

Research article

## Use of Heart Rate Variability to Estimate Lactate Threshold in Coronary Artery Disease Patients during Resistance Exercise

Rodrigo P. Simões<sup>1</sup>✉, Renata G. Mendes<sup>1</sup>, Viviane Castello-Simões<sup>1</sup>, Aparecida M. Catai<sup>1</sup>, Ross Arena<sup>2</sup> and Audrey Borghi-Silva<sup>1</sup>

<sup>1</sup>Cardiopulmonary Physical Therapy Laboratory, Department of Physical Therapy, Federal University of Sao Carlos, Sao Carlos – Sao Paulo, Brazil; <sup>2</sup>Department of Physical Therapy and Integrative Physiology Laboratory - College of Applied Health Sciences, University of Illinois at Chicago, Chicago, Illinois, USA.

### Abstract

The aim of this study was to investigate whether it is possible to identify the first turn point of blood lactate (BL) concentration (1<sup>st</sup> lactate threshold - LT1) during a discontinuous resistance exercise protocol in coronary artery disease (CAD) patients and verify if heart rate variability (HRV) responses are consistent with BL responses. A total of 22 elderly men, 12 with CAD and 10 apparently healthy (control group = CG), underwent one-repetition maximum (1RM) testing on an inclined leg press. Discontinuous resistance exercise testing (DRET) was initiated at 10% of the 1RM with subsequent increases of 10% until 30% and after this percentage, 5% increments of 1RM was carried out. The load corresponding to LT1 was approximately 30% 1RM in both groups; and the LT1 estimate by HRV was associated with BL responses. HRV indices representing parasympathetic modulation decreased with increasing loads until LT1 and stabilized thereafter in both groups, and HRV indices representing sympathetic and parasympathetic modulations only increased in the CAD group from 30% 1RM with higher values after this load in relation to the CG. We conclude HRV appears to be an effective tool to estimate the LT1 during discontinuous resistance exercise in patients with CAD. In addition, these results may have an impact on the prescription of endurance resistance exercise in the CAD population, as cardiac vagal modulation is an important indicator of cardiovascular protection and the over-activity of sympathetic modulation is related to cardiovascular risk.

**Key words:** Exercise, strength exercise, autonomic cardiac control, blood lactate, cardiovascular disease.

### Introduction

The lactate threshold (LT) is a parameter of great importance during exertional assessments (Svedahl and MacIntosh, 2003), both to evaluate submaximal aerobic capacity (Svedahl and MacIntosh, 2003) and to establish an individualized exercise prescription in different populations, from those who are apparently healthy to those diagnosed with a chronic disease, such as cardiac patients (Beckers et al., 2012; De Sousa et al., 2012).

Considering the three-phase model to define the threshold concepts (Skinner and McLellan, 1980), two LTs are discerned during exercise. The first turn point of blood lactate (BL) concentration during exercise is defined as first lactate threshold (LT1). During the transition from rest to LT1 (phase 1), there is a balance between lactate production and elimination in working muscle;

therefore the BL values remain at resting level. However at intensities between LT1 and second lactate threshold (LT2) (phase 2) the lactate production rate is higher than metabolizing capacity in the muscle and the lactate will appear in the blood (increasing the BL concentration), but with possibility of stabilization in steady-state exercise. Above LT2 (phase 3), the muscular lactate production rate exceeds the systemic lactate elimination rate without attainment of steady-state during a constant work-load (Binder et al., 2008; Tscharkert and Hofmann, 2013). From the physiological point of view, these concepts are important to define the phases of energy supply during exercise and to define the parameters for the development of an optimally individualized exercise program (Binder et al., 2008).

Although dynamic aerobic exercise on a cycle ergometer or treadmill is widely used as primary exercise modalities for the identification of the workload corresponding to LT, recent studies have also shown the feasibility of identifying LT during resistance exercises (RE) in apparently healthy individuals using discontinuous protocols (Simões et al., 2010; 2013b; 2014).

The identification of LT1 has been achieved through blood lactate (Moreira et al., 2008; Simões et al., 2010; 2013b) and heart rate variability (HRV) analysis (Marques-Neto et al., 2012; Simões et al., 2013b; 2014). Comparatively, HRV holds advantages for identifying LT as it is non-invasive and cost efficient approach. Furthermore, the evaluation of HRV indices during exercise provides information related to the control of cardiac autonomic modulation (Mourot et al., 2004; Machado et al., 2011; Machado-Vidotti et al., 2014) and these indices are important predictors related to cardiovascular risk (Task Force, 1996). In patients with coronary artery disease (CAD), studies have shown that RE is an important component of cardiac rehabilitation due to the beneficial effects related to: 1) improved muscular strength and endurance; 2) improved functional capacity and quality of life; 3) improved cardiac autonomic modulation; and 4) reduced risk for subsequent cardiac events (Caruso et al., 2015; 2016a; 2016b; Price et al., 2016; Pollock et al., 2000; Williams et al., 2007).

Nevertheless, it has been shown that cardiac autonomic balance is impaired in CAD patients and consequently HRV is altered due to a decrease in parasympathetic and an increase in sympathetic modulation, which can lead to a higher risk of arrhythmias and sudden death

(Billman and Kukielka, 2006). Although RE promotes benefits and in general has been considered safe even in patients groups, depending on the duration and intensity of effort, there may be an increase the cardiac risks (Billman and Kukielka, 2006; Caruso et al., 2016a). In this sense, considering the risks related to cardiac autonomic impaired in CAD patients, this type of exercise must be carefully prescribed (Caruso et al., 2016a; Pollock et al., 2000).

However, we are unaware of any previous study that used HRV analysis during discontinuous RE to evaluate cardiac autonomic control to estimate LT in patients with CAD. In this sense, the analysis of these variables in CAD patients would be important in clinical practice to non-invasively determine LT in a cost-efficient manner, assisting in the definition of safe and appropriate exercise intensity parameters related to cardiac autonomic modulation. In this regard, this protocol may have an impact on the prescription of exercise based on improvement of aerobic capacity and muscular endurance during a resistance training program in CAD patients.

Therefore, the purpose of this study was to address the following research questions: 1) Determine if HRV responses are consistent with estimation of LT1 by BL in patients with CAD; and 2) Determine if CAD patients exhibit different patterns in HRV indices compared to apparently healthy controls during an endurance RE protocol.

