Original Article

Relationship between Cardiac Adrenergic Image and Exercise Testing in Heart Failure

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Abstract

Backgrounds: The exercise treadmill test can be used in ventricular dysfunction patients for functional capacity or predicting prognosis. The cardiac image with 123I MIBG shows cardiac sympathetic activation.

Objective: To evaluate the relationship between exercise treadmill test variables and cardiac image changes in 123I MIBG.

Methods: 23 patients with LVEF ≤ 45% performed scintigraphy cardiac with 123I MIBG and divided into two groups. G1: Washout rate < 27%; G2: ≥ 27%. Systolic blood pressure (SBP), heart rate (HR) and functional capacity were evaluated. It was performed Student t test or Mann-Whitney U test, Spearman coefficient and linear regression.

Results: SBP at exercise peak (G1: 181.00 ± 28.01; G2: 153.27 ± 27.71 mmHg, p = 0.027), SBP variation [G1: 64(47.5-80.5); G2: 36(25-47) mmHg, p = 0.015], the HR at exercise peak (G1: 136.91 ± 19.66; G2: 118.45 ± 13.98 bpm, p = 0.018) and chronotropic response (G1: 70.42 ± 17.94; G2: 49.47 ± 14.89%, p = 0.006), and functional capacity [G1: 8.37(6.47-10.27); G2: 4.42(2.46-6.38) METs, p = 0.003] were smaller in G2 group. There was negative correlation between Washout rate and SBP at exercise peak (r = -0.505, p = 0.014), variation in SBP (r = -0.493, p = 0.017) and functional capacity (r = -0.646, p = 0.001). Nevertheless, SBP at exercise peak (r = -0.422, p = 0.016) and functional capacity (r = -0.804, p = 0.004) were the only variables associated with Washout rate, after linear regression.

Conclusion: In heart failure patients, the SBP at exercise peak and functional capacity were the variables associated with Washout rate. (Arq Bras Cardiol 2011;96(5):370-376)

Keywords: MIBG, exercise test; heart failure.

Introduction

In heart failure (HF), exercise testing (ET) is used to evaluate functional capacity, symptoms and therapy[1]. Some of the parameters used in ET are the behavior of systolic blood pressure (SBP) intrastress and chronotropic reserve, which are recognized predictors of prognosis[2-4]. The adrenergic hyperactivity, a characteristic of HF, may lead to chronotropic incompetence, decrease in cardiac contractile response to catecholamines and decreased sympathetic reserve during exercise. An inadequate response in SBP and heart rate (HR) has been associated with a twofold risk of mortality and adverse cardiovascular events[2,5-7]. Both for the population[8], and in the population with HF[2,9], functional capacity is an important predictor of prognosis and is not related to measures of ventricular function at rest nor with left ventricular ejection fraction[10].

The activity and cardiac sympathetic innervation can be evaluated by scintigraphy with metaiodobenzylguanidine labeled with iodine 123 (I[123] MIBG)[11-13]. Studies have found[13-16] that an early image represents the integrity of presynaptic nerve terminals and the density of betarreceptors. The presynaptic neuronal imaging contributes to the late image, combining information of neural function including capture, storage and release of norepinephrine in the presynaptic vesicles. The washout rate is a parameter that evaluates the degree of sympathetic activity. HF patients may have: (1) reduced tracer imaging due to loss of sympathetic neurons and/or disorders in primary uptake of norepinephrine; and (2) increased washout rate, reflecting the spillover of noradrenaline to the blood stream[11,14,17-19]. A washout rate smaller than 27% is a strong predictor descriptor of survival[20].

So far, there is no evidence that the adrenergic hyperactivation at rest is associated with hemodynamic changes during exercise, or if the ET variables are associated with the scintigraphy variables. Therefore, the purpose of this study is to assess whether conventional ET variables in HF can detect patients with sympathetic dysfunction in I[123] MIBG scintigraphy. These findings could allow the assessment of risk with a technique available in our area, selecting those patients most likely to present changes to scintigraphy.

