Is Abnormal Adrenergic Activation Associated with Abnormal Heart Rate Recovery?

Leandro Rocha Messias[1], Maria Angela M. de Queiroz Carreira[1], Sandra Marina Miranda[1], Jader Cunha de Azevedo[1,2], Isabela Ambrósio Gava[1], Ronaldo Campos Rodrigues[1], Elisabeth Maróstica[1], Claudio Tinoco Mesquita[1,]

Universidade Federal Fluminense[1], Niterói, RJ; Hospital Procardíaco[2], Rio de Janeiro, RJ – Brazil

Abstract

Background: Heart Rate Recovery (HRR) reflects the capacity of the cardiovascular system to reverse the vagal withdrawal caused by exercise. Scintigraphy with metaiodobenzylguanidine (I^{123} MIBG) evaluates innervation and cardiac adrenergic activation. The association of these two methods is not well established.

Objective: To evaluate the association between HRR and washout rate (WO) of I^{123} MIBG in patients with heart failure (HF).

Methods: wenty-five patients with ejection fraction ≤ 45% underwent exercise testing, and analysis of the variation of HRR from the 1st to the 8th minute after exertion. Submitted to I^{123} MIBG, they were separated into groups by WO: G1) <27% and G2) ≥ 27%. For the statistical analysis Mann-Whitney's U test and Spearman's correlation coefficient were used.

Results: G2 showed a slower variation of HRR: 1st minute: G1: 21.5 (16.12 to 26.87) vs. G2: 11.00 (8.5 to 13.5) bpm, p = 0.001; 2nd minute: G1: 34 (29-39) vs. G2: 20 (14 - 26) bpm, p = 0.001; 3rd minute: G1: 46 (37.8 – 54.1) vs. G2: 30 (22 – 38) bpm, p = 0.005; 5th minute: G1: 51.5 (42 - 61) vs. G2: 39 (31.5 to 46.5) bpm, p = 0.013, and in the 8th minute: G1: 54.5 (46.5 – 62.5) vs. G2: 43 (34 – 52) bpm, p = 0.037. HRR in the 1st (r = -0.555, p = 0.004), and in the 2nd minute (r = -0.550, p = 0.004) were negatively correlated with WO.

Conclusion: Patients with high HF and WO showed an abnormal HRR compared with patients with normal WO. These findings suggest that adrenergic activation may influence the HRR. (Arq Bras Cardiol 2012;98(5):398-405)

Keywords: Heart rate; stroke volume; heart failure; heart/radionuclide imaging

Introduction

Heart Rate (HR) increases during dynamic exercise due to parasympathetic inhibition and sympathetic activation[1]. The recovery period after exercise is accompanied by dynamic changes in autonomic tone that occur so that there is a gradual return of HR to values near resting[2]. This period is characterized by parasympathetic and sympathetic withdrawal[3]. It reflects the ability of the cardiovascular system to reverse the vagal withdrawal caused by exercise[4,5], d is an excellent method to evaluate the parasympathetic nervous system[6]. Slow Heart Rate Recovery (HRR) post-exercise reflects an inadequate return of cardiac vagal activity, and has proved to be a good marker of cardiovascular events in both heart disease and in healthy individuals[7-11]. The relationship between HRR and cardiovascular prognosis seems to be independent of symptoms[12], of Left Ventricular Ejection Fraction (LVEF)[13] and the severity of coronary lesions on coronary angiography[14].

Cardiac activity and sympathetic innervation can be assessed by myocardial scintigraphy with metaiodobenzylguanidine labeled with iodine 123 (I^{123} MIBG)[15,16]. Studies have shown[17-19] that early imaging is the integrity of presynaptic nerve terminals, and the density of the beta-adrenergic receptors. The presynaptic neuronal uptake contributes to a later imaging, combining information of neural function, including capture, storage and release of norepinephrine in the presynaptic vesicles. The washout rate (WO) assesses the degree of sympathetic activity. Patients with heart failure may have: (1) reduced tracer uptake due to loss of sympathetic neurons and/or disorders in primary uptake of noradrenalin; and (2) increased WO, reflecting the shedding of noradrenalin to the blood stream[15,17,20-22]. WO rates greater than 27% have been described as a strong predictor of shorter survival in patients with cardiac failure[23].

So far, there is no evidence that abnormalities found in I^{123} MIBG scintigraphy are associated with abnormalities in HRR post-exercise. The purpose of this study is to evaluate the association between HRR and WO of I^{123} MIBG in patients with heart failure, comparing the behavior of HRR in patients with normal and abnormal WO.

Mailing Address: Leandro Rocha Messias •
Rua Noronha Torrezão, 46, Apto 805, Santa Rosa – 24240-182 – Niterói, RJ - Brazil
E-mail: lmessias@cardiol.br, leandromess@gmail.com
Manuscript received September 28, 2011; revised manuscript received September 28, 2011; accepted December 26, 2011.