## Methods

### Design and study population

This was a cross-sectional, controlled study. Thirty-two elderly men recruited from the Health Unit of the University (2006-2008) were initially assessed for study eligibility; 22 (between 60 and 75 years of age) were enrolled and completed the protocol. The subjects were allocated into two groups: 1) 12 patients with a clinical diagnosis of CAD (CADG); and 2) 10 healthy controls (CG). Age, anthropometric measures, risk factors, adverse clinical events and medications are listed in Table 1. All volunteers in the CADG had been participating in a cardiac rehabilitation program 2-3 times a week for at least 12 months that included only aerobic exercises. In the CG, the volunteers practiced physical activity 1-3 times a week in the form of walking or running but not practicing REs regularly. The inclusion criteria for the CADG were: 1) clinical diagnosis of CAD for at least one year; and 2) no use of tobacco, alcohol and beta-blockers drugs. The inclusion criteria for the CG were: 1) apparently healthy status based on clinical examinations; and 2) no use of any type of medication, tobacco or alcohol. Exclusion criteria for the CADG consisted of: 1) uncontrolled cardiac arrhythmias; 2) unstable angina; 3) uncontrolled hypertension; 4) pulmonary comorbidities; 5) chronic renal disease; and 6) orthopedic, neurologic and musculoskeletal disorders. Exclusion criteria for the CG were conditions that could limit performance during exercise protocols (e.g., orthopedic/musculoskeletal limitations or neurological disorders)

All volunteers were informed of the experimental procedures and objectives of the study and after agreeing, they signed a written consent. Furthermore, the study was approved by the Human Research Ethics Committee of the University (n.258/2006) and has been conducted according to the principles expressed by the Declaration of Helsinki.

### Measures

All volunteers were evaluated in a period of the morning to avoid different responses of physiological variables due to circadian changes. The experiments were carried out in a climatically controlled room at 22-24°C and relative air humidity at 50-60%, and performed on different days separated by a seven day interval. Before the day of the experiment, the participants were taken to the experimental room for familiarization with the procedures and the equipment to be used.

### Clinical evaluation

A clinical evaluation was performed by a cardiologist and this examination consisted of anamnesis, blood pressure measurement, resting 12-lead electrocardiography (ECG), blood analysis and an incremental symptom-limited exercise test performed on treadmill. On the same day of clinical evaluation, all eligible volunteers were submitted to anthropometric evaluation, body composition and answered a questionnaire about physical activity patterns.

**Table 1. Age, anthropometric measures, risk factors, clinical event and medications of volunteers.**

	CADG (n=12)	CG (n=10)
<b>Age and Anthropometric measures</b>		
Age, years	65 ± 7	64 ± 4
Height, m	1.67 ± .07	1.67 ± .05
Weight, kg	72 ± 6	70 ± 7
BMI, kg·m <sup>-2</sup>	26 ± 2	25 ± 2
<b>Risk Factors</b>		
Dyslipidemia, n	3	0
Hypertension, n	4	0
Hypothyroidism, n	2	0
Smoking / former smoker, n	0 / 2	0 / 1
Stress, n	3	2
<b>Clinical Event</b>		
Myocardial infarction, n	9	-
Coronary artery bypass grafting, n	8	-
Association of MI and CABG, n	5	-
<b>Medications</b>		
Acetylsalicylic acid, n	5	-
Anti-arrhythmic, n	2	-
ACE inhibitors, n	2	-
Calcium-channel blockers, n	1	-
Angiotensin II receptor antagonists, n	2	-
Antihypercholesterolemic, n	3	-
Diuretics, n	3	-

Data of age and anthropometry measures are presented as mean ± SD; data of risk factors, clinical event and medications are presented with the number of individuals (n) related to these variables. CADG = coronary artery disease group; CG = control group; BMI = body mass index; MI = myocardial infarction; CABG = coronary artery bypass grafting; ACE = angiotensin converting enzyme.

### Regular physical activity pattern

The physical activity pattern was assessed by information regarding occupation, sports activities and leisure habits that were detailed and quantified by the modified Baecke et al. (1982) questionnaire for epidemiological studies. This questionnaire consists of a scale from one to five (5 representing the most active) with eight questions about occupation, four about sport activities and four about habitual leisure habits. Results are reported as sum of scores (with minimum score of 4.5 and maximum of 14.5).

### One repetition maximum (1RM) testing

Prior to the one repetition maximum (1RM) testing, the participants underwent a familiarization period and were taught the correct execution of the movement, as well as correct breathing during the exercise (exhale during extension of the knees and hips) to avoid the Valsalva maneuver (Wilborn et al., 2004). The 1RM testing was applied by gradually increasing the resistance until the volunteer succeeded in performing no more than one repetition on a 45° leg press (Pro-Fitness, Sao Paulo, Brazil) (Simões et al., 2010). It was expected that the 1RM was found within 6 attempts (Kraemer & Fry, 1995) and, if this did not occur, the test was performed on another day.

### Discontinuous resistance exercise testing (DRET)

Initially the participants remained at rest on the equipment for 10 min. The discontinuous resistance exercise testing (DRET) was initiated at a load of 10% of 1RM, with subsequent increases of 10% until reaching a load of 30%. Subsequently, 5% increments of 1RM were utilized with the objective of increasing the number of steps and allowing better visualization of the physiologic adjustments with increasing load. At each percentage of effort, participants underwent 4 min of exercise at a movement rhythm of 12 repetitions/min, maintaining respiratory cadence (taught during the 1RM testing), with each repetition performed in 5 s (2 s of extension and 3 s of knee and hip flexion), with the rhythm controlled by verbal commands. The recovery period between trials was 15 min established so that heart rate (HR) and blood pressure (BP) could return to baseline, and in this period, the volunteers remained at rest (passive) while on the equipment. Throughout the protocol, monitoring consisted of ECG, blood pressure (pre and post-effort), and both fatigue and pain in the lower limbs by the modified Borg Scale (Borg, 1982) at the end of each maneuver.

