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Do Interleukin-1β Levels Correlate with MIBG and Exercise Parameters in Heart Failure?

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Abstract

Background: Interleukin 1β (IL 1β) levels are associated with prognosis in heart failure. The cardiac adrenergic activity as assessed by metaiodobenzylguanidine (I^{123} MIBG) scintigraphy along with exercise parameters are important predictors of prognosis. The relationship between these variables is not fully established.

Objective: To evaluate the association of IL 1β levels with exercise and I^{123} MIBG parameters.

Methods: Evaluating 25 consecutive patients with heart failure and ejection fraction lower than 45% by means of: determination of IL 1β levels; I^{123} MIBG parameters [early and late heart/mediastinum ratio, washout rate (WR)]; and treadmill exercise test using the ramp protocol.

Results: The patients were divided into two groups according to their IL 1β levels (normal vs. increased). The group with increased levels showed lower reserve double product (RDP); lower functional capacity (FC); slower heart rate recovery at the first (HRR 1º) and second minute (HRR 2º); and higher WR. In the univariate analysis, all variables correlated with IL 1β; RDP: r = 0.203, p = 0.024; FC: r = 0.181, p = 0.034; HRR 1º: r = 0.182, p = 0.034; HRR 2º: r = 0.204, p = 0.023; WR: r = 0.263, p = 0.009. In the multivariate analysis, only WR maintained a significant correlation (r^2 = 0.263, p = 0.009).

Conclusion: Adrenergic overactivity was the main determinant of IL 1β levels, thus demonstrating that an excessive sympathetic activity influences the systemic inflammatory response. Exercise test variables were not able to identify patients with high IL 1β levels (Arq Bras Cardiol 2013; 100(5):395-403).

Keywords: Interleukin, Heart Failure; Exercise testing; MIBG.

Introduction

Heart failure (HF) is an inflammatory neuroendocrine syndrome associated with worsening of the functional capacity, decreased quality of life, and increased morbidity and mortality[1,2]. In this syndrome, there is a renin-angiotensin-aldosterone axis activation and adrenergic overstimulation, thus configuring a neurohumoral imbalance[2] which is directly related to left ventricular dysfunction, regardless of the functional class[3], and is correlated with a worse prognosis[4].

The cardiac activity and sympathetic innervation may be evaluated by iodine 123 metaiodobenzylguanidine scintigraphy (I^{123} MIBG)[5,6]. The early imaging represents the presynaptic nerve ending integrity and beta-receptors density. Presynaptic neuronal uptake contributes to the late imaging, combining information on the neural function including norepinephrine uptake, release and storage in the presynaptic vesicles. The washout rate is a parameter which assesses the degree of sympathetic activity[6]. Patients with HF may present with: reduced radiotracer uptake due to the loss of sympathetic neurons and/or primary norepinephrine uptake disturbances; and increased washout rate reflecting norepinephrine overflow to the blood stream[5,7].

In HF, peripheral and intracardiac levels of inflammatory cytokines are elevated, and the increase in their serum levels is proportional to the clinical deterioration and severity of the disease, also contributing to endothelial dysfunction, oxidative stress, anemia, pulmonary congestion, and loss of muscle mass[8-10]. Among the cytokines which are elevated in HF is interleukin 1β (IL 1β), which depresses cardiac contraction and is involved in myocardial apoptosis, hypertrophy and arrhythmogenesis[9,11].

The indications for an exercise test in HF include evaluation of the presence of symptoms and treatment; detection of the presence of ischemia; and determination

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of the functional capacity and heart rate recovery are some of the parameters assessed that are known to be predictive of prognosis[13,14].

It is not clear whether IL 1β correlates with adrenergic innervation and/or exercise parameters. Therefore, the objective of our study is to evaluate the association of IL 1β levels with exercise test and I[123] MIBG scintigraphy parameters in patients with HF and reduced ejection fraction.

Methods

Evaluating 25 consecutive patients with heart failure. The patients selected showed a left ventricular ejection fraction equal to or lower than 45% as measured by echocardiography using Simpson's technique. Patients presenting with atrial fibrillation, diabetes, ventricular pacing device, endocrine diseases, Parkinson's disease, ferver patient, chronic inflammatory diseases, as well as pregnant women or those who were breastfeeding were excluded from the study.