Methods

We selected 23 consecutive patients treated at the HF outpatient clinic of Hospital Universitário Antônio Pedro, Universidade Federal Fluminense. The selected patients had heart failure and left ventricular ejection fraction smaller than or equal to 45% measured by echocardiography by Simpson's technique. The study excluded patients who had: atrial fibrillation, diabetic patients, patients with ventricular pacing device, endocrine disorders, Parkinson's disease, pregnant or breastfeeding women. No medication has been suspended for the study and all patients were treated with optimized doses of standard drugs for HF, including beta-blocker (carvedilol). Volunteers signed a consent form agreeing to be part of the project. The project was approved by the Research Ethics Committee of Hospital Universitário Antônio Pedro, under number 011/09.

Patients underwent symptom-limited ET (ErgoPC 13 software version 2.2) on a treadmill, brand Imbramed, properly calibrated to manufacturer's directions, in the ramp protocol. We evaluated the behavior of systolic blood pressure (SBP), intrastress heart rate (HR) and functional capacity. The blood pressure measurement was performed by the indirect method using mercury column sphygmomanometer, duly calibrated, measured in the left arm of patients in the standing position. Heart rate was measured through RR interval of eletrocardiogram (ECG) by the software. SBP and HR at peak exercise, SBP variation at peak exercise compared to rest (Δ PAS) and index of chronotropic reserve were evaluated using the formula: *("{[HR at peak exercise - resting HR / (220 - age) - resting HR] x 100}")*[4]. Functional capacity was estimated by the software according to the workload achieved.

Patients underwent myocardial scintigraphy with I^{123} MIBG to assess cardiac adrenergic innervation, through radiotracer, by studying the heart/mediastinum relationship (H/M) for early images (30 minutes) and late images (4 hours), besides calculation of the washout rate *{[(H/M early - H/M late) / (H/M early)] x 100}*[11]. All scintigraphic examinations were performed at Serviço de Medicina Nuclear do Hospital Pró-Cardíaco do Rio de Janeiro in Anger type digital CT scintillation camera (Single Photon Emission Computed Tomography) brand Siemens, E-Cam dual detector model, with low energy collimator and high resolution.

Patients were divided into two groups according to the washout (WO) rate: Group 1 (G1), washout rate < 27% (normal); Group 2 (G2), washout rate ≥ 27% (amended)[21]. For the statistical analysis, software SPSS version 15 was used. For the evaluation of qualitative variables, we used the chi-square test. To evaluate the quantitative variables we used the Student t test or Mann-Whitney U test, according to data distribution. We used the Spearman correlation coefficient to evaluate the correlation of the variables of exercise with the WO. We used stepwise linear regression to identify variables associated with sympathetic hypertonia evaluated by the washout rate. Statistical significance was considered when $p < 0.05$.

Results

Patient characteristics are shown in Table 1. There were no significant differences in age, sex, body mass index, etiology of HF, left ventricular ejection fraction, medications and dosage of carvedilol between groups.

The groups were similar at rest. At peak exercise, there was a significant difference between G1 and G2, but the latter had lower absolute values of SBP and HR, smaller intrastress SBP variation, lower rate of chronotropic reserve and a lower functional capacity. The parameters of the exercise are shown in Table 2 and Figure 1 shows the differences in SBP during exercise.

Though divided by the washout rate, there was no significant difference in the early C/M ratio of I^{123} MIBG (G1: 1.78 ± 0.25 vs G2: 1.74 ± 0.22, p = 0.710) and in late H/M ratio (G1: 1,74 ± 0,20 vs G2: 1,60 ± 0,22; p = 0.129). Figure 2 illustrates the cardiac imaging with I^{123} MIBG in a patient with HF presenting normal HF parameters (functional capacity of 8.23 METs, intrastress SBP variation of 65 mmHg and chronotropic reserve index of 68%). The MIBG imaging was normal and the washout rate was 21%.