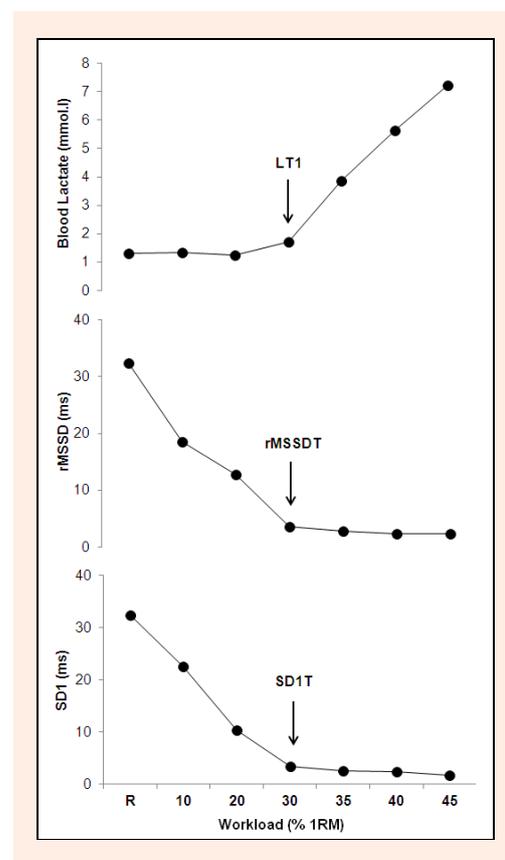
During the entire test period, HR and R-R intervals (R-Ri) were recorded using the Polar S810i telemetry system (Polar Electro Oy, Kempele, Oulu, Finland). In addition, blood samples were taken before the first effort (after the initial 10 min of rest on the equipment) and immediately after each resistance exercise load. Blood samples were obtained via earlobe puncture and blood lactate concentration was determined by an electroenzymatic method (YSI-1500 Sports Lactate Analyze, Yellow Springs, OH, USA).

### Data analysis

#### HRV analysis

The HRV data were analyzed in Kubios HRV analysis

software (MATLAB, version 2 beta, Kuopio, Finland). The sections selected for analysis were the initial rest period with the volunteer positioned on the equipment and during each load applied as a percentage of 1RM. The section selected during the effort period was the last portion of the test containing 2 min (between 2 and 4 min of effort), that was considered a more stable phase for analysis. The initial phase of exercise was discarded due to the period that corresponds to rapid vagal withdrawal. HRV was analyzed in the time domain by: 1) the square root of the mean squared differences of successive RR intervals (rMSSD); 2) the standard deviation of the mean of all normal RR intervals (SDNN); 3) standard deviation of instantaneous R-R interval variability (SD1) and; 4) long term standard deviation of continuous R-Ri (SD2) (Antila, 1979; Task Force, 1996; Mourot et al., 2004).



**Figure 1.** Graphics representation of threshold determination applied to blood lactate concentration (top); rMSSD (middle) and SD1 (bottom), signals of one representative volunteer (coronary artery disease patient). The arrow indicates the point where the threshold has been identified. LT1 = first lactate threshold; rMSSDT = rMSSD threshold (rMSSD = square root of the mean squared differences of successive RR intervals); SD1T = SD1 threshold (SD1 = standard deviation of Poincaré plot perpendicular to the line of identify).

### Determination of LT1

The LT was individually determined by lactate curves observed by two independent investigators (visual inspection). The LT1 was defined as the intensity at which BL concentration began to increase in an exponential manner (first turn point) (Davis et al., 2007; Simões et al., 2010; Simões et al., 2013a) (see a single example in Figure 1). In addition, the HRV threshold was determined in a simi-

lar way, observing the behavior of the SD1 index (SD1 threshold – SD1T), which was defined as the intensity with a smaller difference between two consecutive stages (Antila, 1979) (Figure 1). Finally, the threshold obtained by the rMSSD index (rMSSD threshold - rMSSDT) was determined by the point at which the index stabilized between two stages (Simões et al., 2010; Simões et al., 2013b, Simões et al., 2014) (Figure 1).

### Statistical analysis

Based on the rMSSD index in a previous study (Simões et al., 2010), a sample size for the current study that would provide sufficient statistical power ( $\beta = 0.8$ ) to detect a significant difference ( $\alpha = 0.05$ ) was estimated to be 8 participants per group. A normal data distribution was verified by the Shapiro-Wilk test and data were expressed as mean and standard deviation. The unpaired Student t-test was used to compare the 1RM load between the CADG and CG. Two-way analysis of variance (ANOVA) for repeated measurements was used to compare the variables during discontinuous resistance exercise testing (at different percentages of 1RM), to compare the different methods for identifying LT1 (LT, SD1T, rMSSDT) and the group effect (CG vs. CADG). When differences were significant, the Tukey-Kramer post-hoc test was utilized to identify differences. The correlations between LT and SD1T and between LT and rMSSDT were made utilizing the Pearson correlation and additionally, the degree of concordance between the methods utilized to determine LT was evaluated by Bland-Altman concordance analysis (Bland and Altman, 1986). The probability of Type 1 error occurrence was established at 5% for all tests ( $\alpha = 0.05$ ).

## Results

Fifteen apparently healthy volunteers and seventeen CAD patients were initially recruited and four were excluded for presenting with an abnormal increase in systolic pressure during an incremental symptom-limited exercise test (3 CG and 1 CAD), three CAD for beta-blocker use and three individuals decided to discontinue participation (2 CG and 1 CAD).

### Regular physical activity pattern

On the basis of the Baeck questionnaire (Baeck et al., 1982), the CADG had a mean score of  $8.7 \pm 0.6$  (range 8.1 - 9.8) and the CG had a mean score of  $9.0 \pm 1.2$  (range 8.1- 10.1), indicating all participants were physically active. None of the participants were currently participating in a regular RE program.

### 1RM testing

In relation to the resistance load achieved during 1RM, the CG showed greater values than the CADG, both in absolute terms ( $316 \pm 68$  kg vs.  $253 \pm 59$  kg;  $p < 0.01$ ) as well as the 1RM load/total body mass ratio (CG =  $4.5 \pm 0.9$  and CADG =  $3.5 \pm 0.8$ ;  $p < 0.05$ ).

