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Letter to the Editor

Heart failure patients with B1-adrenoreceptor polymorphisms have augmented carvedilol response as detected by cardiac I123-MIBG scintigraphy

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B1-adrenergic receptor is the target of most endogenous catecholamines and B-blockers agents, and has critical role in heart failure (HF) progression and treatment [1]. Current guidelines for HF management have been recommended the use of B-blocker agents, such as metoprolol, bisoprolol and carvedilol, which act as blocking B1-adrenoceptors. Carvedilol therapy has been showed to improve cardiac sympathetic activity, as indicated by imaging with ^{123}iodine-metaiodobenzylguanidine (^{123}I-MIBG), a norepinephrine analog radiotracer [2].

Functional B1-adrenoceptor polymorphisms, Ser49Gly and Arg389Gly, have been considered as predictors of susceptibility to HF, response to B-blockers therapy and prognosis [3]. Therefore, the purpose of this longitudinal prospective study was to determine if beta1-adrenoceptors polymorphisms (Ser49Gly and Arg389Gly) of systolic HF patients could influence in cardiac sympathetic analysis (with ^{123}I-MIBG), before and after a short-term carvedilol therapy.

Patients admitted to the HF outpatient clinic at the Antonio Pedro University Hospital were recruited through a clinical screening. All patients have no previous history of use of any B-blocker. Eligibility criteria involved age ≥ 18 years, New York Heart Association (NYHA) class II or III, left ventricular ejection fraction < 45% (radionuclide ventriculography or echocardiography) and no alternative cause for the symptoms. Drug prescription did not change for at least 4 weeks before the study. Eligible patients provided a consent form after receiving verbal and written details regarding the procedures adopted in the study, which was approved by the Ethics Committee of our institution.

Subjects underwent ^{123}I-MIBG scintigraphy to evaluate the sympathetic neuronal integrity, quantified by the heart/mediastinum uptake ratio (H/M) early and late myocardial anterior planar images were, respectively, acquired 30 min and 4 h after the radiotracer infusion. Sympathetic activation was estimated by washout rate (WR). Normal results were defined based on Ogita's study, considering as normal WR ≤ 27% and H/M ratio > 1.80 [4]. Polymerase chain reaction–restriction fragment length polymorphism (PCR–RFLP) analysis was performed to identify beta1-adrenergic polymorphisms, Arg389Gly and Ser49Gly [5]. The dose of carvedilol has followed the guideline recommendations. Patients were re-evaluated after 3 months of carvedilol therapy. Data are presented as mean and standard deviation. Delta variables were obtained by subtraction of initial values (before therapy) from end values (after therapy). Statistical significance was accepted at the 0.05 level. T-Student and paired *T*-test were used for univariate parametric analysis; and, Mann–Whitney and Wilcoxon signed-rank test for nonparametric variables analysis. The chi-square test was performed to confirm that both polymorphisms frequencies were in Hardy–Weinberg equilibrium.

Twenty eight patients were evaluated in the present study. Overall mean age was 55 ± 12 years, and mean LVEF was 28%. At baseline, early (30 min) H/M MIBG was presented higher in Gly49 carriers (Gly49: +1.72 vs. Ser49Ser: +1.57, p = 0.046). Arg389Arg patients presented higher WR (Arg389Arg: +0.38 vs. Gly389: +0.27, p = 0.039), seen in Table 1. After 3 months of carvedilol therapy, Arg389Arg patients presented an increase on late (4 h) H/M MIBG (before: +1.54 vs. after: +1.66, p = 0.035), seen in Fig. 1. Ser49Ser showed a significant

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Table 1
Demographic and MIBG features at baseline, according to genotype polymorphisms Gly49 and Arg389Gly.

Variables	Ser49Ser n = 15	Gly49 n = 13	p value	Arg389Arg n = 13	Gly389 n = 15	p value
Male – n (%)	11 (73.3)	7 (53.8)	0.433	8 (61.5)	10 (66.7)	1.000
Ischemic etiology (%)	5 (33.3)	4 (30.8)	0.887	2 (15.4)	7 (46.7)	0.083
Age (mean years + SD)	57.7 ± 11	52.0 ± 13	0.214	53.5 ± 12	56.4 ± 12	0.524
LVEF (mean + SD)	24.1 ± 8.4	30.1 ± 6.6	0.051	25.9 ± 8.0	27.7 ± 8.3	0.565
MUGA LVEF (mean + SD)	24.7 ± 8.9	30.6 ± 10.6	0.119	26.0 ± 11.2	28.7 ± 9.0	0.492
Heart rate (mean ± SD)	85.6 ± 15.9	83.3 ± 10.7	0.664	81.5 ± 11.6	87.1 ± 14.9	0.284
MIBG 30 min	**1.57 ± 0.2**	**1.72± 0.2**	**0.046**	1.67 ± 0.2	1.61 ± 0.2	0.397
MIBG 4 h	1.51 ± 0.2	1.61 ± 0.2	0.195	1.54 ± 0.2	1.57 ± 0.2	0.694
WR	0.31 ± 0.2	0.33 ± 0.1	0.623	**0.38 ± 0.2**	**0.27 ± 0.1**	**0.039**
TPF	326.7 ± 229.8	207.5 ± 116.7	0.103	277.5 ± 213.5	266.0 ± 80.0	0.878

*LVEF = Left ventricular ejection fraction, MUGA = multigated acquisition (radionuclide), and WR = washout rate/TPF = time to early peak filling (diastolic function). Data with statistical significance difference are in bold. MIBG 30 min and WR are the only that achieved $p < 0.05$.

increase on WR, compared to WR delta of Gly49 carriers (Gly49: −0.094 vs. Ser49Ser: +0.691, $p = 0.039$).