Patients with New York Heart Association (NYHA) functional classes I and II were selected for observation of the inflammatory and adrenergic profiles in their group and, consequently, for observation of whether these parameters would influence exercise variables. All patients were being treated with optimized doses of standard medications for HF, and no medication was discontinued for the study to be conducted. Volunteers gave written informed consent to participate in the study. The project was approved by the Institutional Research Ethics Committee, under number 011/09

The following criteria were used for the classification of the cause of HF: ischemic (covering history of acute myocardial infarction; presence of an inactive area on electrocardiogram or coronary angiography showing left main coronary artery lesion equal to or greater than 50%, or lesion equal to or greater than 70% in one of the three main systems – anterior descending, circumflex and right coronary)[15]; hypertensive (covering history of hypertension and absence of criteria for ischemic etiology); and other (covering patients not classified as having ischemic or hypertensive etiology, for instance: idiopathic dilated cardiomyopathy, post-myocarditis, *peripartum*).

For patients to undergo I[123] MIBG myocardial scintigraphy, they had to be previously prepared for thyroid protection with 10 mL of oral potassium iodide administered 48 h prior to the imaging test. On the day of the test, the patients were instructed not to take any caffeine-containing beverages (coffee, black tea, sodas, chocolate), and to remain fasted for two hours. Planar images were obtained using a 5 mCi dose of I[123]-labelled MIBG. The semiquantitative measure of I[123] MIBG myocardial uptake was obtained by calculating the heart/mediastinum ratio (H/M) for early imaging (30 minutes after radiotracer injection) and the late imaging (4 hours after injection), in addition to the calculation of the washout rate using the formula $\{[(H/M\ early - H/M\ late) / (H/M\ early] \times 100\}$[5].

All tests were carried out in a Siemens, E-Cam double detector model, with low-energy collimator and high-resolution Anger digital tomographic scintillation chamber (Single Photon Emission Computed Tomography).

Medications used for the treatment of heart failure were not discontinued and none of the study patients was on other medication, such as tricyclic antidepressants, reserpine, guanethidine, phenylephrine, pseudoephedrine, phenylpropanolamine, antipsychotic drugs, or calcium-channel blockers, which could influence the I[123] MIBG results.

On the day of the exercise test, the patients were instructed not to drink any caffeine-containing beverages, not to smoke, to eat a light meal at most three hours prior to the test (they should not be fasting), not to practice extenuating physical exercises, not to drink alcoholic beverages on the day before and on the day of the test, and to keep taking their regular medications. Two tests were performed. The exercise test was symptom-limited (software program ErgoPC 13 version 2.2), in an Imbramed treadmill duly calibrated according to the manufacturer's instructions. The first test was performed using the Naughton's protocol in order to train the patients and better adapt them to the treadmill.

After a 7 to 10-day interval, the second test was performed using the ramp protocol, starting at a speed of 1.6 km/h, with no inclination. Speed and inclination were programmed so that the VO$_2$ estimated in the first test would be achieved in 10 minutes in the second test. No patient performed the test in less than 8 minutes of exercise. The study variables were obtained in the second test.

Behavior of blood pressure during exercise, of heart rate during exercise and recovery, and the estimated functional capacity were evaluated. Heart rate was measured using the RR interval in the ECG tracing with the software program itself. Blood pressure was measured using the indirect method with a mercury-column sphygmomanometer duly calibrated, placed on the left arm of the patients in the standing position. Functional capacity was estimated by the software program by means of the number of METs reached. The modified BORG scale[16] was used to determine the peak exercise, and only patients who completed the test for maximum exhaustion (BORG 10) participated in the study.

The recovery protocol was the same for all patients: 2 minutes in active recovery (speed 1.6 km/h; no inclination) and 4 minutes in passive recovery in the standing position on the treadmill. The heart rate recovery (HRR) value was determined by subtracting the absolute heart rate value at the peak exercise from the absolute heart rate value in the first and second minutes of recovery.

Prior to the exercise test, a blood sample was collected by right antecubital venipuncture after applying a tourniquet on the right arm. After proper aseptic technique with alcohol 70% to clean the puncture site, 10 mL of blood were collected by means of a 20-mL syringe and 25x8 needle and distributed into two tubes containing EDTA. The sample was centrifuged at 100 rpm, and the plasma was separated from the cells; the plasma IL 1β level was then determined. The Quantikine immunoassay kit (R&D Systems, Inc, Minneapolis, USA) consisting of a solid-phase ELISA with 3.5 – 4.5 h duration was

used. This is a quantitative sandwich immunoassay and the determinations were made according to the manufacturer's recommendations. The normal reference value used was lower than 4.0 pg/mL.