### Discontinuous resistance exercise testing

Regarding discontinuous testing, all volunteers in both groups presented with leg fatigue as a criterion for interruption of DRET (Borg of 9.3 to CADG and 9.1 to CG), and no test was interrupted because of ECG alterations or an excessive rise in systolic blood pressure or exceeding the submaximal HR (i.e. 85% of maximal HR). All volunteers achieved at least 40% of 1RM during the DRET, which was a maximum load for three participants in the CG and for eight in the CADG. For the remaining volunteers: 1) three from each group had stopped at 45% of 1RM; 2) three participants in the CG and one in the CADG stopped at 50% of 1RM; and 3) one in the CG stopped at 55% of 1RM.

Figure 2 shows the behavior of HRV, BL and delta of HR with the increase of loads during DRET achieved by all volunteers (40% of resistance load denominated isoload). There was a significant reduction in the rMSSD and SD1 from 30% of 1RM in relation to rest for both groups (Figure 2A and B, respectively), and a reduction in SDNN from 30% of 1RM in relation to rest only in the CG (Figure 2D). A significant increase was observed in BL and in delta of HR in both groups from 35% of 1RM (Figure 2E and F). However, an increase in SD2 and SDNN from 30% of 1RM compared with values at rest was only apparent in the CADG (Figure 2C and D). When comparing the values between groups, higher SD2 and SDNN values at 30%, 35% and 40% of 1RM was apparent in the CADG (Figure 2C and D).

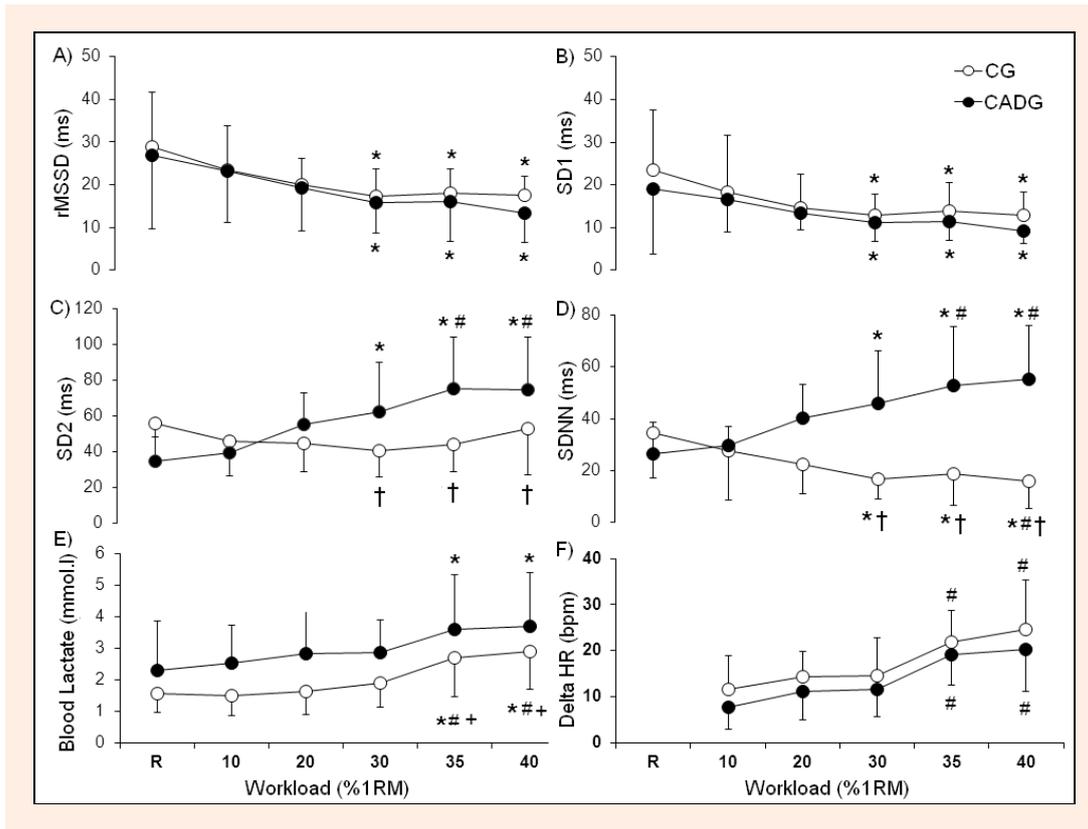
### LT1 identification

The LT1 was determined for each volunteer by the analysis of SD1, rMSSD, and BL, expressed as absolute and relative resistance load values. No significant difference between the methods and between the groups regarding the absolute values (LT: CG =  $101 \pm 32$  kg, CADG =  $81 \pm 22$  kg; SD1T: CG =  $95 \pm 27$  kg, CADG =  $74 \pm 28$  kg and; rMSSDT: CG =  $96 \pm 21$  kg, CADG =  $75 \pm 21$  kg;  $p > 0.05$ ) and relative values (LT: CG =  $30 \pm 6\%$ , CADG =  $32 \pm 5\%$ ; SD1T: CG =  $29 \pm 6\%$ , CADG =  $29 \pm 5\%$  and; rMSSDT: CG =  $29 \pm 5\%$ , CADG =  $30 \pm 6\%$ ;  $p > 0.05$ ) were verified. In contrast, there was a significant correlation between LT and rMSSDT ( $r = 0.72$ ,  $p < 0.01$ ) and between LT and SD1T ( $r = 0.75$ ,  $p < 0.01$ ).

