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Association of cardiac cachexia and atrial fibrillation in heart failure patients

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ABSTRACT

Background: Cachexia is a common complication in patients with advanced heart failure (HF) associated with inflammatory response activation. Atrial fibrillation (AF) is the most frequent arrhythmia (26%), probably both exacerbate the cardiac cachexia (CC).
Objectives: Evaluate the association of cardiac cachexia and atrial fibrillation in heart failure patients.
Material and methods: In a case control study, CC was diagnosed by electrical bioimpedance with vectorial analysis (BIVA). Subjects with congenital heart disease, cancer, HIV, drug use and other causes than HF were excluded.
Results: Of the 359 subjects analyzed (men: 52.9%) median age 65 years (55–74). Those with CC were older [72 (61–67)] vs. without [62 (52–70) years old, $p < 0.01$]. During follow-up 47.8% of subjects developed CC and 17.27% AF, this was significantly more frequent in cachectic patients CC (23% vs 12.11%, OR: 2.17, 95% CI: 1.19-4.01, $p = 0.006$). Subjects, with AF had lower left ventricular ejection fraction (25.49 ± 12.96 vs. 32.01 ± 15.02, $p = 0.08$), lower posterior wall thickness (10.03 ± 2.12 vs. 11.00 ± 2.47, $p = 0.007$), larger diameter of the left atrium (49.87 ± 9.84 vs. 42.66 ± 7.56, $p < 0.001$), and a higher prevalence of CC (85.42% vs. 69.77%, $p = 0.028$). The 50.58% of was in NYHA class I. In NYHA III, 22.95% were in AF vs. 12.10% with not AF ($p = 0.027$).
Conclusion: The frequent coexistence of CC and AF as HF complications indicate greater severity of HF, regardless of its type of HF.

1. Introduction

Cardiac Cachexia (CC) is a common complication in advanced heart failure (HF) associated with inflammatory response activation that contributes to poor quality of life and 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. Water retention may account for an increase in body weight and body mass index despite severe body wasting and loss of body weight may be obscured by fluid retention. The bioelectrical impedance vector analysis (BIVA) is useful methods for the determination of changes in tissue hydration and body composition, besides it is easy-to-use, noninvasive, and safe [2,3].

The prevalence of CC reported in HF patients is from 8 to 42% depending on the definition used for its identification [4].

Heart failure patients are also at greater risk than the general population of developing atrial fibrillation (AF) [5], with an increase in the incidence of stroke by up to 50% and greater degree of ventricular dysfunction [6]. The prevalence of AF is 4% in NYHA I and up to 15–40% in those with NYHA II-IV, respectively [7–16].

The risk of AF is higher in left heart failure with left ventricular preserved ejection fraction (LVpEF) [17]. In those with reduced ejection fraction (LVrEF) and asymptomatic ventricular dysfunction, the prevalence of AF is around 6% [18]. In individuals older than 40 years of age it is 26% in men and 23% in women. [19] Hypertension, diabetes and HF are among the risk factors associated with the development of AF [20–23].

The clinical consequences of AF result from the loss of organized atrial activity, the deterioration in the atrial contraction and blood stasis. These factors promote the formation of thrombi, particularly in the left atrium, with a 5 fold greater risk of stroke in HF patients [24,25], as well

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as a significantly increased risk of dementia [26], and nearly twice the risk of death [27,28].

In the Framingham study the development of AF in people with CHF was associated with increased mortality (RR: 1.6 men 2.7 women) during a follow-up of 4.2 years [29]. Likewise, in a European population the prevalence of AF is 5.5%, (increasing with age to 17.8% at ≥85 years [30]) and health costs are up to 5 times higher in people with AF compared with those who do not have it [31].

HF and AF have a deleterious effect on cardiac function, fibrosis, vasoconstriction and neurohormonal activation and progressively reduce ventricular function. When they coexist thromboembolism prevention is the primary therapeutic goal [32].

In a Heart failure Clinic of a tertiary care hospital in Mexico City, a frequency of acute HF of 5 per 1000 patients and an AF prevalence of 23.5% were found. The prevalence of AF associated with specific types of HF was: 48.5% for LVpEF, 3.7% for LVrEF, 27.5% for mixed (LV preserved or reduced EF + right failure), and 22% for isolated right heart failure [33].

Cardiac cachexia is associated with malnutrition, musculo-skeletal wear, exercise intolerance, deteriorating cardiac function, chronic diseases, anemia, hypoalbuminemia, decreased serum levels of prealbumin, total cholesterol, lymphopenia, weight loss, edema, elevated neuropeptide Y levels, low or normal leptin levels, low levels of ghrelin, low levels of selenium and thiamine and high levels of cobalt and sodium [1].

The factors involved in the development of CC and AF, both with high prevalence in HF, are relevant to cardiac damage.

2. Objective

Evaluate the association of atrial fibrillation and cardiac cachexia in heart failure patients.

3. Methods

In a case control study covering the period from January 2002 to December 2014, study subjects were selected from a total of 757 patients of our Heart Failure Clinic (CLIC). A minimum follow-up of one year after the initial office visit was taken into consideration and the proportion of subjects with and without CC.

Patients >18 years old with an established diagnosis of HF by echocardiogram and/or radionuclide ventriculography (MUGA) were included. Subjects with congenital heart disease, cancer, HIV, drug use and those with CC due to an etiology other than HF, as well as those with incomplete or inaccurate data, were excluded.

