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Cardiac I123-MIBG Correlates Better than Ejection Fraction with Symptoms Severity in Systolic Heart Failure

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Abstract

Background: The association of autonomic activation, left ventricular ejection fraction (LVEF) and heart failure functional class is poorly understood.

Objective: Our aim was to correlate symptom severity with cardiac sympathetic activity, through iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy and with LVEF in systolic heart failure (HF) patients without previous beta-blocker treatment.

Methods: Thirty-one patients with systolic HF, class I to IV of the New York Heart Association (NYHA), without previous beta-blocker treatment, were enrolled and submitted to ^{123}I-MIBG scintigraphy and to radionuclide ventriculography for LVEF determination. The early and delayed heart/mediastinum (H/M) ratio and the washout rate (WR) were performed.

Results: According with symptom severity, patients were divided into group A, 13 patients in NYHA class I/II, and group B, 18 patients in NYHA class III/IV. Compared with group B patients, group A had a significantly higher LVEF (25% ± 12% in group B vs. 32% ± 7% in group A, p = 0.04). Group B early and delayed H/M ratios were lower than group A ratios (early H/M 1.49 ± 0.15 vs. 1.64 ± 0.14, p = 0.02; delayed H/M 1.39 ± 0.13 vs. 1.58 ± 0.16, p = 0.001, respectively). WR was significantly higher in group B (36% ± 17% vs. 30% ± 12%, p= 0.04). The variable that showed the best correlation with NYHA class was the delayed H/M ratio (r= -0.585; p=0.001), adjusted for age and sex.

Conclusion: This study showed that cardiac ^{123}I-MIBG correlates better than ejection fraction with symptom severity in systolic heart failure patients without previous beta-blocker treatment. (Arq Bras Cardiol. 2013;101(1):4-8)

Keywords: Heart Failure; Stroke Volume; 3-Iodobenzylguanidine; Sympathetic Nervous System.

Introduction

Heart failure (HF) is one of the major problems in public and private health systems. Coronary heart disease is the first etiology of HF accounting for 34% of the cases, followed by idiopathic etiology (26%)[1]. In HF, a dysfunction on the left ventricle triggers processes to restore cardiac output. These responses can eventually become a part of the disease process itself, worsening the cardiac function. Among these mechanisms, the hyperactivation of the sympathetic nervous system provides inotropic support to the failing heart and peripheral vasoconstriction to maintain arterial pressure[2-5]. This neurohormonal exacerbation has deleterious effects for myocardial cells and can lead to cell apoptosis, decreased neuronal density or both[6,7].

The adrenergic hyperactivation is a strong indicator of adverse prognosis, regardless of functional class[8,9].

Cardiac imaging with iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) can assess sympathetic system function in HF patients, providing valuable information for treatment and prognosis[10-12]. Recently, a meta-analysis showed that low delayed ^{123}I-MIBG heart/mediastinum ratio (H/M) and increased washout rate (WR) were associated with a higher incidence of adverse events and mortality, respectively[13]. The ADMIRE-HF trial demonstrated that ^{123}I-MIBG cardiac imaging carries additional independent prognostic information for risk-stratifying in HF patients, above the commonly used markers, such as left ventricular ejection fraction (LVEF) and B-type natriuretic peptide[14,15].

The exercise intolerance presented by HF patients is another important prognostic marker[16] and there is a close association between ^{123}I-MIBG uptake and New York Heart Association (NYHA) functional class[17], although no study has assessed whether symptom severity is more related to LEVF than cardiac sympathetic activity, by ^{123}I-MIBG.

Our aim was to establish the correlation of NYHA functional class with myocardial uptake of ^{123}I-MIBG, and with LVEF in systolic HF patients without previous beta-blocker treatment.

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Methods

A total of 31 consecutive subjects with New York Heart Association (NYHA) functional class I-IV HF, without previous beta-blocker treatment and with left ventricular ejection fraction (LVEF) < 45% were studied. The LVEF was measured by gated equilibrium radionuclide ventriculography. Subjects underwent ^{123}I-MIBG scintigraphy to evaluate the sympathetic neuronal integrity, quantified by the heart/mediastinum uptake ratio (H/M) on 30-minute and on 4-hour planar images. Sympathetic activation was estimated by the washout rate. Patients were divided into two groups according to NYHA: group A - patients in NYHA class I, II; and, group B - patients in NYHA class III, IV. Symptom severity was estimated by the NYHA classification.

Exclusion criteria were: primary valvular disease; diabetes mellitus (fasting glucose $\geq$ 126 mg/dL); atrial fibrillation; artificial cardiac pacemaker; second-degree atrioventricular block; previous use of beta-blockers; pregnancy; Parkinson's disease or any condition that could affect the sympathetic nervous system.