The SPSS version 15 was used for the statistical analysis. Values were expressed as percentage, median and interquartile range. The chi square test was used for the analysis of qualitative variables. The Mann-Whitney U test was used for the analysis of quantitative variables because of the non-parametric data distribution. Univariate and multivariate analyses were used to study the correlation between the variables analyzed and IL 1β. The level of statistical significance was set at $p < 0.05$.

Results

The patients were evaluated according to their degree of inflammatory activity, and the sample was divided into two groups: Group 1 (G1): IL 1β < 4.0 pg/mL (no inflammation); and Group 2 (G2): IL 1β ≥ 4.0 pg/ml (with inflammation). The overall characteristics of the groups are shown in Table 1. No significant differences were observed as regards age, gender, body mass index, presence of hypertension, dyslipidemia, smoking habit, and ventricular ejection fraction. The etiology of HF in most of the patients of our sample was hypertension: Group 1, 7 patients (70%), and Group 2, 10 patients (66.7%). The etiology of HF in the remaining patients of Group 1 was: one patient (10%) had ischemic HF and two (20%) were classified as having non-ischemic, non-hypertensive HF; one of these was peripartum and the other, idiopathic. In Group 2, two patients (13.3%) had ischemic HF, whereas three (20%) had HF of other causes (one peripartum and two idiopathic). No significant differences were observed regarding the etiology of HF, medications used, or NYHA functional class.

As regards the scintigraphy parameters, no significant difference was observed in the early heart/mediastinum ratio (H/M) (G1: 1.76 (1.48 – 1.96) vs. G2: 1.76 (1.64 – 1.99), p = 0.579) or late H/M ratio (G1: 1.76 (1.48 – 1.96) vs. G2: 1.65 (1.5 – 1.83), p = 0.437). However, there was a significant difference regarding the washout rate (G1: 20.5% (12 – 26.1) vs. G2: 31% (23.5 – 36.3), p = 0.003), thus demonstrating that the group of patients with the worst inflammatory profile also showed an adrenergic overactivity status at rest.

During the exercise test, Group 2 showed lower intra-exercise systolic blood pressure variation, lower reserve double product, lower functional capacity, and slower HRR at the 1º and 2º minutes, as shown in Table 2.

Since we considered that other variables could influence the results, uni and multivariate analyses were carried out to determine which variables were more correlated with IL 1β (dependent variable). Table 3 shows that in the univariate analysis, the I[123] MIBG washout rate, double-product reserve, functional capacity and 1º and 2º minute HRR were variables associated with IL 1β; in the multivariate analysis, the I[123] MIBG washout rate was the only variable that really correlated with serum IL 1β levels.

Graph 1 shows the correlation between IL 1β and the I[123] MIBG washout rate.

Discussion

After multivariate analysis, we observed that IL 1β correlated with the I[123] MIBG washout rate (an adrenergic overactivity marker). We can presume that the resting adrenergic activity influenced the serum levels of this marker. Thus, I[123] MIBG myocardial scintigraphy was superior to conventional exercise test in the detection of patients with HF and a worse inflammatory profile.

There are several hypotheses to explain the pathophysiological mechanism of increased cytokines in HF. The central mechanism hypothesis proposes that an event, whether acute or chronic, such as myocardial ischemia, which results in a decrease in cardiac output and/or increase in filling pressures, would lead to increased ventricular wall stress, thus activating intraventricular baroreceptors and stimulating the sympathetic activity[17]. This increased cardiac sympathetic activity associated with myocardial lesion would be the triggering factor for the myocardial production of cytokines[18]. Once produced, these cytokines will activate local monocytes and macrophages, thus triggering the local inflammatory process. Later, the cytokines are released in the bloodstream, activating peripheral monocytes and macrophages and increasing systemic production of these substances. In addition to stimulating the cardiac production of cytokines again, this systemic elevation also depresses the myocardial function. By a direct (acting on the central control base) or indirect (myocardial depression) mechanism, it will perpetuate the hyperadrenergic status characteristic of heart failure, which is also a stimulating factor for the inflammatory response, thus generating a positive feedback vicious cycle[19].