Methods

We conducted an observational and transversal study, selecting 25 consecutive patients treated in outpatient care specializing in heart failure. The selected patients had heart failure (diagnosed by the use of Framingham[24] criteria) and Left Ventricular Ejection Fraction (LVEF) smaller than or equal to 45% measured by echocardiography by Simpson's technique. The study excluded patients who had atrial fibrillation, diabetes, heart valve disease, patients with ventricular stimulation device, endocrine disorders, Parkinson's disease, pregnant or breastfeeding women. No medication was suspended for this study. Volunteers signed a consent form agreeing to be part of the project. The project was approved by the Ethics Committee in Research of the University, under number 011/09.

To classify the etiology of heart failure, we have used the following criteria: ischemic (history of myocardial infarction, or presence of inactive zone on electrocardiogram, or coronary angiography showing left coronary artery damage greater than or equal to 50%, or damage greater than or equal 70% in one of three main systems - anterior descending, circumflex and right coronary artery[25]), hypertension (history of hypertension and absence of criteria for ischemic etiology) and others (the latter involving patients who were neither classified as ischemic, nor as hypertensive: for example, idiopathic dilated cardiomyopathy, post-myocarditis, peripartum).

Patients underwent myocardial scintigraphy with I^{123} MIBG to assess cardiac adrenergic innervation upon uptake of radiotracer, with study of the heart to mediastinum ratio (H/M) for early images (30 minutes) and late images (4 hours) besides the calculation of WO {WO = [(early H-M - late H-M) / (early H-M)] x 100}[14]. All scintigraphic examinations were performed in Anger type digital tomographic scintillation camera (Single Photon Emission Computed Tomography), Siemens E-Cam dual detector model with low-energy high-resolution collimator. Based on the study of Ogita et al[26], who evaluated the WO as a predictor of survival in heart failure, patients were divided into two groups: Group 1 (G1); WO <27% (normal group), Group 2 (G2), WO ≥ 27% (group with abnormal WO).

Patients underwent symptom-limited exercise test (software ErgoPC[13] version 2.2) on an Imbramed treadmill properly calibrated according to manufacturer's guidelines on Ramp protocol. To determine maximal exhaustion, we used the modified Borg scale[27] and only those patients who completed examination by maximal exhaustion (Borg 10) participated in the study. We evaluated the variation of heart rate recovery (HRR) in the 1st to the 8th minute post-exercise (Δ HR = HRR at peak exercise less HRR from the 1st to the 8th minute). The heart rate measurement was performed by the RR interval of the ECG trace through the software itself. The recovery protocol was uniform for all patients: 2 minutes of active recovery at a speed of 1.6 km/h without inclination and 6 minutes of passive recovery in orthostatic position.

Statistical analysis was performed using the software SPSS version 15. To evaluate the qualitative variables, we used the chi-square test. To evaluate the quantitative variables, Mann-Whitney's U test was used because of nonparametric distribution of data. We used the Spearman's correlation coefficient to evaluate the association of HRR with WO. Multivariate analysis was performed to assess which variables best correlated with the WO. P value < 0.05 was considered statistically significant.

Results

Patient characteristics are shown in Table 1. There were no significant differences between groups in age, sex, body mass index, etiology of heart failure, LVEF, and use of medication, early and late heart / mediastinum ratio.

The groups had no significant differences at rest. In HR at peak exercise there was no significant difference between G1 and G2, the latter showing a lower absolute value. In recovery, there were no significant differences in the absolute values of HRR, but the G2 had a smaller variation of HRR (Δ HRR) from the 1st to the 8th minute, as observed in Table 2. Figure 1 compares the variation of HRR post-exertion between the groups.

When we evaluated the association between WO and the variation of HRR using the correlation coefficient of Spearman, we observed a significant negative correlation between the WO and 1st minute Δ HRR ($r = -0.555$; $p = 0.004$) and 2nd minute Δ HRR ($r = -0.550$, $p = 0.004$). No statistical significance was observed in the 3rd to the 8th minute of recovery. Figure 2 shows the correlation between WO and 1st minute ΔHRR, while figure 3 shows the correlation between WO and 2nd minute ΔHRR.

Because of possible factors influencing the behavior of HRR (e.g., heart failure etiology and drug administration), we performed a multivariate analysis, putting the WO as the dependent variable. We found that the 2nd minute Δ HRR was the variable that best correlated with WO: $r = 0.246$, $p = 0.012$.