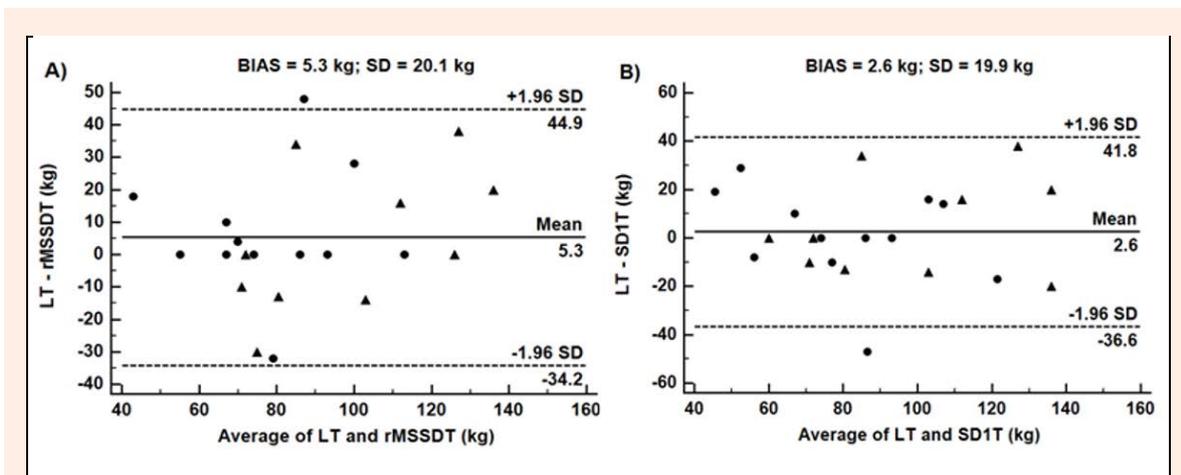
Analysis of concordance between methods to determine the LT1 was carried out by Bland-Altman analysis (Bland & Altman, 1986), considering BL analyses as the “gold standard,” LT vs. rMSSDT and LT vs. SD1T were plotted. As shown in Figure 3A, the mean of differences, or the concordance, to identify the LT1 point by LT and rMSSDT methods, was  $5.3 \pm 20.1$  kg, and the mean difference between LT and SD1T (Figure 3B) was  $2.6 \pm 19.9$  kg. Therefore, it was possible to state concordance between methods of LT1 determination in both analyses performed.

## Discussion

Our main findings are summarized as follows: 1) LT1 determination by HRV was associated with BL responses; the load corresponding to LT1 was approximately 30%



**Figure 2.** Data are presented as mean  $\pm$  SD. Behavior of variables at isoload with the resistance increments in percentage of 1 repetition maximum (% 1RM). A) rMSSD = square root of the mean squared differences of successive RR intervals; B) SD1 = standard deviation of Poincaré plot perpendicular to the line of identify; C) SD2 = standard deviation of Poincaré plot along to the line of identify; D) SDNN = standard deviation of the mean of all normal RR intervals; E) Blood lactate; F) delta HR = HR of peak – HR of rest (pre-effort). CG = control group; CADG = cardiac artery disease group. \* $p < 0.05$  in relation to rest condition (R); #  $p < 0.05$  in relation to 10% of 1RM; †  $p < 0.05$  in relation to 20% of 1RM; ‡  $p < 0.05$  CG in relation CADG (Two-way ANOVA for repeated measures).



**Figure 3.** Bland and Altman plotting shows the concordance between LT and rMSSDT (A) and between LT and SD1T (B). (●) coronary artery disease; (▲) healthy group. Bias = mean of the differences between the means;  $\pm 1.96$  = concordance limit of 95%; LT = lactate threshold; rMSSDT = rMSSD threshold (rMSSD = square root of the mean squared differences of successive RR intervals); SD1T = SD1 threshold (SD1 = standard deviation of Poincaré plot perpendicular to the line of identify).

1RM in both groups; 2) A pronounced reduction in vagal modulation was verified at 30% of 1RM in both groups, however, after this workload, the CADG showed a more pronounced sympathetic modulation compared to apparently healthy controls.

**Characterization of subjects**

Regarding characterization of volunteers, there were no differences between groups in relation to age and anthropometric measures, such as level of physical activity of the volunteers (all classified as physically active), suggesting that the groups were homogeneous. As expected, the patients of CADG showed higher prevalence of risk factors for cardiovascular disease, however, blood lipid

levels and blood pressure were well controlled by medications in CADG.

Despite being a medication widely used in patients with CAD, we selected in our sample only individuals who did not use beta-blockers drugs, a drug that interferes directly in cardiac autonomic modulation and consequently could influence the HRV analysis (Task Force, 1996). However, when analyzing the HRV of volunteers who were on medication, such as angiotensin converting enzyme inhibitors, calcium-channel blockers, angiotensin II receptor antagonists or anti-arrhythmic drugs, we observed no consistent change in its behavior during the imposed loads. Despite this, it should be noted that a small sample size was evaluated in the current study and thus, it is not possible to state categorically that there were indirect influences related to the use of these drugs. On the other hand, we believe it would be important to evaluate patients who used different classes of drugs since it reflects a clinical reality in cardiac rehabilitation programs.

### 1RM testing and DRET

The CADG showed lower 1RM values in relation to the CG, which shows that the former group, even though participating in an aerobic exercise program, had lower muscle strength in relation to the healthy group. However, it is worth emphasizing that despite the differences between groups, both showed relatively high values of 1RM load considering the cohort evaluated in this study (both apparently healthy elderly and patients with CAD). This can be explained by the type of equipment used, which was a 45° leg press with mobile platform and not with a mobile cart.

In relation to responses of the HRV indices during the DRET, these results may contribute to understanding cardiovascular responses during this specific type of exercise in older apparently healthy and CAD patients. The behavior of cardiac autonomic modulation is mediated by neuro-regulatory activity. The electrical signal reaching the heart through these reflexive pathways and through the sympathetic and parasympathetic pathways modulate beat-to-beat heart activity. At rest there is a predominance of parasympathetic modulation, keeping HR at lower values. However, during incremental exercise, there is an initial abrupt reduction in vagal modulation and subsequent predominance of sympathetic modulation, thus promoting an increase in HR (Mitchell, 1990).

In our study, we observed a progressive reduction of rMSSD and SD1 indices in both groups with increasing loads followed by stabilization at 30% of 1RM (Figure 2A and B). These indices are representative of cardiac vagal modulation and, therefore, this behavior reflects reduced parasympathetic modulation (Mourot *et al.*, 2004; Task Force, 1996) with increasing intensities followed by stabilization at an intensity corresponding to LT1. There were no differences between the groups in relation to these indices, suggesting similar parasympathetic cardiac modulation.