All patients were submitted to clinical evaluation, chest radiography and echocardiogram. The cardiac ^{123}I-MIBG scintigraphy was performed after an overnight fast and previous thyroid block with oral intake of iodine potassium solution, administered two days before and after the procedure. 370 MBq of ^{123}I-MIBG (IEN/CNEN) was injected intravenously and anterior planar images of the chest, in a 256 x 256 matrix, were acquired 30 minutes after (early image) and 4 hours after (delayed image). Image acquisition lasted 10 minutes using a dual head gamma camera (E.CAM Duet-Siemens) with low energy high-resolution collimators in a 20% window around the 159-keV photopeak. Left ventricular ^{123}I-MIBG uptake was quantified by region of interest (ROI) drawn manually around the cardiac projection and related to background uptake quantified by ROI placed over the upper mediastinum area. The heart-to-mediastinum (H/M) ratio was then computed to quantify cardiac ^{123}I-MIBG uptake, taking radioactive decay into account, as previously described by Ogita et al[18]. Normal results were defined based on Ogita's study, considering the WR $\leq$ 27% and the H/M ratio >1.80 as normal[18,19].

All results were expressed as mean and standard deviation. Univariate analyses and multivariate stepwise regression were used to elucidate the associations between the variables and parameters of ^{123}I-MIBG. All statistical analyses were performed in IBM SPSS Statistics software 17.0 for Windows. The parametric variables were analyzed by the T-Student test and the non-parametric variables were analyzed by Spearman's test correlation. The statistical significance was defined as p <0,05. The study protocol was approved by the Ethics Committee of our institution (UFF/Huap #2006/14) and all patients signed the written consent form.

Results

Mean age was 58 $\pm$ 12 years in the 31 patients evaluated in the study. Group A consisted of 13 NYHA Class I/II patients and group B of 18 NYHA Class III/IV patients. Table 1 shows the main clinical features of the studied population.

The overall mean LVEF was 27 $\pm$ 11%. Compared with group B patients, group A patients had a significantly higher LVEF (25% $\pm$ 12% in group B vs. 32% $\pm$ 7% in group A, p = 0.04). Group B early and delayed H/M ratios were lower than group A ratios (early H/M 1.49 $\pm$ 0.15 vs. 1.64 $\pm$ 0.14, p = 0.02; delayed H/M 1.39 $\pm$ 0.13 vs. 1.58 $\pm$ 0.16, p = 0.001, respectively) (Figure 1). WR was significantly higher in group B than in group A (36% $\pm$ 17% vs. 30% $\pm$ 12%, p = 0.04) (Figure 2).

The variable that showed the best correlation with NYHA class was the delayed H/M ratio (r= -0.585; p=0.001), adjusted for age and sex. Additionally, early H/M (r = -0.399; p=0.032) and WR (r = 0.410; p = 0.027) showed a significant correlation with NYHA class, adjusted for age and sex. NYHA class correlation with LVEF (r = -0.323; p=0.087) did not reach statistical significance.

Discussion

The main finding of our study was that ^{123}I-MIBG correlates better than LVEF with symptom severity in systolic HF patients without previous beta-blocker treatment. More specifically, the delayed H/M ratio was independently correlated with NYHA class.

Katoh et al[20] demonstrated that preserved LVEF HF patients with advanced NYHA functional class had a significantly lower ^{123}I-MIBG delayed H/M ratio and a significantly higher WR (NYHA functional class I-II vs. III: 1.90 $\pm$ 0.34 vs. 1.49 $\pm$ 0.32, p < 0.0001; 25.9 $\pm$ 13.4 vs. 46.9 $\pm$ 16.3%, p < 0.0001, respectively)[20]. These data are similar to our findings: the NYHA functional class III-IV group showed a significantly lower H/M ratio, 1.39 vs. 1.58 (p<0.001) and significantly higher WR, 36 vs. 30 (p=0.04). The aforementioned study[20] with preserved LVEF HF patients also showed that ^{123}I-MIBG WR was not correlated with LVEF and had a weak correlation with plasma BNP levels (r = 0.207, p = 0.0346); moreover, patients with high WR had a poor clinical outcome (p = 0.0033).

Ekman et al[16] reported that a decreased MIBG uptake is better related to survival than LVEF. The ADMIRE-HF study also demonstrated that sympathetic nuclear imaging of the heart could identify which patients were more prone to worse prognosis[15]. A meta-analysis of Japanese ^{123}I-MIBG studies indicates that both a decreased cardiac ^{123}I-MIBG H/M and an increased WR rate are indicative of poor prognosis in chronic HF patients[21]. A low H/M indicates a high risk of cardiac death with an odds ratio of 5.2:1; and, a high WR was also associated with lethal events, with an odds ratio of 2.8:1 [21]. In another recent study, a higher risk of cardiac death was confirmed in patients with an elevated WR, with a relative risk of 3.3 (p = 0.01)[22]. They also showed that the WR (p = 0.0002) was an independent predictor of cardiac death[22].