When we analyzed the correlation between exercise variables and the washout rate, we observed a significant negative correlation between the washout rate and the following variables: SBP at peak exercise, intrastress SBP variation and functional capacity (Table 3). No statistical significance was found in correlation with HR at peak exercise and chronotropic reserve index with WO (Table 3).

After stepwise linear regression, the variables associated with dysautonomia by the washout rate were: SBP at peak exercise (r = -0.422; p = 0.016) and functional capacity in METs (r = -0.804; p = 0.004).

Table 1 - Characteristics of groups

	G1 (n = 12) WO < 27%	G2 (n = 11) WO ≥ 27%
Age (years)	56.50 ± 11.94	54.18 ± 15.99
Sex (male/fem)	8/4	7/4
BMI (%)	27.05 ± 3.42	26.54 ± 5.66
Etiology (%)		
Ischemic	8.33	27.27
Hypertensive	83.34	45.46
Others	8.33	27.27
Medications (%)		
Beta-blocker	100	100
ACEI/AIIRA	66.66	63.63
Aldactone	100	90.90
Digital	50	54.54
Diuretic drugs	91.66	90.90
Carvedilol dosage*mg	43.75 (26.56 - 60.94)	25 (10.98 - 39.01)
LVEF (%)	35.75 ± 8.12	33.27 ± 8.68
WO* Median value (%)	22 (17.06 - 26.94)	36 (31.5 - 40.5)[†]

Values expressed as mean ± standard deviation or (*) median (interquartile range); (†) p < 0.001; G1 - group 1; G2 - group 2; WO - Washout rate; n - number; male - male; female - female; BMI - body mass index; ACEI - inhibitor of angiotensin-converting enzyme II; ARA II - angiotensin II receptor antagonist; mg - milligrams; LVEF - left ventricular ejection fraction.

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Table 2 - Parameters of exercise according to group distribution

	G1 (n = 12) WO < 27%	G2 (n = 11) WO ≥ 27%
SBPIN (mmHg)	119.00 ± 15.59	113.27 ± 19.92
DBPIN (mmHg)	80 ± 9.76	74.18 ± 7.06
HRIN (bpm)	74.08 ± 7.94	73.90 ± 7.70
PESBP (mmHg)	181.00 ± 28.01	153.27 ± 27.71[†]
PHR (bpm)	136.91 ± 19.66	118.45 ± 13.98[†]
Δ SBP* (mmHg)	64 (47.5 - 80.5)	36 (25 - 47) [†]
CRI %	70.42 ± 17.94	49.47 ± 14.89[‡]
FC*	8.37 (6.47 – 10.27)	4.42 (2.46 – 6.38) [‡]

Values expressed as mean ± standard deviation or (*) median (interquartile range); (†) p < 0.05; (‡) p ≤ 0.01; G1 - group 1; G2 - group 2; n - number; WO - Washout rate; SBPIN - systolic blood pressure at the start of exercise; DBPIN - diastolic blood pressure at the start of exercise; HRIN - heart rate at the start of exercise; PESBP - systolic blood pressure at peak exercise; PHR heart rate at peak exercise; Δ SBP - variation in systolic blood pressure at the start of test and measurement at peak exercise; CRI - chronotropic reserve index; FC - functional capacity in number of METs achieved.