We believe this is the pathophysiological mechanism that accounts for the correlation between the I[123] MIBG washout rate and IL 1β demonstrated in our study.

Another hypothesis to explain the inflammatory activity in HF is the peripheral mechanism, in which, as a result of the low cardiac output, the hypoperfused muscle would activate cytokine production by peripheral monocytes, thus leading to more depression of the ventricular function, and further worsening of the peripheral perfusion[19]. Lastly, the intestinal mechanism hypothesis: mesenterial hypoxia associated with intestinal loop edema would lead to translocation of bacteria and/or their endotoxins from the bowel into the bloodstream, thus activating and perpetuating the systemic inflammatory response[20].

In the heart, IL 1β causes a dose-dependent depression of myocardial contractility and is involved in myocardial apoptosis, myocyte hypertrophy, and arrhythmogenesis[9,18]. After an acute myocardial infarction episode, IL 1β regulates the inflammatory response and is one of the factors responsible for ventricular remodeling[21].

In a recently completed study analyzing patients with ST-segment elevation acute myocardial infarction, Abbate et al[22] observed favorable effects of IL 1β receptor blockade with anakinra, administered for 14 days, on ventricular remodeling observed at 90 days after infarction. Van Tassel et al[23] demonstrated that increased IL 1β levels in patients with HF contributed to worse exercise tolerance, and IL 1β receptor blockade by means of por anakinra improved VO_2 peak with better ventilatory efficiency, as assessed by the VE/VCO_2 slope. In our study, we could observe that patients with increased IL 1β levels also showed poorer functional capacity.

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Table 1 - Comparison of groups divided according to IL 1β values

Variable	G1 (normal) IL 1β < 4.0 pg/ml	G2 (with inflammation) IL 1β ≥ 4.0 pg/ml	p
N	10	15	
Age (years)	52.5 (44 – 58.75)	60 (45 – 66)	0,255
Gender (F/M)	5/5	4/11	0,243
BMI (Kg/m²)	26 (24.05 – 28.97)	27.47 (23.6 – 32.8)	0,739
SAH	80%	80%	0,996
Dyslipidemia	50%	60%	0,629
Smoking habit	30%	20%	0,574
Etiology			0,886
Ischemic	10%	13.3%	
Hypertensive	70%	66.7%	
Other	20%	20%	
LVEF (%)	34 (29.75 – 44.25)	36 (29 – 39)	0,358
Betablocker	100%	100%	1
ACEI/ARA II	60%	73.3%	0,667
Spironolactone	100%	93.3%	0,414
Diuretics	90%	93.3%	0,768
Digitalis	50%	46.7%	0,873
Hydralazine	20%	0	0,077
Nitrate	20%	6.7%	0,325
ASA	20%	26.7%	0,708
Statin	50%	60%	0,629
NYHA			0,607
I	70%	66.7%	
II	30%	33.3%	
IL 1β	0.87 (0.72 – 3.57)	4.64 (4.35 – 5.14)	0,0001

Numerical variables are expressed as median and interquartile range; categorical variables, as number or percentage. G1: group 1; G2: group 2; IL 1β: interleukin 1 beta; pg/mL: picograms per milliliters; N: number; F: female gender; M: male gender; BMI: body mass index; Kg/m²: kilogram per square meter; SAH: systemic arterial hypertension; LVEF: left ventricular ejection fraction; ACEI: angiotensin II converting enzyme inhibitor; ARA II: angiotensin II receptor antagonist; ASA: acetylsalicylic acid; NYHA: New York Heart Association functional class.

The washout rate is considered a sympathetic activity marker, so that sympathetic overactivity is characterized by high washout and low I[123] MIBG myocardial uptake[24], which could more accurately reflect the catecholamine kinetics attributed to the adrenergic activity, because it is independent of the amount of adrenergic neurons, measuring the myocardial MIBG reuptake ability[25].