Discussion

In our study, we evaluate both components of the autonomic nervous system, knowing that heart failure is marked by an increase in sympathetic, parasympathetic withdrawal and reduced tolerance to exercise[28]. These characteristics are due to neurohumoral activity involved in its physiopathology[28]. We evaluated the parasympathetic system through HRR[3,7], and the sympathetic system through myocardial scintigraphy with I^{123} MIBG[16]. After the exercise, parasympathetic reactivation occurs (immediate mechanism), and later, the progressive withdrawal of the sympathetic system, so that HR may return to levels similar to the beginning of exercise[3]. Previous studies reveal the prognostic value of HRR in heart failure[8,29], and that the main causes of attenuation of HRR in this population are: increased sympathetic activity, decreased parasympathetic activity and abnormal regulation of the cardiopulmonary baroreflex[30]. By analyzing the adrenergic hyperactivity using the WO of I^{123} MIBG as a marker, we observe that patients with heart failure and abnormal WO had a smaller variation

Table 1 - Characteristics of the groups

	G1 (N =14) WO < 27%	G2 (N =11) WO ≥ 27%	p
Age (years)	55 (45,87 – 64,12)	60 (47,5 – 72,5)	0,742
Gender (M/F)	9/5	7/4	0,974
IMC (Kg/m2)	26,7 (22,79-30,46)	26,9 (21,25–32,55)	0,427
Etiology (%)			0.648
Ischemic	7,15	18,18	
Hypertensive	78,57	45,45	
Others	14,28	36,37	
Medications (%)			
Beta-blocker (Carvedilol)	100	100	1
ACEI/ARB II	71,42	63,63	0,685
Spironolactone	100	90,90	0,259
Diuretic drugs	92,85	90,90	0,861
Digital	42,85	54,54	0,569
LVEF (%)	33 (25,12–40,87)	36 (31 -41)	0,826
30min H-M	1,77 (1,57-1,96)	1,70 (1,47-1,93)	0,827
4h H-M	1,76 (1,56-1,95)	1,58 (1,44-1,71)	0,112
WO %	22 (17,18 – 26,81)	35,5 (31,7–39,3)	<0,001

Results expressed as median and interquatil range; G - group; N - number; WO - washout rate; M - male; F - female; BMI - body mass index; ACEI - angiotensin-converting enzyme inhibitors; ARA II - angiotensin II receptor antagonist; LVEF - left ventricular ejection fraction; 30min H-M - early heart-mediastinum ratio; 4h H -M- late heart-mediastinum ratio.

Table 2 - Variables at the beginning of exercise and post-exercise recovery

	G1 (N =14) WO < 27%	G2 (N =11) WO ≥ 27%	p
SBP at rest (mmHg)	119 (107.75 – 130.25)	104 (83 – 125)	0.311
DBP at rest (mmHg)	80 (70.75 – 89.25)	72 (68 – 76)	0.044
HR at rest (bpm)	75 (69.87 – 81.12)	73 (67 -79)	0.741
HR peak exercise (bpm)	142 (127.25 – 156.75)	121 (108 – 134)	0.009
1st min HRR (bpm)	115.5 (101.75 – 129.25)	107 (96 – 118)	0.258
1st min Δ HRR (bpm)	21.50 (16.12 – 26.87)	11.00 (8.5 – 13.5)	0.001
2nd min HRR (bpm)	108 (96.75 – 119.25)	100 (88 – 112)	0.528
2nd min Δ HRR (bpm)	34 (29 – 39)	20 (14 – 26)	0.001
3rd min HRR (bpm)	95.5 (85.12 – 105.87)	88 (80 – 96)	0.38
3rd min Δ HRR (bpm)	46 (37.87 – 54.12)	30.0 (22.0 – 38.0)	0.005
5th min HRR (bpm)	91.5 (81.62 – 101.3)	86 (78.5 – 93.5)	0.169
5th min Δ HRR (bpm)	51.5 (42.0 – 61.0)	39.0 (31.5 – 46.5)	0.013
8th min HRR (bpm)	90.5 (82.37 – 98.62)	82 (75 -89)	0.037
8th min Δ HRR (bpm)	54.5 (46.5 – 62.5)	43 (34 – 52)	0.037

Results expressed as median and interquatil range; G - group; N - number; WO - washout rate; SBP - systolic blood pressure; DBP - diastolic blood pressure; mmHg - millimeters of mercury; HR - heart rate; bpm - beats per minute; HRR - heart rate recovery; min- minute; Δ HRR - variation in heart rate recovery.