The SD2 and SDNN indices reflects the total HRV (sympathetic and parasympathetic modulation) (Task Force, 1996) and some investigators consider the SDNN

index to represent the sympathetic limb of the autonomic nervous system (Ranpuria *et al.*, 2008). In our study, these indices showed a progressive decrease with increasing loads followed by stabilization at 30% of 1RM in the CG. However, these indices increased significantly in the CADG from 30% of 1RM onward (Figure 2C and D). These results may suggest a heightened sympathetic modulation with increasing effort in the CADG, confirming a previous study that suggests an intensive activation of the central command in patients with CAD that leads to an excessive sympathetic outflow (Koba *et al.*, 2006). This more pronounced sympathetic modulation in these patients increases the risk of cardiac arrhythmias, including atrial fibrillation, ventricular tachycardia and sudden cardiac death (Zipes and Rubart, 2006). However, the mechanism by which the pronounced sympathetic modulation promotes cardiac arrhythmias is not completely understood, nevertheless, one hypothesis is that the heightened sympathetic activity causes cardiac electrical instability, which may result in cardiac arrhythmias (Malpas, 2010).

In this sense, these results may have an impact on the prescription of endurance RE in patients with CAD, as cardiac vagal modulation is an important indicator of cardiovascular protection and the overactivity of sympathetic modulation is related to cardiovascular risk.

Furthermore, in relation to delta HR (Figure 2F), we observed a marked change in the behavior of this variable from 35% of 1RM (significant increase) in both groups, a fact that was not observed with conventional analysis of the HR, which showed only a gradual increase in the variable with increasing workloads (date not showed). This significant increase in the delta HR was probably due to the marked increase in sympathetic modulation following LT1. Therefore, this simple analysis can be a useful tool for estimating the load corresponding to the LT1, and also indicate the intensity at which the cardiac sympathetic modulation becomes more pronounced, which is of great importance related to cardiac risk, especially in patients with CAD.

Regarding the behavior of BL values obtained in DRET; they were virtually the same up to 30% of maximum intensity, increasing sharply at intensity after this level in both groups (Figure 2E). Considering the lactate shuttle theory with two thresholds and three phases of metabolism for description of BL changes, the sharp increase of BL verified after 30% of 1RM is related with the LT1, which is considered the “point of optimal ventilatory efficacy” and delimits the moment in which the metabolism changes from predominantly oxidative to progressively anaerobic. Above the LT1, the lactate cannot be oxidized in the skeletal muscle and will appear in the blood and leads to an increase in the BL concentration, but with possibility of stabilization in steady-state exercise. Therefore, despite the increased BL at intensities above the LT1, with the protocol applied in this study, involving a higher number of repetitions at each percentage of 1RM, possibly there is still stabilization of BL with exercises performed at these intensities (i.e., below LT2).

Another justification for the metabolic changes observed after 30% of 1RM in this study, would be the

greatest recruitment in the number of motor units from this intensity, besides the increase in the recruitment of more type II fibers to supply the required demand with increasing intensity, resulting in an increase in glycogenolysis and lactate production (Brooks, 1991; Mazzer and Tanaka, 2001).

### **Relationship between heart rate variability and blood lactate**

The LT1 was close to 30% of 1RM in both groups with no difference between the methods of analysis, i.e., BL and HRV (SD1 and rMSSD indices). In addition, there was a good concordance (Figure 3) and good correlation between the methods (LT and rMSSDT; and LT and SD1T). Thus, it is possible to infer a close relationship between metabolic and central nervous system responses in both groups, and that possible peripheral factor such as the increase of catecholamines, increase of recruitment of motor units and type II fibers, and reducing blood flow of active muscles due to the increase in intramuscular pressure, causing a collapse in blood capillaries (Rowell, 1992). These factors are responsible for the activation of peripheral receptors, such as the mechanoreceptors and metaboreceptors (III and IV fibers) that send information by the afferent pathway to the central nervous system (ventrolateral medullary region), resulting in increased sympathetic discharge to the cardiovascular system (efferent response) (Mitchell, 1990).

Therefore, our results showed that the analysis of HRV indices (rMSSD and SD1) were effective to estimate the LT1. These findings are important with respect to practical application since the HRV is a noninvasive, low cost tool that is relatively easy to apply. In addition HRV reflects changes in control of cardiac autonomic modulation during exercise, which is related to the risk cardiovascular. Lastly, HRV was also effective in determining the LT1, which is an important delimiter of metabolic changes that occur during exercise and may prove to be a useful tool for RE prescription in the CAD population.

Higher loads (60-80% of 1RM) with few repetitions (8-12) are common parameters for a RE program with the purpose of increasing strength and muscle hypertrophy. Lower loads (0-60% of 1RM) and more repetitions (10-25 repetitions, or more) are indicated when the objective of RE training is to increase muscular endurance (ACSM, 2009). Moreover, in specific patient populations, such as patients with CAD, RE training at a lower intensity may strike the right balance of positive physiologic gains and safety in these patients (Bjarnason-Wehrens et al., 2004).

Caruso et al. (2015) investigated the effects of high repetition, low load RE training (with leg press 45°) program on HRV and muscular strength and endurance in patients with CAD. The subjects underwent 8 weeks of training at an intensity of 30% of 1RM (considered as intensity close to the LT1). The authors concluded that there was a positive improvement in HRV, as well as muscle strength and endurance in these patients.

### **Limitations and methodological considerations**

Despite the fact the leg press is a multi-joint RE, it involves only lower limb muscle groups. The discontinuous protocol applied was relatively long, with a large number of repetitions at each percentage of 1RM which may have caused a cumulative effect during the loads and possibly induced the volunteers to reach peak effort at relatively low loads. Furthermore, due to the small number of intensities performed with this protocol, it was not possible to identify the LT2 in this study, which theoretically could provide information related to maximal lactate steady state and consequently with the upper limit of intensity during RE endurance training. However, the long period of data collection during each load allowed the capture of a greater number of points, enabling more reliable HRV analysis. Moreover, despite the long period of passive recovery performed between each intensity in the protocol (15 min.), which may have become the most exhausting portion of the protocol, this time was required to ensure the return to baseline levels of the variables, especially in the CADG. Therefore, future studies applying shorter protocols are necessary to check for similarity in the results and to better align this type of protocol for clinical practice. Finally, although we postulate differences in sympathetic modulation during exercise between groups, only the SDNN and SD2 indices, that reflect both sympathetic and parasympathetic modulation, were evaluated (i.e., sympathetic modulation was not assessed in isolation in this study).

