (64.1)	0.16
Symptoms				
Anorexia, *n* (%)	110 (21.2)	52 (26.7)	58 (17.9)	0.02
NYHA III/IV, *n* (%)	134 (25.9)	73 (37.4)	60 (18.7)	<0.0001
Dyspnea, *n* (%)	246 (47.4)	78 (40)	168 (52)	0.03
Edema, *n* (%)	273 (52.6)	142 (72.4)	131 (40.6)	<0.0001
Orthopnea, *n* (%)	155 (29.8)	430 (22.0)	111 (34.4)	0.049
Comorbidities				
Dyslipidemia, *n* (%)	366 (70.6)	126 (64.4)	240 (74.3)	0.03
Hypertension, *n* (%)	372 (71.7)	131 (67)	241 (74.6)	0.07
Diabetes, *n* (%)	236 (45.4)	95 (48.5)	141 (43.6)	0.28
Renal failure, *n* (%)	65 (12.5)	28 (14.1)	37 (11.5)	0.4

ACE inhibitor, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor blockers; ARA, aldosterone receptor antagonists; BIVA, bioelectrical impedance vector analysis

Continuous variables are presented as mean ± standard deviation, whereas categorical variables are expressed as numbers (percentage)

* Based on χ^2 test for categorical variables and unpaired *t* test for continuous variables.

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Table 2
Anthropometric parameters, body composition, and markers of nutritional status

Variable	All patients ($n = 519$)	CHF with BIVA-cachexia ($n = 196$)	CHF without BIVA-cachexia ($n = 323$)	P value*
Body composition				
Weight (kg)	72.1 ± 20.3	65.9 ± 17.0	75.8 ± 21.2	<0.0001
Body mass index (kg/m^2)	28.8 ± 7.0	26.2 ± 5.6	30.4 ± 7.2	<0.0001
Waist circumference (cm)	95.2 ± 15.9	91.9 ± 16.4	97.2 ± 16.4	<0.0001
Body mass index <20 (%)	32 (6.2)	23 (11.7)	8 (2.5)	0.0001
Arm circumference (cm)	29.8 ± 5.2	27.5 ± 4.3	31.3 ± 5.2	<0.0001
Resistance/height (ohms/m)†	339.7 ± 83.1	352.8 ± 88.5	331.7 ± 78.8	
	F: 387.6 ± 81.5	F: 427.2 ± 79	F: 371.6 ± 77.1	<0.0001
	M: 300.3 ± 59.6	M: 314.2 ± 62.7	M: 289.6 ± 54.9	
Reactance/height (ohms/m)†	30.0 ± 8.8	25.3 ± 6.7	32.8 ± 8.7	
	F: 32.1 ± 9.7	F: 26.5 ± 7.6	F: 34.4 ± 9.6	0.005
	M: 28.4 ± 7.4	M: 24.9 ± 6.2	M: 31.2 ± 7.1	
Phase angle (°)	5.1 ± 1.3	4.2 ± 0.9	5.7 ± 1.1	<0.0001
Handgrip strength (kg)	22.5 ± 10.2	19.5 ± 8.8	24.4 ± 10.7	<0.0001
Decreased muscle strength (%)	121 (23.3)	84 (42.8)	37 (11.5)	<0.0001
Weight loss >6%	65 (12.5)	28 (14.3)	37 (11.5)	0.50
Laboratory parameters				
Albumin (g/dL)	3.6 ± 0.6	3.4 ± 0.6	3.7 ± 0.6	0.010
Hypoalbuminemia (%)	145 (27.9)	77 (39.3)	64 (19.8)	<0.0001
Hemoglobin (g/dL)	14.2 ± 2.2	14 ± 2.3	14.3 ± 2.1	0.10
Hematocrit (%)	42.1 ± 6.7	41.5 ± 7.7	42.5 ± 6.1	0.15
Anemia (%)	109 (21.0)	54 (27.6)	53 (16.4)	0.007
Cholesterol (mg/dL)	177.6 ± 54.0	164.4 ± 45.6	184.3 ± 57.1	0.005
Triglycerides (mg/dL)	139 (101-195)	124 (92-174)	150 (108-206)	0.004

Values are expressed as mean ± standard deviation; median (interquartile range) or numbers (percentage) when appropriate
* Based on χ^2 test for categorical variables and unpaired t-test for continuous variables.
† Data are presented also by F, female; M, male.