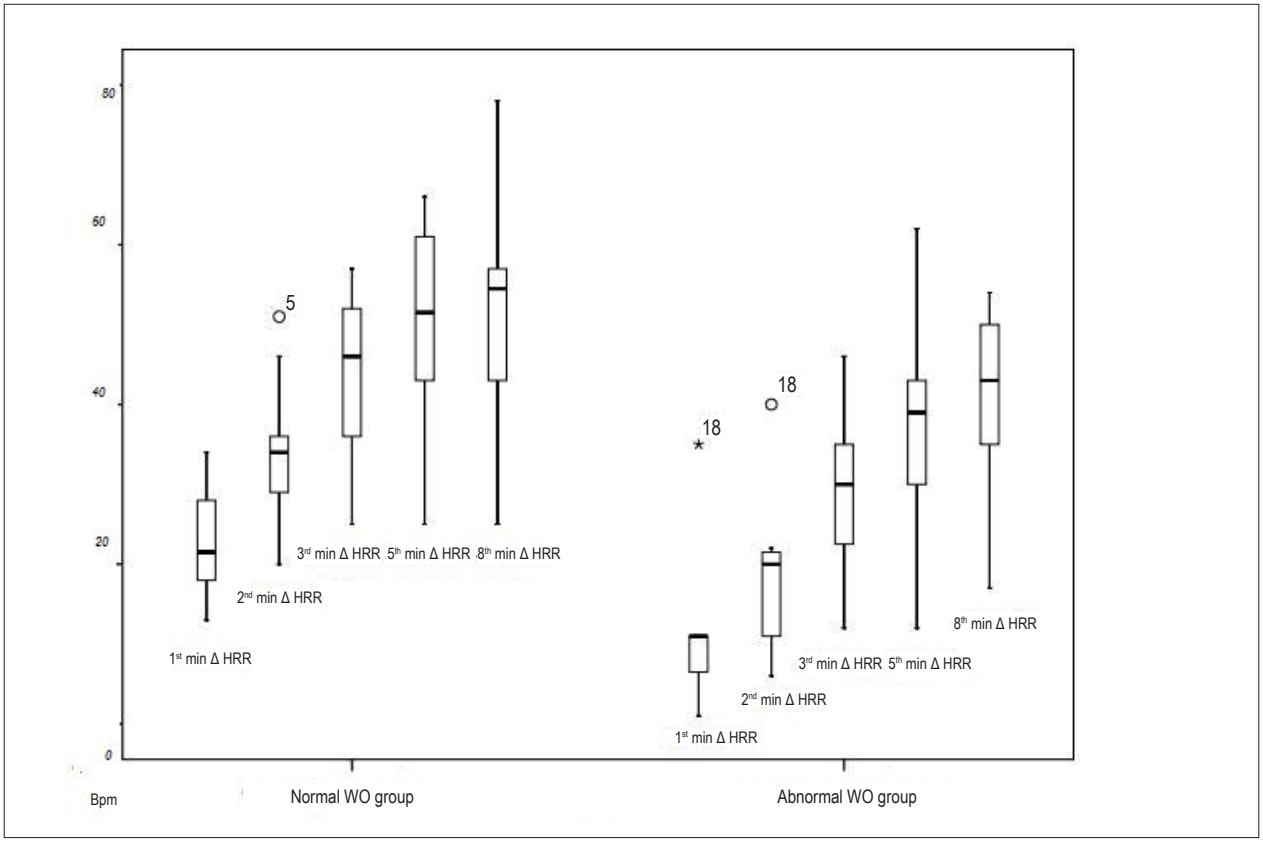

Figure 1 - *Comparison of heart rate variation in early and late recovery. Δ HRR - variation in heart rate recovery in relation to heart rate at peak exercise; min - minutes; BPM - beats per minute.*

of early and late HRR, demonstrating that both components of the autonomic nervous system are altered after exercise, and an association between these two major variables of great prognostic importance[26,29]. The presence of a negative correlation between the WO and the HRR from the 1st to the 2nd minute of recovery leads us to agree that increased sympathetic activity at rest (determined by abnormal WO) contributes to changes in HRR, especially in the 2nd minute, as observed after a multivariate analysis whose mechanisms are the parasympathetic re-entry along with sympathetic withdrawal[1,30,31].

In a previous study, we evaluated, in heart failure, the influence of adrenergic hyperactivity in the variables during exercise, showing that patients with abnormal WO had a lower functional capacity, and lower inotropic and chronotropic response during exercise compared to patients with normal WO[32]. To date, there is no description in the literature of the association between the abnormal behavior of HRR post-exercise and abnormalities in cardiac adrenergic innervation by I^{123} MIBG.

Treatment with beta-blockers improves sympathetic hyperactivity[33], but some patients are resistant to beta-blocker therapy, perpetuating this state of adrenergic hyperactivity. In our study, we found that patients on beta-blockers still in a state of adrenergic hyperactivity have an abnormal HRR compared to patients without this characteristic. A program of supervised exercise could be a therapeutic option for this group of patients with heart failure who have adrenergic hyperactivity even on use of beta-blockers. The dynamic exercise improves vagal activity and adrenergic hyperactivity[7,34].