Discussion

In our study, we found that in patients with HF, SBP at peak exercise and functional capacity, measured by the number of METs achieved, are associated with changes in cardiac adrenergic innervation, as evidenced by the washout rate obtained by myocardial scintigraphy with I[123] MIBG. During ET, in patients with altered washout rate (state of adrenergic hypertonia at rest), we found that SBP at peak exercise and the number of METs showed lower values when compared
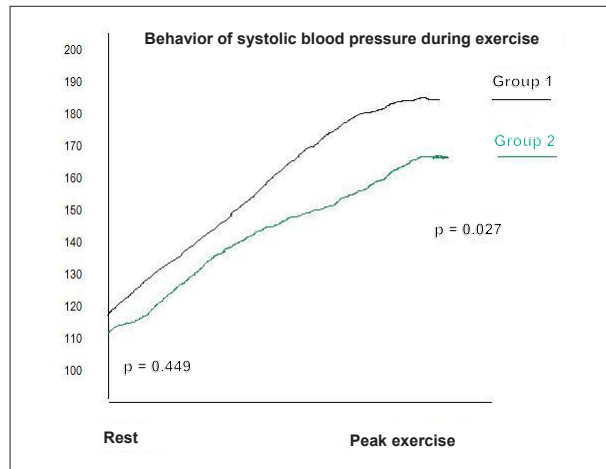

Figure 1 - *Behavior of blood pressure during exercise. Note the significant difference between groups at peak exercise.*

with patients with normal washout rate. So far, there are no descriptions in literature of the association between such abnormal behavior in SBP and changes in cardiac adrenergic innervation by I[123] MIBG.

The variation in SBP during exercise is directly associated with cardiac output during exercise: a lower increase in intrastress SBP may result from inotropic deficit during the exercise, which is a common phenomenon in patients with ventricular dysfunction, and this finding is associated with a worse prognosis[2]. Fargard et al[22] in a sample of patients eligible for heart transplantation, demonstrated that an inadequate variation in SBP in response to submaximal exercise is a predictor of cardiac events.
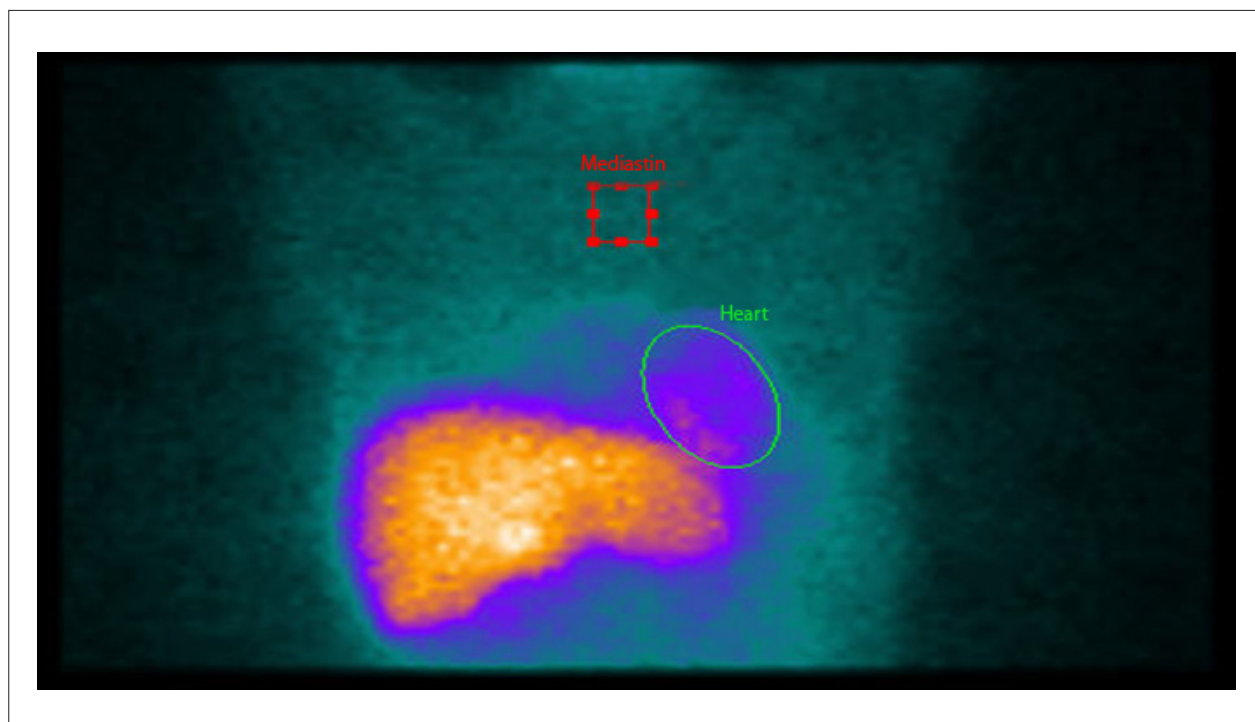