Biochemical analysis

Fasting blood samples were collected and immediately processed to perform the following determinations, according to the routine laboratory procedures in our hospital: hemoglobin, hematocrit, plasma creatinine, sodium, albumin, triglyceride, and total cholesterol concentrations.

Anemia was defined as hemoglobin <12 g/dL and hypoalbuminemia as albumin <3.2 g/dL [2].

Clinical data

Symptoms like anorexia, dyspnea, edema, orthopnea, and NYHA functional class were evaluated during the medical interview. All patients underwent echocardiograms to assess cardiac function. All these evaluations were performed by a cardiologist blinded to the study groups.

Statistical analysis

Analyses were performed using a commercially available package (SPSS for Windows, Rel. 10.0 1999; SSPS, Inc., Chicago, IL, USA) and the BIVA Software 2002 [15].

Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables were presented as absolute and relative frequency. Comparisons among groups were made with χ^2 test for categorical variables and unpaired t test for continuous variables. Hotelling's T^2 test was used for vector analysis. The data were analyzed in comparison to the tolerance ellipses using the BIVA method. The BIVA software is based on a bivariate Hotelling analysis.

Kaplan-Meier survival curve with Log rank significance test was also performed to assess survival considering the presence or absence of BIVA cachexia. Multivariate analysis was performed by Cox for proportional hazards, regression analysis to estimate adjusted relative risks (RR), and 95% confidence intervals for potential predictors of death. The Cox model included variables found to be statistically different in the bivariate comparisons between survivors and non-survivors.

An acceptable level of statistical significance was a priori established at $P < 0.05$.

Results

From the 519 patients included in the present study, 196 (37.8%) were classified as cachectic and 323 were classified as non-cachectic. Clinical characteristics of both groups are given in Table 1. Distribution by sex was significantly different between groups. The cachectic patients were older with significantly lower ejection fractions and higher creatinine levels. Anorexia, NYHA III/IV, and edema were more prevalent in the patients with BIVA-cachexia. No significant differences in frequency of patients with ischemic etiology, hypertension, diabetes, and renal failure were found between groups. There were also no significant differences in sodium levels and medications between groups.

Anthropometric evaluation, body composition, and markers of nutritional status are presented in Table 2. Weight, BMI, waist and arm circumferences, reactance/height, phase angle, handgrip strength, albumin, total cholesterol, and triglycerides levels

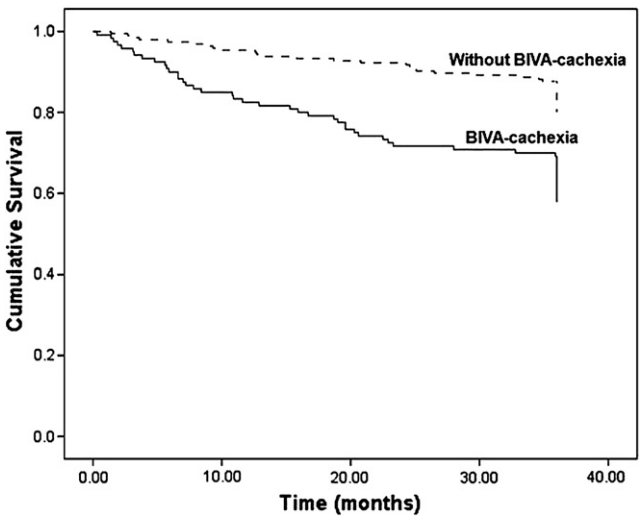

Fig. 1. Kaplan-Meier survival and cumulative hazard curves for 36 mo of patients with chronic heart failure.