Other groups of research[35-37] studied both components of the autonomic nervous system in patients with heart failure using myocardial scintigraphy with I^{123} MIBG, and RR variability (variable that reflects the sympathetic and parasympathetic action on the sinus node)[7,35]. Yamada et al[35] compared the prognostic value of I^{123} MIBG with RR variability. As the RR variability depends on postsynaptic transmission reflecting the final response of the sinus node to the stimulus received, and cardiac imaging through I^{123} MIBG promotes information about the presynaptic function and integrity of sympathetic nerve endings, these variables would complement each other. Following this reasoning, the authors showed that although cardiac imaging with I^{123} MIBG has been a stronger predictor than the RR variability, the association of these two variables promotes additional information on both, thus improving risk stratification in heart failure. In our study, we used HRR as a marker of parasympathetic activity, and there was association between WO and HRR. According to the study of Tamaki et al[36], WO was the best predictor of sudden death. The relationship between I^{123} MIBG WO and sudden death could be explained by the sympathetic hyperactivity that can modulate mechanisms of reentry and hyperautomatism, which could be the trigger for fatal arrhythmias. In the study of Koutelou et al[37], WO had a positive correlation with the number of complex ventricular

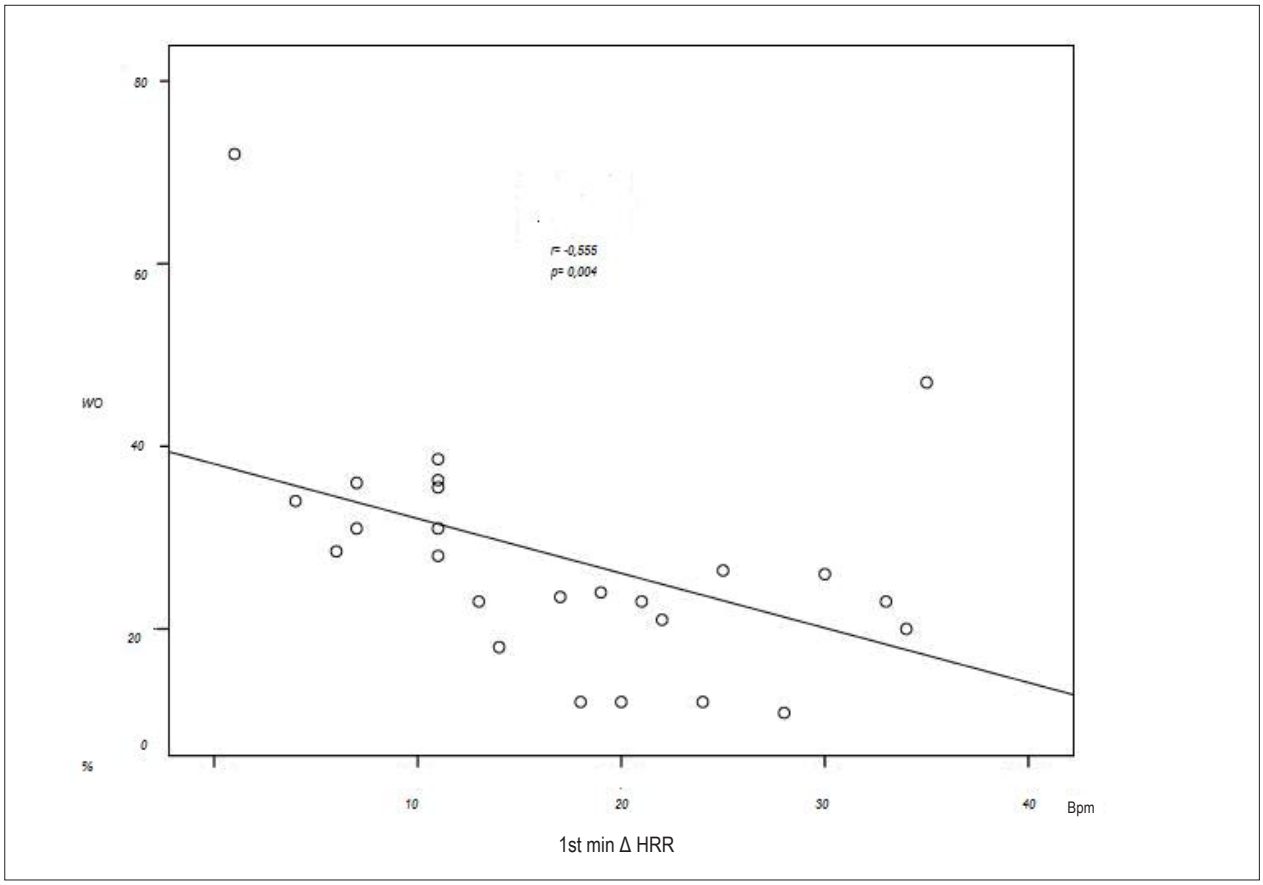

Figure 2 - *Correlation of washout rate and heart rate variation in the 1st minute of recovery. WO - washout rate; Δ HRR - heart rate recovery variation; min- minutes; BPM - beats per minute.*

arrhythmias detected by studying the ICD implanted in patients with heart failure.

Exercise testing is a simple test widely available that can promote important information about the autonomic function of more complex and less available imaging tests that have been employed to evaluate. An important suggestion would be to use exercise testing as a screening method to assess which patients with heart failure will be more likely to have altered adrenergic innervation to select patients who will most benefit from I^{123} MIBG scintigraphy.