Ogita et al[26] studied the prognostic power of the washout rate to predict morbidity and mortality in patients with heart failure. The 27% value was a good predictor of prognosis, because the group of patients with values above this cut-off point showed higher mortality rates, higher hospital readmission rates, and clinical worsening of HF. Carrió et al[27] also demonstrated that patients with a washout rate higher than 27% showed higher rates of sudden death. In our study, we found that patients of the group with inflammation had washout rates higher than 27%, thus corroborating the

findings described[26,27]; this group has a higher probability of the occurrence of adverse events. In the ADMIRE-HF study[28], the washout rate was also associated with an increased risk of cardiac events; however, it was not superior to the late heart/mediastinum (H/M) ratio.

According to Patrianakos et al's study[29], the levels of inflammatory cytokines, including IL 1β, were increased in patients with dilated cardiomyopathy and diastolic dysfunction (restrictive pattern), and was associated with a decreased functional capacity. The authors concluded that the diastolic dysfunction may contribute to the increase in cytokine levels and to the reduction of the functional capacity. In our study, we did not evaluate the diastolic function; however, the group of patients with a worse inflammatory profile was also the group with a worse estimated functional capacity. Parthenakis et al[30] studied patients with HF and demonstrated that increased serum levels of inflammatory cytokines are related to reduced

Table 2 - Comparison of groups, as divided by IL 1β levels, during the exercise test

| Variable	G1 (normal) IL 1β < 4.0 pg/ml	G2 (with inflammation) IL 1β ≥ 4.0 pg/ml	p
SBP Rest (mmHg)	114 (103.5 – 131.5)	122 (96 -132)	0.637
DBP Rest (mmHg)	79 (72 – 90.5)	78 (70 – 82)	0.241
HR Rest (bpm)	73 (70 – 75.75)	76 (68 – 83)	0.636
SBP PRest (mmHg)	172 (154 – 207)	160 (140 – 188)	0.202
HR P (bpm)	135 (122.5 – 150)	122 (107 – 137)	0.149
SBP PIN (mmHg)	61 (43.5 – 71)	42 (32 – 58)	0.04
CRI (%)	62.4 (55.57 – 80.67)	56.38 (45.45 – 73.86)	0.12
DP max (mmHg.bpm)	26361 (18201-28212)	18800 (16940-24320)	0.096
RDP (mmHg.bpm)	17908 (11106-18942)	10570 (7854-14744)	0.015
FC (METs)	8.23 (5.85 – 9.53)	5.95 (3.32 – 7.55)	0.035
HRR 1 min (bpm)	21.5 (17 – 28.5)	11 (7 – 19)	0.019
HRR 2 min (bpm)	31 (28.5 – 37.75)	21 (12 – 35)	0.028

SBP Rest: systolic blood pressure in rest; mmHg: millimeters of mercury; DBP Rest: diastolic blood pressure in rest; HR Rest: heart rate before in rest; bpm: beats per minute; SBP P: systolic blood pressure at peak exercise; HR P: heart rate at peak exercise; SBP PRest: variation of systolic blood pressure during exercise: CRI: chronotropic reserve index; DP: double product; max: maximum; RDP: reserve double product; FC: functional capacity; HRR 1: heart rate recovery at the first minute of recovery; min: minute; HRR 2: heart rate recovery at the second minute of recovery.

Table 3 - Uni and multivariate analyses of the variables analyzed using IL 1β as a dependent variable

Analysis	Univariate r	p	Multivariate r²: 0.263	p
Age	0.033	0.384		0.201
Gender	0.057	0.252		0.227
BMI	0.023	0.469		0.094
Dyslipidemia	0.01	0.639		0.36
Smoking habit	0.013	0.585		0.277
Etiology	0.001	0.890		0.311
LVEF	0.045	0.311		0.83
ACEI/ARA II	0.02	0.504		0.255
Spironolactone	0.028	0.426		0.199
ASA	0.006	0.716		0.288
Statin	0.021	0.488		0.223
Early H/M	0.013	0.593		0.564
Late C/M	0.032	0.39		0.843
WR	0.263	0.009		0.009
SBP PRest	0.139	0.066		0.562
RDP	0.203	0.024		0.212
FC	0.181	0.034		0.335
HRR 1 min	0.182	0.034		0.228
HRR 2 min	0.204	0.023		0.211

BMI: body mass index; LVEF: left ventricular ejection fraction; ACEI: angiotensin II converting enzyme inhibitor; ARA II: angiotensin II receptor antagonist; ASA: acetylsalicylic acid; H/M: heart mediastinum ratio; WR: washout rate; SBP PRest: variation of systolic blood pressure during exercise; RDP: reserve double product; FC: functional capacity; HRR 1: heart rate recovery at the first minute of recovery in comparison to peak exercise; min: minute; HRR 2: heart rate recovery at the second minute of recovery in comparison to peak exercise.

