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

Lilia Castillo-Martínez Ph.D. [a], Eloisa Colín-Ramírez Ph.D. [a], Arturo Orea-Tejeda M.D. [a,*], Dulce Gabriela González Islas B.Ch.D. [a], Wendy Daniella Rodríguez García B.Ch.D. [a], Cira Santillán Díaz B.Ch.D. [a], Ana Elizabeth Gutiérrez Rodríguez B.Ch.D. [a], Marisela Vázquez Durán B.Ch.D. [a], Candace Keirns Davies M.D. [b]

[a] *Heart Failure Clinic, Cardiology Department, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán", Del Valle, Benito Juárez CP, Mexico*
[b] *Massachussets General Hospital, Boston, Massachusetts, USA*

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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.

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

* Corresponding author. Tel/fax: (5255) 55-13-93-84.
E-mail address: oreatart@gmail.com (A. Orea-Tejeda).

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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 etilology, *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.