### **Conclusion**

To our knowledge, this is the first study that investigated the behavior of cardiac autonomic modulation at varying percentages of 1RM load during the leg press in elderly subjects with a clinical diagnosis of CAD compared to a group of healthy older men. The HRV responses were consistent with the BL responses in the determination of LT1 (which occurred approximately at 30% of 1RM) during an endurance protocol of discontinuous resistance exercise in both CAD and healthy elderly men. A pronounced reduction in vagal modulation was verified at 30% of 1RM in both groups, however, after this workload, the CADG showed a more pronounced sympathetic modulation compared to healthy controls. These results may have an impact on the prescription of endurance RE in patients with CAD, as cardiac vagal modulation is an important indicator of cardiovascular protection and the over-activity of sympathetic modulation is related to cardiovascular risk.

### **Acknowledgements**

This study was supported by FAPESP (Grant number: 2015/04101-1 to ABS and 2015/12763-4 to RGM) and CNPq (Grant number: 311938/2013-2 to AMC) for the financial support. The authors thank all colleagues from the Unit of Cardiopulmonary Physiotherapy, Federal University of Sao Carlos, for their friendly collaboration. More importantly, however, they are indebted to the volunteers for their effort and enthusiastic cooperation throughout the study. We declare that the experiments comply with the current Brazilian laws, the country in which the experiments were performed. There is no conflict of interest.

### **References**

American College Sports Medicine Position Stand. (2009) The recom

- mended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. *Medicine & Science in Sports & Exercise* **30**(6), 975-991.
- American College of Sports Medicine. (2009) Progression models in resistance training for healthy adults. *Medicine & Science in Sports & Exercise* **41**(3), 687-708.
- Antila, K. (1979) Quantitative characterization of heart rate during exercise. *Scandinavian Journal of Clinical and Laboratory Investigation* **153**, 3-68.
- Baecke, J.A.H., Burema, J. and Frijters, J.E.R. (1982) A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *The American Journal of Clinical Nutrition* **36**(5), 936-942.
- Beckers, P.J., Possemiers, N.M., Van Craenenbroeck, E.M., Van Berendoncks, A.M., Wuyts, K., Vrints, C.J. and Conraads, V.M. (2012) Comparison of three methods to identify the anaerobic threshold during maximal exercise testing in patients with chronic heart failure. *American Journal of Physical Medicine & Rehabilitation* **91**(2), 148-155.
- Billman, G.E. and Kukielka, M. (2006) Effects of endurance exercise training on heart rate variability and susceptibility to sudden cardiac death: protection is not due to enhanced cardiac vagal regulation. *Journal of Applied Physiology* **100**(3), 896-906.
- Binder, R.K., Wonisch, M., Corra, U., Cohen-Solal, A., Vanhees, L., Saner, H. and Schmid, J.P. (2008) Methodological approach to the first and second lactate threshold in incremental cardiopulmonary exercise testing. *European Journal of Cardiovascular Prevention and Rehabilitation* **15**(6), 726-734.
- Bjarnason-Wehrens, B., Mayer-Berger, W., Meister, E.R., Baum, K., Hambrecht, R., Gielen, S., German Federation for Cardiovascular Prevention and Rehabilitation (2004) Recommendations for resistance exercise in cardiac rehabilitation. Recommendations of the German Federation for Cardiovascular Prevention and Rehabilitation. *European Journal of Cardiovascular Prevention and Rehabilitation* **11**(4), 352-361.
- Bland, J.M. and Altman, D.G. (1986) Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* **1**(8476), 307-310.
- Borg, G.A. (1982) Psychophysical bases of perceived exertion. *Medicine & Science in Sports & Exercise* **14**(5), 377-381.
- Brooks, G.A. (1991) Current concepts in lactate exchange. *Medicine & Science in Sports & Exercise* **23**(8), 895-906.
- Caruso, F.R., Arena, R., Phillips, S.A., Bonjorno, J.C.Jr., Mendes, R.G., Arakelian, V.M., Bassi, D., Nogi, C. and Borghi-Silva, A. (2015) Resistance exercise training improves heart rate variability and muscle performance: a randomized controlled trial in coronary artery disease patients. *European Journal of Physical and Rehabilitation Medicine* **51**(3), 281-289.
- Caruso, F.R., Junior, J.C., Mendes, R.G., Sperling, M.P., Arakelian, V.M., Bassi, D., Arena, R. and Borghi-Silva, A. (2016a) Hemodynamic and metabolic response during dynamic and resistance exercise in different intensities: a cross-sectional study on implications of intensity on safety and symptoms in patients with coronary disease. *American Journal of Cardiovascular Disease* **6**(2), 36-45.
- Caruso, F.R., Bonjorno, J.C.Jr., Arena, R., Phillips, S.A., Cabiddu, R., Mendes, R.G., Arakelian, V.M., Bassi, D. and Borghi-Silva, A. (2016b) Hemodynamic, Autonomic, Ventilatory, and Metabolic Alterations After Resistance Training in Patients With Coronary Artery Disease: A Randomized Controlled Trial. *American Journal of Physical Medicine & Rehabilitation*, in press.
- Davis, J.A., Rozenek, R., DeCicco, D.M., Carizzi, M.T. and Pham, P.H. (2007) Comparison of three methods for detection of the lactate threshold. *Clinical Physiology and Functional Imaging* **27**(6), 381-384.
- De Sousa, N.M., Magosso, R.F., Pereira, G.B., Souza, M.V., Vieira, A., Marine, D.A., Perez, S.E. and Baldissera, V. (2012) Acute cardiorespiratory and metabolic responses during resistance exercise in the lactate threshold intensity. *International Journal of Sports Medicine* **33**(2), 108-113.
- Garber, C.E., Blissmer, B., Deschenes, M.R., Franklin, B.A., Lamonte, M.J., Lee, I.M., Nieman, D.C. and Swain, D.P., American College of Sports Medicine. (2011) American College of Sports Medicine - Position Stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Medicine & Science in Sports & Exercise* **43**(7), 1334-1359.
- Koba, S., Gao, Z., Xing, J., Sinoway, L.I. and Li, J. (2006) Sympathetic responses to exercise in myocardial infarction rats: a role of central command. *American Journal of Physiology. Heart and Circulatory Physiology* **291**(6), H2735-H2742.
- Kraemer, W.J. and Fry, A.C. (1995) Strength testing: assessment and evaluation of methodology. In *Physiological assessment of human fitness*. Champaign IL, Human Kinetics. 115-138.
- Machado, H.G., Simões, R.P., Mendes, R.G., Castello, V., Di Thommaso, L., Almeida, L.B., Lopes, S.L., Catai, A.M. and Borghi-Silva, A. (2011) Cardiac autonomic modulation during progressive upper limb exercise by patients with coronary artery disease. *Brazilian Journal of Medical and Biological Research* **44**(12), 1276-1284.
- Machado-Vidotti, H.G., Mendes, R.G., Simões, R.P., Castello-Simões, V., Catai, A.M. and Borghi-Silva, A. (2014) Cardiac autonomic responses during upper versus lower limbs resistance exercise in healthy elderly men. *Brazilian Journal of Physical Therapy* **18**(1), 9-18.
- Marques-Neto, S.R., Maior, A.S., Maranhão Neto, G.A. and Santos, E.L. (2012) Analysis of heart rate deflection points to predict the anaerobic threshold by a computerized method. *Journal of Strength & Conditioning Research* **26**(7), 1967-1974.
- Mazzeo, R.S. and Tanaka, H. (2001) Exercise prescription for the elderly - current recommendations. *Sports Medicine* **31**(11), 809-818.
- Malpas, S. (2010) Sympathetic nervous system overactivity and its role in the development of cardiovascular disease. *Physiol Rev* **90**(2), 513-557.
- Mitchell, J.H. (1990) Wolffe memorial lecture. Neural control of the circulation during exercise. *Med Sci Sports Exerc* **22**(2), 141-54.
- Moreira, S.R., Arsa, G., Oliveira, H.B., Lima, L.C., Campbell, C.S. and Simões, H.G. (2008) Methods to identify the lactate and glucose thresholds during resistance exercise for individuals with type 2 diabetes. *Journal of Strength & Conditioning Research* **22**(4), 1108-1115.
- Mourot, L., Bouhaddi, M., Perrey, S., Rouillon, J.D. and Regnard, J. (2004) Quantitative Poincaré plot analysis of heart variability: effect of endurance training. *European Journal of Applied Physiology* **91**(1), 79-87.
- Pollock, M.L., Franklin, B.A., Balady, G.J., Chaitman, B.L., Fleg, J.L., Fletcher, B., Limacher, M., Piña, I.L., Stein, R.A., Williams, M., Bazzarre, T., AHA Science Advisory (2000) Resistance exercise in individuals with and without cardiovascular disease: benefits, rationale, safety, and prescription: An advisory from the Committee on Exercise, Rehabilitation, and Prevention, Council on Clinical Cardiology, American Heart Association; Position paper endorsed by the American College of Sports Medicine. *Circulation* **101**(7), 828-833.
- Price, K.J., Gordon, B.A., Bird, S.R. and Benson, A.C. (2016) A review of guidelines for cardiac rehabilitation exercise programmes: Is there an international consensus? *European Journal of Preventive Cardiology*, in press.
- Ranpuria, R., Hall, M., Chan, C.T. and Unruh, M. (2008) Heart rate variability (HRV) in kidney failure: measurement and consequences of reduced HRV. *Nephrology Dialysis Transplantation* **23**(2), 444-449.
- Rowell, L.B. (1992) Reflex control of the circulation during exercise. *International Journal of Sports Medicine* **13**(Suppl 1), S25-S27.
- Simões, R.P., Mendes, R.G., Castello, V., Machado, H.G., Almeida, L.B., Baldissera, V., Catai, M., Arena, R. and Borghi-Silva, A. (2010) Heart-rate variability and blood-lactate threshold interaction during progressive resistance exercise in healthy older men. *Journal of Strength & Conditioning Research* **24**(5), 1313-1320.
- Simões, R.P., Bonjorno Jr, J.C., Beltrame, T., Catai, A.M., Arena, R. and Borghi-Silva, A. (2013a) Slower responses of heart rate and oxygen consumption kinetics in on and off transient during discontinuous incremental exercise: effect of aging. *Brazilian Journal of Physical Therapy* **17**(1), 69-76.
- Simões, R.P., Castello-Simões, V., Mendes, R.G., Archiza, B., Santos, D.A., Machado, H.G., Bonjorno Jr, J.C., Oliveira, C.R., Reis, M.S., Catai, A.M., Arena, R. and Borghi-Silva, A. (2013b) Lactate and heart rate variability threshold during resistance exercise in the young and elderly. *International Journal of Sports*