HF patients usually present a reduced uptake of ^{123}I-MIBG and that correlates to the downstream of neuronal norepinephrine and to worse prognosis. A higher myocardial uptake suggests better responder patients to B-blocker therapy. The ADMIRE-HF trial has showed that HF patients, NYHA class II or III, with H/M ratio < 1.6 (low capture on ^{123}I-MIBG) presented higher mortality in 2 years (19.1%), compared with mortality of 1.8% in patients with H/M ratio > 1.6.

The major findings of our study were that Arg389Arg patients 1) presented worse initial adrenergic profile with a higher WR, 2) but had a greater improvement after therapy in late (4 h) H/M MIBG uptake; and, Gly49 carriers 3) presented a better initial adrenergic profile as observed on early (30 min) H/M MIBG uptake, and 4) a better behavior in WR under carvedilol therapy compared to a WR increase (worsening) seen in Ser49Ser group.

Several factors can influence the clinical response and evaluation of HF patients. Scintigraphy with ^{123}I-MIBG is one of the most advanced techniques to estimate adrenergic status. Polymorphisms in genes involved in cardiac contraction can have an impact in ^{123}I-MIBG evaluation as showed by a previous work [6] where patients with another polymorphism, α2c Del322-325, had presented higher late MIBG uptake compared with patients without this polymorphism. The influence of Arg389Gly and Ser49Gly receptor polymorphisms on the magnitude of reverse adrenergic remodeling in response to B-blocker therapy could have some implications.

A recent meta-analysis reported that Arg389 homozygotes present a significant improvement in LV remodeling and better LVEF improvement after therapy, when compared with Gly389 carriers [3]. Some authors have showed that the presence of Arg389 allele in patients under B-blocker therapy is associated with enhanced LVEF and reduced heart dimensions. LV function improves more when B-blocker therapy is initiated in Arg389Arg HF patients compared to Gly389 subjects [7]. The BEST study evaluated the use of a non-selective B-blocker (bucindolol) to treat patients at NYHA classes III–IV. The BEST-Genetic substudy [8] reported that Arg389Arg patients showed improvement on survival and reduced hospitalizations, in contrast to Gly389 carriers. However, in a MERIT-HF substudy [9] with 600 patients, results have suggested that differences in response to B-blockers were not related to these polymorphisms.

Gly49 carriers show an improvement on LV remodeling after therapy with metoprolol, compared with homozygous Ser49Ser [10]. Same study [10], when evaluated systolic HF patients with LVEF <40% and under metoprolol 200 mg/day, found that homozygous Arg389Arg patients had an improvement on LVEF after 3 months, with reduction on systolic and diastolic diameters, compared with the Gly389.

Studies have shown that ^{123}I-MIBG imaging, particularly H/M ratio, separates very effectively high from low risk patients, regardless of LVEF and NYHA class. In fact, patients with a normal H/M ratio have an excellent prognosis despite other abnormal cardiac parameters, such as LVEF and brain natriuretic peptide (BNP), and by multivariate analysis, H/M has consistently shown to provide independent incremental risk stratification power. Our findings suggest that Arg389Arg HF patients and Gly49 carriers present augmented response to short-term therapy with carvedilol, as demonstrated respectively by increased late MIBG uptake and by reduced WR.

Conflict of interest

There is no conflict of interest.

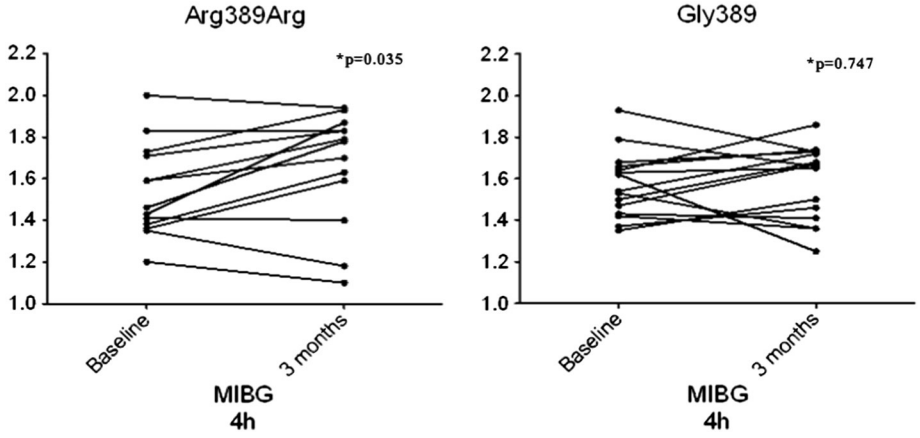

Fig. 1. Dot-plot of 4 h MIBG of Arg389Arg patients (left), and Gly49 patients (right), before–after carvedilol therapy.

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