Cardiac sympathetic imaging with ^{123}I-MIBG is a noninvasive tool to stratify the risk of HF patients. In patients with ischemic and non-ischemic cardiomyopathy, cardiac ^{123}I-MIBG activity can be very helpful to predict survival. Cardiac sympathetic imaging can improve our view on how sympathetic hyperactivity exerts deleterious effects, and its use may result in better therapy and outcome for the HF patient. The ^{123}I-MIBG

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Table 1 - Clinical variables of the studied population

Variable	Frequency (%)
Sample size (m/w)	31 (71% / 29%)
Etiology	
Ischemic	5 (16%)
Non-ischemic	14 (45%)
Unknown	12 (39%)
LVEF (mean ± sd)	27% ± 10%
NYHA Functional Class	
I / II	13 (42%)
III / IV	18 (58%)
Medication	
ARBs/ ACE Inhibitors	23 (74%)
Digoxin	15 (48%)
Diuretics - Furosemide	15 (48%)
- Hydrochlorothiazide	8 (26%)
Spironolactone	15 (48%)
Nitro-derivatives	5 (16%)
Beta-blockers	0 (0.0%)
Comorbidities	
Family history	10 (32.3%)
Dyslipidemia	10 (32.3%)
Diabetes	0 (0.0%)
Hypertension	15 (48.4%)
Smoker	11(35.5%)
Previous MI	1 (3.2%)

LVEF: left ventricular ejection fraction; ARB: angiotensin receptor blocker; ACE: Angiotensin converting enzyme; MI: myocardial infarction.

delayed H/M ratio and WR have been used to monitor response to medical treatment[23]. The ^{123}I-MIBG imaging is also associated with increased risk of ventricular arrhythmias and death[24].

Heart failure syndrome comprises a large spectrum of clinical aspects and has many compensatory mechanisms, being continuously activated to maintain ventricular function and system homeostasis. Left ventricular function can vary within a wide range depending on its own physiology requirements, and some compensatory mechanisms could be deleterious and not effective in long-term periods[25]. Thus, LVEF does not have a direct and strong correlation with symptom severity, as observed in asymptomatic patients with severe left ventricular systolic dysfunction, while some patients with severe quality of life limitations could have HF with normal ejection fraction[26]. Thus, the degree of functional impairment, measured by NYHA functional classification, can indicate increased adrenergic activation status and therefore, together with other parameters, a worse long-term prognosis. Studies with normal ejection fraction HF patients suggest that these patients have similar mortality to HF patients with reduced ejection fraction[27,28]. Collectively, these data suggest that the final common mechanism that influences HF patients' prognosis is the degree of adrenergic activation, regardless of the HF model. Among the limitations of our study, we should mention the relatively small sample size. Another limitation is the use of a subjective parameter to quantify the functional impairment of HF patients over the use of objective parameters. However, NYHA class is widely used in clinical practice and has been proved to be reliable and reproducible, and is still being used in recent studies[29].

Conclusion

The cardiac ^{123}I-MIBG correlates better than ejection fraction with symptom severity in systolic heart failure patients without previous beta-blocker treatment. These findings could have important implications for a better understanding of HF syndrome, to improve diagnostic accuracy and to develop new approaches on risk stratification of HF patients.
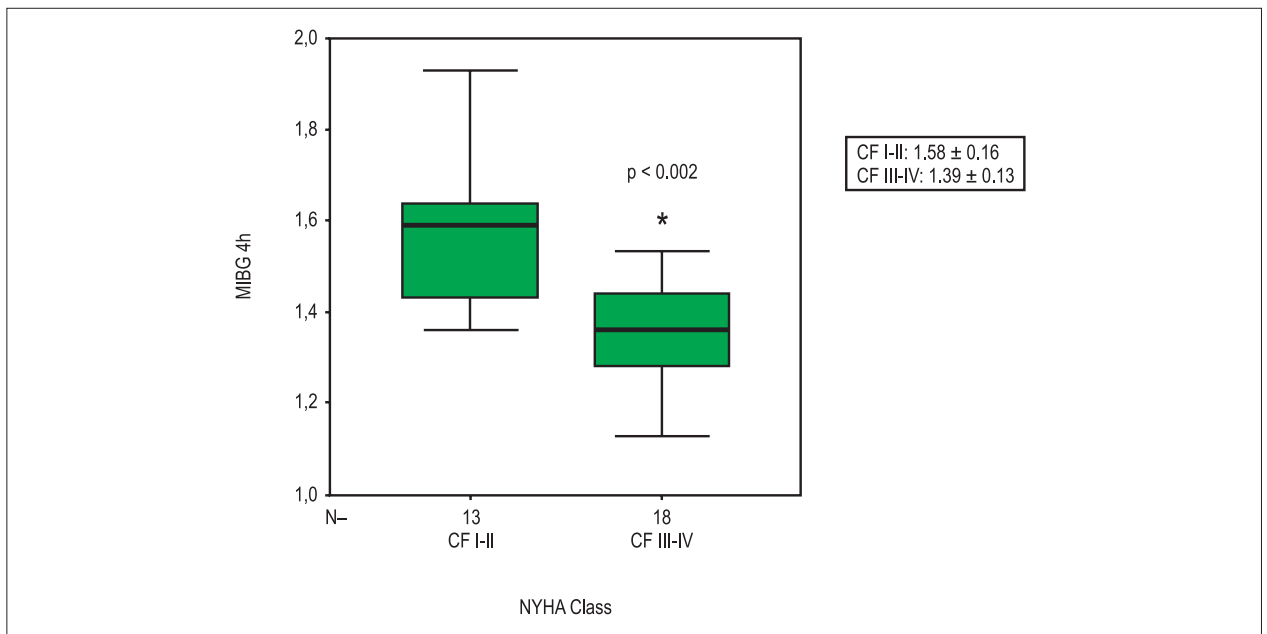
Acknowledgments