All patients underwent routine laboratory tests (blood count, blood chemistry, serum electrolytes, liver function tests, thyroid, and kidney).

Body composition by bioelectrical impedance were measured using tetrapolar and multiple-frequency equipment (BodyStat QuadScan 4000; Body- stat Ltd., Isle of Man, UK). All measurements were made according to the tetrapolar method reported on the existing literature [34]. The measurements were conducted by the same operator, in the morning, in a confortable area, free of drafts and portable electric heaters. The subjects were on fasting state and should not have exercised 8 h before or consumed alcohol 12 h before the study. During the entire study the subject placed his legs and arms in a 300 abduction position. Using 50-kHz frequency resistance (R50), reactance (Xc50). R50 and Xc50 are adjusted by height (H). BIVA software was used to plot the vectors of R/H and Xc/H on the specific-gender graphs [35]. The 50%, 75%, and 95% tolerance ellipses were calculated according the Mexican healthy population reference. [36] The ellipses were divided into four quadrants named: obese, athletic, lean, and cachectic. Patients vectors out the 95% tolerance ellipse and positioned in the lower right quadrant were classified as cachectic [37].

4. Statistical analysis

The statistical package STATA version 12 and BIVA software 2002 [38] was used. For qualitative variables a X [2] test or Fisher's exact test were used. Quantitative variables were compared as averages using Student's *t*-test. The *U* Mann-Whitney test was used for variables that did not show normal distribution. Risk was calculated with odds ratio, with 95% confidence interval and the association with multivariate logistic regression analysis.

According to the Helsinki Declaration of 2008 and the Regulations of the General Law of Health in Research for Chapter Health 17, the study did not present any risk given that a database was built from medical records, and anonymity and confidentiality of patient data were maintained.

5. Results

From the total HF population, 359 patients had no missing data and were included; 52.92% of them were males. Cardiac cachexia was found in 47.08% of the subjects. These patients were older than those without CC (72 vs. 62 years, $p < 0.001$). As respects functional class, 83.6% were in NYHA I–II. In both groups the time elapsed from the HF diagnosis to CLIC admission was an average of 3 months.

During one year of follow-up, 47% patients developed CC and 17.27% AF. In patients with AF the presence of CC was significantly more frequent (23% vs. 12.11%, $p = 0.006$) than in those without AF.

In comparison with patients without CC, patients with cachexia had a higher frequency of edema, lower cholesterol ($p = 0.005$) and triglycerides, and lower weight, BMI (normal weight: 28.99% vs. 17.89%, $p = 0.013$) and obesity (30.18% vs. 41.58%, $p = 0.025$, Table 1).

In subjects in NYHA class III/IV 23.08% were in AF vs. 12.11% not in AF ($p = 0.0006$). Regarding the type of ventricular dysfunction in patients with and without AF, 59.31% of those in AF had LVpEF, 40.6% LVrEF, and 41.7% right failure 41.7%, as well as lower left ventricular ejection fraction (25.49% ± 12.96 vs. 32.01% ± 15.02, $p = 0.08$), greater left atrial diameter (49.87 mm ± 9.84 vs. 42.66 mm ± 7.56, $p < 0.001$), and lower posterior wall thickness (10.03 mm ± 2.12 vs. 11.00 mm ± 2.47, $p = 0.007$).

In subjects with CC right ventricular diastolic diameter was more frequently increased compared with patients without CC (41.82 mm ± 9.80 vs. 37.23 mm ± 9.52, $p = 0.028$). Between subjects with or without CC, no differences were found in drug treatment: ACE inhibitors, beta blockers, digitalis, or angiotensin receptor blockers. The patients with atrial fibrillation are at greater risk of developing cardiac cachexia, compared with those patients without AF (OR: 2.17 95% CI 1.19–4.01; $p = 0.006$).

6. Discussion

In the Framingham study, heart occurred before atrial fibrillation in 41% of patients while in 21% both were diagnosed at the same time [39]. Thus, AF can be cause and consequence of HF by several mechanisms. Loss of atrial systole in AF impairs left ventricular filling and can decrease cardiac output by up to 25%, particularly in patients with diastolic dysfunction [40]. However, in both types of ventricular dysfunction the neurohormonal imbalance and activation of the renin–angiotensin–aldosterone system (RAAS) leads to maladaptive physiological changes that increase filling pressures and afterload [41].

The renin–angiotensin–aldosterone system also contributes directly to proarrhythmic remodeling, as angiotensin II causes atrial fibrosis and anisotropic conduction [42]. Thus, these alterations in neurohormonal activation, electrophysiological changes and mechanical factors of HF, together contribute to AF, which decreases ventricular function and exacerbates HF manifestations 3 [8–33,39–45].

Heart failure patients who develop atrial fibrillation are at high risk of morbidity and mortality and the development of complications including cardiac cachexia, a condition with multifactorial etiology. In our cases, this was present in 47.08%, similar to data reported by Anker et al. [46]. However, as our cases demonstrate, cachectic patients are at high risk of developing AF. Of all the patients with cachexia 23.08% were in atrial fibrillation and showed important clinical deterioration compared with those without AF (40.98% in NYHA II and 22.95% in III). Similar results have been reported by Maisel and Stevenson [7], who also found a higher incidence of AF in patients in advanced stages of heart failure. In addition, several