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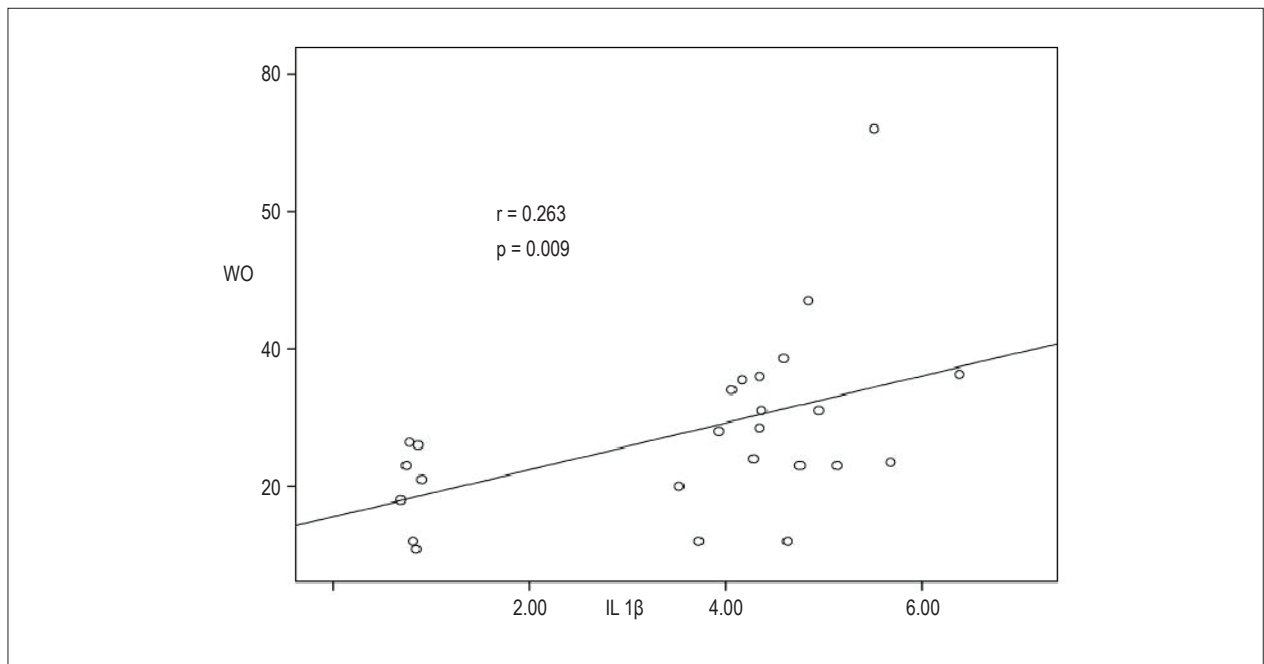
Graph 1: *Graph of the correlation between interleukin 1β and I[123] MIBG washout rate. IL 1: interleukin 1β; WO: washout rate.*

cardiac sympathetic innervation. The authors demonstrated that there was a relationship between myocardial I[123] MIBG uptake, tumoral necrosis factor α (TNF-α), IL 1β, parameters of the left ventricular function, and VO_2 peak. They concluded that changes in the cardiac sympathetic innervation have a significant correlation with cytokine levels, thus corroborating the hypothesis that an abnormal cardiac adrenergic activity and its cardiovascular consequences lead to a loss of the inhibitory effect on the production of inflammatory cytokines, which contributes to the elevation of their plasma levels.

Turpeinen et al[5] studied another HF cohort and analyzed the correlation between changes in the cardiac sympathetic innervation, inflammation and neurohumoral activity. The authors concluded that changes in the cardiac adrenergic innervation would lead to increased cytokine levels, which, in turn, would contribute to perpetuate the cardiac autonomic dysfunction. In our study, we demonstrated that there is an association between the washout rate and IL 1β (multivariate analysis), IL 1β and heart rate recovery (HRR) at the 1st and 2nd minutes post-exercise (univariate analysis), which leads us to assume that the adrenergic overactivity at rest was the factor that contributed to the post-exercise parasympathetic dysfunction, as has already been demonstrated in another study[31].