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Table 3
Predictors of 36-mo all-causes mortality in patients with heart failure by multivariate Cox regression analysis

	B	S.E.	Wald	Df	B coefficient	95.0% C.I. for Exp (B)		*P* values
						Lower	Upper	
Age (y)	0.027	0.008	10.91	1	1.03	1.01	1.04	0.001
Ejection fraction (%)	−0.013	0.007	3.46	1	0.99	0.97	1.001	0.06
BIVA-cachexia (yes/no)	0.504	0.234	4.64	1	1.66	1.05	2.62	0.03
Renal failure (yes/no)	0.137	0.285	0.23	1	1.15	0.66	2.00	0.63
NYHA (I-IV)	0.25	0.147	2.83	1	1.28	0.96	1.71	0.09
Hypoalbuminemia (yes/no)	1.08	0.288	14.11	1	2.95	1.68	5.18	<0.0001

were significantly lower in HF patients with BIVA-cachexia. Resistance/height was significantly higher in the BIVA-cachexia group. The frequency of patients with BMI <20, decreased muscle strength, hypoalbuminemia, and anemia was higher in groups with BIVA-cachexia. No significant differences existed in hemoglobin and hematocrit levels, and the frequency of patients with weight loss was >6% between the groups.

During a follow-up of 29 ± 11 mo, death occurred in 39 (19.9%) of the 196 patients with BIVA-cachexia and in 38 (11.7%) of the 323 patients without BIVA-cachexia ($P < 0.0001$) (Fig. 1).

Variables associated with outcome were age, ejection fraction, renal failure, NYHA, hypoalbuminemia, and BIVA-cachexia. A multivariate Cox-regression model that included these six variables showed that age, hypoalbuminemia, and BIVA-cachexia were independent predictors of mortality (Table 3).

Figure 2 displays the mean impedance vectors of the survivors and non-survivors in women and men, with and without edema. A significant displacement of the vector due to both reduced Xc/H and increased R/H values in the non-survivors group was observed in both gender and independently of edema presence.

Discussion

The results of the present study suggest that BIVA-cachexia is a risk factor for mortality in patients with HF and is associated with anorexia, anemia, low serum albumin, decreased muscle strength, and NYHA functional class features that are included in the diagnostic criteria for the definition established at the Cachexia Consensus Conference in December 2006 [2].