Figure 2 - *I[123] MIBG Scintigraphy in a patient with heart failure (LVEF 38%) showing early and late C/M ratio, and normal washout rate (2.1; 1.92; 21%, respectively).*

Table 3 - Correlation of exercise variables to the washout rate

	PESBP	PHR	Δ SBP	CRI	FC
Correlation coefficient of WO	-0.505	-0.302	-0.493	-0.399	-0.646
P		0.014	0.161	0.017	0.059	0.001

WO - Washout rate; PESBP - systolic blood pressure at peak exercise; HR - heart rate at peak exercise; Δ SBP - variation in systolic blood pressure at the start of test and measurement at peak exercise; CRI - chronotropic reserve index; FC - functional capacity in number of METs achieved.

Willians et al[23] evaluated patients with HF of different functional classes, demonstrating that simple parameters from the test, such as the duration and peak exercise SBP, are strong predictors of prognosis through multivariate analysis, exceeding the left ventricular ejection fraction and N-terminal proBNP ejection fraction (NT-proBNP).

Nishiyama et al[2] evaluated the blood pressure response during exercise as a predictor of prognosis in patients with HF. Through univariate analysis, SBP and HR at peak exercise, and their variations during exercise (ΔSBP/ΔHR = peak exercise - rest) were predictors of mortality. In this study, the group not surviving presented significantly lower values of these variables. After multivariate analysis, the Δ SBP and functional capacity, obtained through the number of METs achieved, were the best predictors of mortality, regardless of the use of beta-blockers.

Maximal oxygen consumption (VO_2) is a parameter used to assess, in patients with heart failure, eligible to cardiac transplantation[24], and is also a powerful predictor of prognosis[24-26]. Willens et al[27] studying 40 patients with HF, functional class II and III of the New York Heart Association (NYHA), have shown that VO_2 max, both by indirect measurement (according to the time of the year), and by direct measurement, through the Cardiopulmonary Exercise Testing, is an important predictor of survival, providing useful information for monitoring patients. Another way to assess VO_2 max by indirect measurement is by the number of METs achieved on the NT[2].

In a study involving healthy individuals Snader et al[8] demonstrated that functional capacity was a powerful predictor of cardiovascular mortality. In this study, the rate of cardiovascular mortality was higher in the group that failed to reach 06 METs on ET, and its association with perfusion defects diagnosed by thallium scintigraphy, put these patients at a risk level even higher for adverse events.

Jeng et al[28] evaluated the influence of exercise tolerance on the quality of life in patients with HF. Patients who had a functional capacity greater than or equal to 05 METs, or a time of ET greater than or equal to 180 seconds, had a better quality of life, showing that the ET is safe, affordable and effective to assess exercise tolerance in this population. Rubim et al[29] showed that the number of METs achieved in ET correlated significantly with mortality.

Myers et al[30], evaluating quality of life scores, 06-minute walking test and number of METs achieved on ET in patients with HF, and correlating these variables with VO_2 max obtained through cardiopulmonary exercise testing, concluded that both reflect the patient's clinical status and have their importance

in this clinical context, without, however, substituting one another. When compared to the distance covered in the 06-minute walking test, the functional capacity determined by the number of METs in ET correlated significantly better with the VO_2 max obtained through direct measurement.

Chandrashekhar et al[31] analyzed the capacity of variables commonly used in ET in predicting VO_2 max. After stepwise regression analysis, the best predictor of VO_2 max was the number of METs achieved. Although the authors assert that the number of METs do not have a high precision, it still is a better predictor than the other clinical variables obtained, such as the HR behavior during exercise.