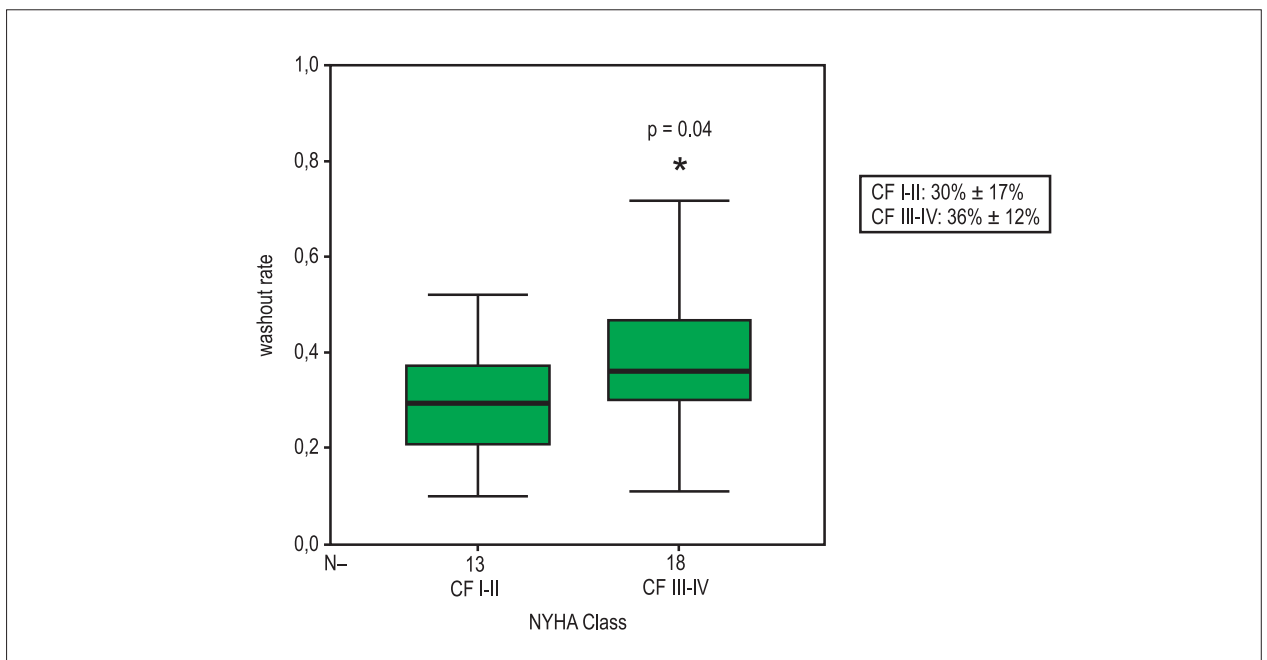**Figure 1 -** *Box plot graph of NYHA class and delayed H/M ratio of ^{123}I-MIBG.*

Figure 2 - *Box plot graph of NYHA class and washout rate of ^{123}I-MIBG.*

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Miranda SM, Mesquita CT; Writing of the manuscript: Miranda SM, Moscavitch SD, Nóbrega ACL, Mesquita ET, Mesquita CT; Critical revision of the manuscript for intellectual content: Miranda SM, Moscavitch SD, Carestiato LR, Felix RM, Rodrigues RC, Messias LR, Azevedo JC, Nóbrega ACL, Mesquita CT.

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