Limitations of the study

The main limitation of this study was the small number of patients. However, through a pilot study with 16 patients, a sample size calculation was performed and the number of 11 patients per group has a 90% statistical power to identify 47.6% difference in 1st minute HRR, and a statistical power of 90% to identify 39.93% difference in 2nd minute HRR between groups.

Another significant limitation was that we failed to perform cardiopulmonary exercise testing (CPET) to attest that the patients performed maximal testing. However, as described above, only those patients who completed the test to exhaustion participated in the study (grade 10 in the BORG's modified rating of perceived fatigue). CPET was not performed because we did not have this device in our institution at the time of this study.

The evaluation of post-exercise HRR, however, can be made with conventional ET and does not require complex methodologies for analysis. Since the ET is a simple and ubiquitous tool, we believe that information derived from this examination may be useful for cardiologists involved in clinical practice for patients with heart failure, since the information obtained from this simple test correlated with the sophisticated analysis of cardiac innervation.

Conclusion

Patients with heart failure and abnormal WO had slower HRR than normal WO patients, both in early and late phases. This slow recovery in patients with adrenergic hyperactivity state at rest suggests that sympathetic changes at rest, typical of heart failure, may contribute to the autonomic changes observed during recovery after exertion.

Potential Conflict of Interest

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

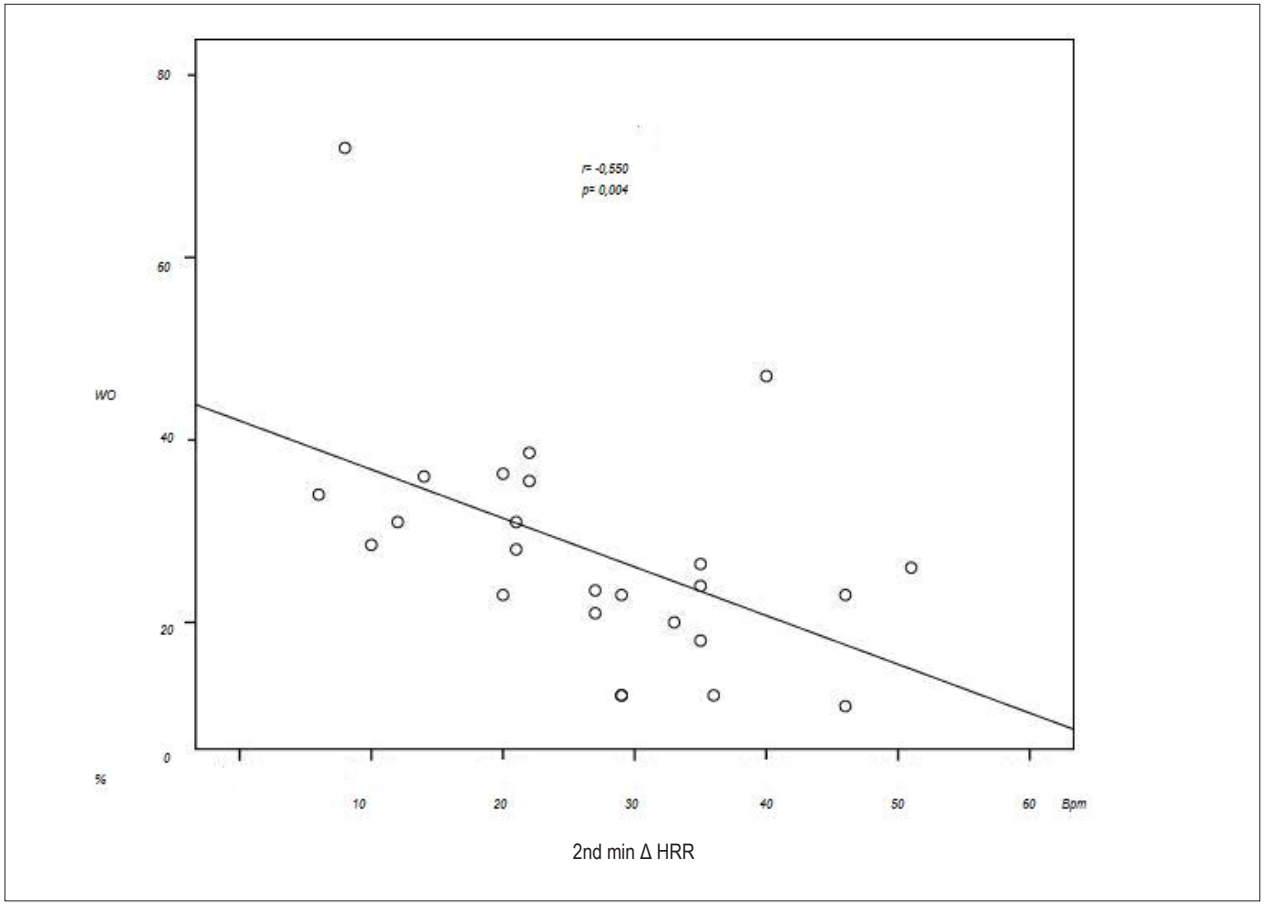

Figure 3 - *Correlation between the washout rate and heart rate variation in the 2nd minute of recovery. WO - washout rate; Δ HRR - variation in heart rate recovery; min - minutes; BPM - beats per minute.*

Sources of Funding

This study was partially funded by FAPERJ and CNPq.