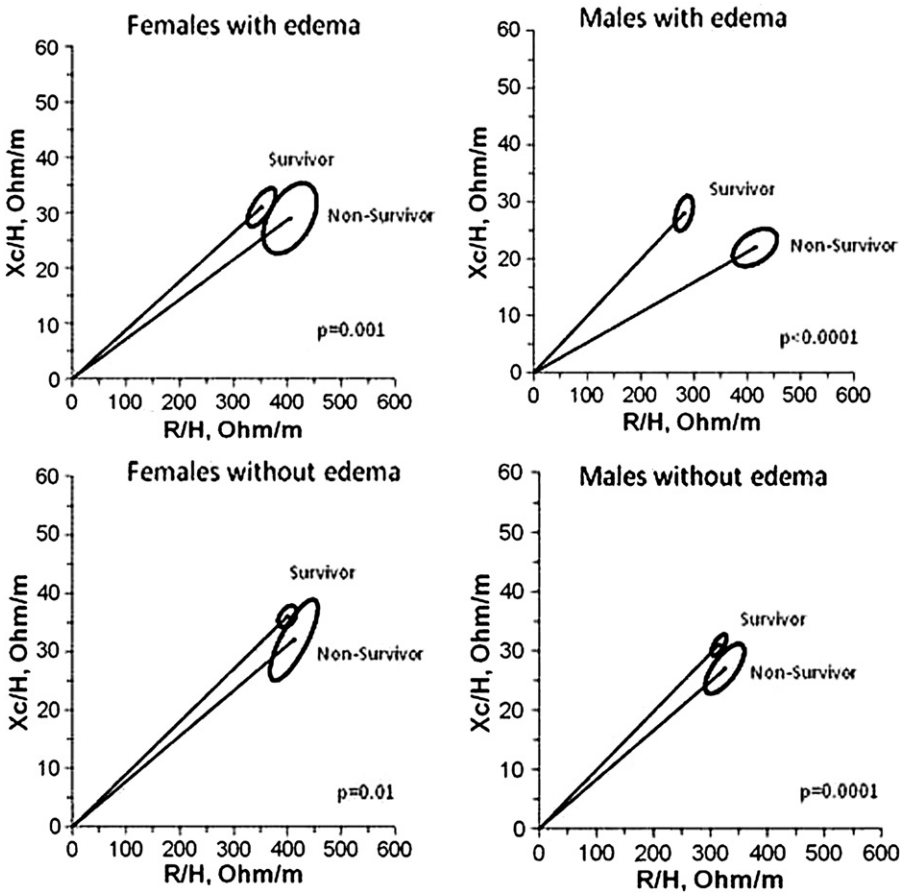

Fig. 2. Significant average vector displacement from the survivor and non-survivor groups by gender and edema presence. *P* value obtained by T^2 Hotelling.

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We propose the use of BIVA because bioimpedance is a combination of resistance (Rz) (i.e., the opposition of an alternating current flowing through intra- and extracellular ionic solutions) and reactance (Xc) (i.e., the capacitance component of tissue interfaces, cell membranes, and organelles) [10]. BIVA thus provides information about integrity of body cell mass because reactance is the capacitance effect produced by the tissue interface and cell membranes of soft tissue [11], perhaps indicating that protein degradation is the major cause of loss of skeletal muscle mass in cachexia [16].

In the present study, we found a significant vector migration in survivors and non-survivors and cachectic patients did not differ in body weight loss with non-cachectic patients. Differences in vector migration and its association with wasting have been presented in previous studies. Norman et al. demonstrated that patients with disease-related malnutrition evaluated by Subjective Global Assessment had significant disturbance in electric tissue properties, which are not seen in underweight patients according to BMI [17]. Furthermore, in another study, Norman et al. showed that both impedance parameters Xc/H and R/H and thus vector migration were associated with changes in functional status as assessed by hand grip strength [18].

Most studies of body wasting in HF have focused on weight alone and have demonstrated that cachexia is a strong independent risk factor for mortality [19-21]. However, in these studies it is necessary to consider the presence of edema, and only patients with non-edematous weight loss can be considered for the definition of cachexia [22]. For this reason, BIVA-cachexia may be an option in patients with edema, as was demonstrated in Figure 2.

Identification of wasting in patients with intravascular volume overload and in those who cannot be weighed, or in whom weight changes are dominated by hydration [18], can be made with BIVA because it works without making any assumption about constant soft tissue hydration body composition, independent of body weight. It also does not require the definition of patient dry weight [6,7,23].

Cachexia evaluation by BIVA can be used in patients with renal failure. This is particularly important because mild renal disease has been documented in 63% of patients with HF [24].

Therefore, BIVA may represent a valuable, low-cost, noninvasive, objective, and rapid tool to complement the clinical evaluation and follow-up of the CHF patient through detection of body composition changes and nutritional status of these patients.

On the other hand, anorexia was one of the symptoms more frequent in patients with BIVA-cachexia as it was also seen in cachectic patients with chronic obstructive pulmonary and renal failure diseases that are also characterized by muscular impairment [25,26]. Inflammation, a landmark of heart, renal failure, and chronic obstructive pulmonary disease (COPD), is a possible contributor [22,27].

The present study has some limitations that must be addressed. We did not evaluate inflammation markers to assess their association with cachexia; the study included a relatively small sample size of selected patients, and it was a prospective, single-center study. These factors may limit the ability to generalize the results observed in this study. However, our findings are particularly encouraging and they should serve as a basis for future research, including larger samples, aimed at enhancing the management of HF patients with suspected cardiac cachexia.

In conclusion, to our knowledge, our study is the first to investigate the prognostic value of cachexia assessed by BIVA and the association between this classification and variables like BMI <20, anorexia, hypoalbuminemia, anemia, and decreased muscle strength.

Acknowledgments

The authors would like to thank Professors A Piccoli and Pastori from the Department of Medical and Surgical Sciences, University of Padova, Padova, Italy, 2002 for giving us the BIVA software.

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