One of the most significant changes in the treatment of heart failure was the introduction of beta blockers. Parikh et al[32], in HF patients, NYHA functional class III and IV, evaluated the effect of the beta-blocker metoprolol on the number of METs achieved on ET and concluded that the optimization of beta-blocker improves exercise performance, measured both by exercising time, and by the number METs.

Some studies suggest that the improvement, which is not universally observed, may be partly due to improved endothelial function due to the use of beta-blockers associated with inhibitor of angiotensin-converting enzyme[33].

Another aspect of risk markers in HF is through the neuroimaging. I^{123} MIBG scintigraphy has been validated as a marker of prognosis, according to a meta-analysis with 1,755 patients, published by Verbene et al[19] who demonstrated that a reduction of the C/M ratio in late imaging or washout rate increase in myocardial scintigraphy I^{123} MIBG is associated with a worse prognosis when compared with patients with normal parameters. In a recent publication, Jacobson et al[34] in a multicenter study with patients with functional class NYHA II and III and left ventricular ejection fraction smaller than 35%, showed that the adrenergic direct assessment of the heart by myocardial scintigraphy with I^{123} MIBG, was predictive of increased cardiac mortality and arrhythmic events, regardless of known prognostic factors such as left ventricular ejection fraction, brain natriuretic peptide levels and NYHA functional class.

Analyzing the functional information obtained by the neuroimaging with Cardiopulmonary Exercise Test, Cohen-Solal et al[14] correlated VO_2 max with I^{123} MIBG uptake and several other variables (left ventricular ejection fraction, hemodynamic parameters such as cardiac index and pulmonary capillary wedge pressure). Observed a significant correlation between adrenergic scintigraphic findings in I^{123} MIBG and VO_2 max in the exercise. Analyzing their outcomes (cardiovascular death and heart transplantation), the major determinant of prognosis was VO_2 max. VO_2 max correlated better with the C/M ratio for late image than with the C/M to ratio for early image and the washout rate. In contrast, our study found a higher correlation with the washout rate with the number of METs achieved, rather than with late C/M ratio as in the study by Cohen-Solal et al[14].

However, there are significant differences between the studies: In our study, we assessed VO_2 max by indirect measurement through the number of METs achieved, while Cohen-Solal et al[14] have used a direct measurement of the

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VO_2. In the study by Cohen-Solal et al, only 13.0% of patients were taking beta-blockers, while in our study, all patients were using this medication. One of the actions of beta blockers is resensibilizing betareceptors, which may influence the C/M ratio, which could explain the differences between findings[5,35].

Study limitations

The main limitation in this study was the small number of patients. However, through a pilot study with 16 patients, a sample calculation was performed and the number of 23 patients has a statistical power of 90% to identify 50% difference in functional capacity and a statistical power of 80% to identify 50% of difference in SBP at peak exercise.

Another significant limitation is that we have employed the functional capacity by the number of METs achieved, rather than the VO_2 max calculated directly through cardiopulmonary exercise testing, because we did not have the necessary equipment at our institution at the time of this study. However, as the ET is a simple tool widely present in our environment, we believe that the information derived from this examination may be useful for cardiologists involved in clinical practice of patients with HF, since it is correlated with the sophisticated analysis of cardiac innervation. Another important variable observed as significant in our study was that SBP at peak exercise, is also derived from ET and does not require complex methodologies for analysis.

Conclusion

Patients with HF and washout rate changed in I^{123} MIBG myocardial scintigraphy showed a lower inotropic and chronotropic response, and a lower functional capacity. SBP at peak exercise and the number of METs were the ET variables most associated with this adrenergic hypertonia assessed by scintigraphy. Conventional ET, through the evaluation of these two variables, can be used as a way to predict the presence of adrenergic hyperactivity in patients with heart failure.

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Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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