Study Association

This article is part of the thesis of Doctoral submitted by Leandro Rocha Messias, from Universidade Federal Fluminense.

References

1. Chapleau MW, Sabharwal R. Methods of assessing vagus nerve activity and reflexes. Heart Fail Rev. 2011; 16(2):109-27.
2. Kannankeril P, Le F, Kadish A, Goldberger J. Parasympathetic effects on heart rate recovery after exercise. J Investig Med. 2004;52(6):394-401.
3. Lahiri MK, Kannankeril PJ, Goldberger JJ. Assessment of autonomic function in cardiovascular disease physiological basis and prognostic implications. J Am Coll Cardiol. 2008; 51(18):1725-33.
4. Myers J, Tan SY, Abella J, Aleti V, Froelicher VF. Comparison of the chronotropic response to exercise and heart rate recovery in predicting cardiovascular mortality. Eur J Cardiovasc Prev Rehabil. 2007; 14(2):215-21.
5. Imai K, Sato H, Hori M, Kusuoka H, Ozaki H, Yokoyama H, et al.. Vagally mediated heart rate recovery after exercise is accelerated in athletes but blunted in patients with chronic heart failure. J Am Coll Cardiol. 1994; 24(6):1529-35.
6. Lauer MS. Autonomic function and prognosis. Cleve Clin J Med.2009; 76(Suppl 2): S18-22.
7. Freeman JV, Dewey FE, Hadley DM, Myers J, Froelicher VF. Autonomic Nervous system interaction with the cardiovascular system during exercise. Prog Cardiovasc Dis. 2006; 48(5):342-62.
8. Arena R, Guzzi M, Myers J, Peberdy MA. Prognostic value of heart recovery in patients with heart failure. Am Heart J. 2006; 151 (4):851.e7-13.
9. Serra SM, Costa RV, Teixeira de Castro RR, Xavier SS, Nobrega AC. Cholinergic stimulation improves autonomic and hemodynamic profile during dynamic exercise in patients with heart failure. J Cardiac Fail. 2009; 15(2):124-9.
10. Antelmi A, Chuang EY, Grupi CJ. Recuperação da frequência cardíaca após teste de esforço em esteira ergométrica e variabilidade da frequência cardíaca em 24 horas em indivíduos sadios. Arq Bras Cardiol. 2008; 90(6): 413-8.

11. Almeida FK, Gross JL, Rodrigues TC. Complicações microvasculares e ddisfunção autonômica cardíaca em pacientes com Diabete Melito Tipo 1. Arq Bras Cardiol. 2011; 96(6):484-9.

12. Cole CR, Foody JM, Blackstone EH, Lauer MS. Heart rate recovery after submaximal exercise testing as a predictor of mortality in a cardiovascularly healthy cohort. Ann Intern Med. 2000; 132(7):552-5.

13. Watanabe J, Thamilarasan M, Blackstone EH, Thomas JD, Lauer MS. Heart rate recovery immediately after treadmill exercise and left ventricular systolic dysfunction as predictors of mortality: the case of stress echocardiography. Circulation. 2001; 104(16):1911- 6.

14. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol. 2003; 42(5):831 - 8.

15. Turpeinen AK, Vanninen E, Magga J, Tuomainen P, Kuusisto J, Sipola P, et al. Cardiac sympathetic activity is associated with inflammation and neurohumoral activation in patients with idiopathic dilated cardiomyopathy. Clin Physiol Funct Imaging. 2009; 29(6):414-9.

16. Agostini D, Carrio I, Verberne HJ. How to use myocardial 123I-MIBG scintigraphy in chronic heart failure. Eur J Nucl Med Mol Imaging. 2009; 36(4): 555-9.

17. Cohen-Solal A, Esanu Y, Logeart D, Pessione F, Dubois C, Dreyfus G, et al. Cardiac metaiodobenzylguanidine uptake in patients with moderate chronic heart failure: relationship with peak oxygen uptake and prognosis. J Am Coll Cardiol. 1999: 33(3); 759-66.

18. Diakakis GF, Parthenakis FI, Patrianakos AP, Koukourai SI, Stathaki MI, Karkavitsas NS, et al. Myocardial Sympathetic Innervation in Patients with Impaired Glucose Tolerance: Relationship to Subclinical Inflammation. Cardiovasc Pathol. 2008: 17(3) :172-7.