Our research team[32] evaluated the relationship between the washout rate and conventional exercise test variables in patients with HF and reduced ejection fraction and demonstrated that the group of patients with increased washout rate showed a lower inotropic and chronotropic response during exercise, as well as a lower functional capacity. In the linear regression analysis, systolic blood pressure at peak exercise and functional capacity in METs were the variables that best correlated with the washout rate.

This association between adrenergic activity and inflammation has also been described in other diseases, as was demonstrated in Diakakis et al's study[33], in which the authors evaluated patients with glucose intolerance and demonstrated that an abnormal cardiac sympathetic innervation and increased adrenergic activity are correlated with a worse inflammatory profile, and can be considered an early atherosclerosis marker. Shinohara et al[34] evaluated diabetic patients and described the association of high IL6 levels with impaired late heart/mediastinum ratio and increased I[123] MIBG washout rate. The authors reported that the mechanism responsible for the adrenergic overactivity related to increased IL6 levels is the $β_2$-adrenergic stimulation and the increased insulin resistance. Insulin resistance is one of the factors responsible for autonomic neuropathy in type-2 diabetes. Thus, $β_2$-adrenergic stimulation would lead to sympathetic overactivity, with increased IL6 levels, and the elevation of this cytokine, in turn, would worsen insulin resistance and result in more cardiac autonomic dysfunction[34].

The variables studied during the exercise test were not able to identify our heart failure cohort with a worse inflammatory profile. After multivariate analysis, we verified that the main factor that influenced our findings was the I[123] MIBG washout rate. The double product reserve, estimated functional capacity, and 1st and 2nd HRR were associated with IL 1β; however, in previous studies[31,32], we had already demonstrated that the washout rate is correlated with these variables. We did not evaluate the intra-exercise RR variability variable, which assesses the action of both components of the autonomic nervous system in the sinus node[35]. However, it has already been reported that there is a correlation between washout rate and RR variability[36].

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We believe that HF is a severe, complex syndrome, and that further understanding of its pathophysiology is fundamental for an improved therapeutic approach. In the search for risk markers, I^{123} MIBG myocardial scintigraphy has emerged as a relatively new, not frequently used method, but it is quite useful in the risk stratification of these patients. The association of its parameters with inflammatory markers and exercise parameters shows the importance of the autonomic nervous system in the pathophysiology of HF.

Study limitations

The main study limitation was the small number of patients. However, by means of a pilot study of 16 patients, a sample calculation was carried out and the total number of 10 patients per group would be necessary to identify a 33.8% difference between the washout rate means for and α error of 5% and a β error of 80%.

Another limitation was the impossibility to perform a cardiopulmonary exercise test (CPET) to ensure that the patients had performed the maximum test. However, as previously described, only patients who completed the test for exhaustion (score 10 in the perceived tiredness scale of modified BORG) participated in the study. We are aware of the fact that the estimated functional capacity has a large error margin; nonetheless, we believe that it is an important parameter in the assessment of patients with HF, because it is directly correlated with VO_2 peak[37] and I^{123} MIBG parameters[31].

CPET was not performed because the equipment was not available in our institution at the time the present study was conducted. However, blood pressure and heart rate may be assessed by conventional exercise test without requiring complex methodology for analysis.

Conclusion

The adrenergic overactivity status, as diagnosed by the I^{123} MIBG washout rate, was the main determinant of IL 1β levels, thus demonstrating that an excessive sympathetic activity has an influence on the systemic inflammatory activity, and inflammation also has an effect on the cardiac autonomic dysfunction. The exercise test variables were not able to identify patients with high IL 1β levels.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Messias LR, Carreira MAMQ, Mesquita ET, Mesquita CT; Acquisition of data: Messias LR, Carreira MAMQ, Miranda SM, Azevedo JC, Benayon PC, Rodrigues RC, Mesquita CT; Analysis and interpretation of the data: Messias LR, Carreira MAMQ, Azevedo JC, Maróstica E, Mesquita ET, Mesquita CT; Statistical analysis, Obtaining funding and Writing of the manuscript: Messias LR, Mesquita CT.

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