19. Dae MW, De Marco T, Botvinick EH, O'Connell JW, Hattner RS, Huberty JP, et al. Scintigraphic assessment of MIBG uptake in globally denervated human and canine hearts-implications for clinical studies. J Nucl Med. 1992; 33(8):1444-50.

20. Ji SY, Travin MI. Radionuclide imaging of cardiac autonomic innervation. J Nucl Cardiol. 2010; 17(4):655-66.

21. Ando MA, Yamamoto T, Hino A, Sato T, Nakamura Y, Matsuzaki M. Norepinephrine spillover during exercise as a novel parameter to evaluate the severity of heart failure. J Nucl Cardiol. 2010; 17(5):968-73.

22. Verberne HJ, Brewster LM, Somsen A, van Eck-Smit BL. Prognostic value of myocardial 123imetaiodobenzylguanidine (MIBG) parameters in patients with heart failure: a systematic review. Eur Heart J. 2008; 29(9):1147-59.

23. Carrio´ I, CowieMC, Yamazaki J, Udelson J, Camici PG. Cardiac sympathetic imaging with MIBG in heart failure. JACC Cardiovasc Imaging. 2010; 3(1): 92–100.

24. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: The Framingham Study. N Engl J Med. 1971; 285(26):1441-6.

25. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, et al. ACC/AHA Guideline for coronary angiography. J Am Coll Cardiol. 1999; 33(6):1756-824.

26. Ogita H, Shimonagata T, Fukunami M, Kumagai K, Yamada T, Asano Y,et al. Prognostic significance of cardiac ^{123}I metaiodobenzylguanidine imaging for mortality and morbidity in patients with chronic heart failure: a prospective study. Heart. 2001; 86(6): 656-60.

27. Wilson RC, Jones PH. A comparison of the visual analogue scale and modified BORG scale for the measurement of dyspnoea during exercise. Clin Sci (Lond) 1989; 76(3): 277-82.

28. Kallistratos MS, Dritsas A, Laoutaris A, Cokkinos DV. Chronotropic and neurohumoral markers for the evaluation of functional capacity in patients with impaired left ventricular function. Hellenic J Cardiol. 2008; 48(1): 26-32.

29. Arena R, Myers J, Abella J, Peberdy MA, Bensimhon D, Chase P, et al. The Prognostic value of the heart rate response during exercise and recovery in patients with heart failure: influence of beta-blockade. Int J Cardiol. 2010; 138(2):166-73.

30. Sheppard R, Racine N, Roof A, Ducharme A, Blanchet M, White M. Heart rate recovery – a potential marker of clinical outcomes in heart failure patients receiving beta-blocker therapy. Can J Cardiol. 2007; 23(14):1135-8.

31. Nishiyama Y, Morita H, Harada H, Koga Y,et al. Systolic blood pressure response to exercise as a predictor of mortality in patients with chronic heart failure. Int Heart J. 2010; 51(2):111-5.

32. Rocha Messias L, de Queiroz Carreira MA, Ribeiro de Miranda SM, Cunha de Azevedo J, Ambrosio Gava I, Campos Rodrigues R, et al. Relação entre imagem adrenérgica cardíaca e teste ergométrico na insuficiência cardíaca. Arq Bras Cardiol .2011; 96(5):370-5.

33. Kasama S, Toyama T, Hatori T, Sumino H, Kumakura H, Takayama Y, et al. Evaluation of cardiac sympathetic nerve activity and left ventricular remodelling in patients with dilated cardiomyopathy on the treatment containing Carvedilol. Eur Heart J. 2007; 28(8):989-95.

34. Bueno CR Jr, Ferreira JC, Pereira MG, Bacuraw AV, Brum PC. Aerobic exercise training improves skeletal muscle function and Ca2+ handling-related protein expression in sympathetic hyperactivity-induced heart failure. J Appl Physiol. 2010; 109(3):702-9.

35. Yamada T, Shimonagata T, Fukunami M, Comparison if the value of cardiac iodine-123 metaiodobenzylguanidine imaging and heart rate variability in patients with chronic heart failure: a prospective study. J Am Coll Cardiol. 2003; 41(2):231-8.

36. Tamaki S, Yamada T, Okuyama Y. Cardiac Iodine-123 Metaiodobenzylguanidine imaging predicts sudden cardiac death independently of left ventricular ejection fraction in patients with chronic heart failure and left ventricular systolic dysfunction. J Am Coll Cardiol. 2009;53(5):426–35.

37. Koutelou M, Katsikis A, Flevari P, Theodorakis G, Livanis E, Georgiadis M, et al.. Predictive value of cardiac autonomic indexes and MIBG washout in ICD recipients with mild to moderate heart failure. Ann Nucl Med. 2009; 23(7):677-84.