*Medicine* **34(11)**, 991-996.

Simões, R.P., Castello-Simões, V., Mendes, R.G., Archiza, B., Dos Santos, D.A., Bonjorno, J.C.Jr., de Oliveira, C.R., Catai, A.M., Arena, R. and Borghi-Silva, A. (2014) Identification of anaerobic threshold by analysis of heart rate variability during discontinuous dynamic and resistance exercise protocols in healthy older men. *Clinical Physiology and Functional Imaging* **34(2)**, 98-108.

Skinner, J.S. and McLellan, T.H. (1980) The transition from aerobic to anaerobic metabolism. *Research Quarterly for Exercise and Sport* **51(1)**, 234-248.

Svedahl, K. and MacIntosh, B.R. (2003) Anaerobic threshold: the concept and methods of measurement. *Canadian Journal of Applied Physiology* **28(2)**, 299-323.

Task Force of European Society of Cardiology and North American Society of Pacing and Electrophysiology. (1996) Heart rate variability: Standards of measurement, physiological interpretation and clinical use. *Circulation* **93(5)**, 1043-1065.

Tscharkert, G. and Hofmann, P. (2013) High-intensity intermittent exercise: methodological and physiological aspects. *International Journal of Sports Physiology and Performance* **8(6)**, 600-610.

Wilborn, C., Greenwood, M., Wyatt, F., Bowden, R. and Grose, D. (2004) The effects of exercise intensity and body poJournal of *Exercise Physiology Online* **7(4)**, 29-36.

Williams, M.A., Haskell, W.L., Ades, P.A., Amsterdam, E.A., Bittner, V., Franklin, B.A., Gulanick, M., Laing, S.T. and Stewart, K.J., American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism (2007). Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. *Circulation* **116(5)**, 572-584.

Zipes, D.P. and Rubart, M. (2006) Neural modulation of cardiac arrhythmias and sudden cardiac death. *Heart Rhythm* **3(1)**, 108-113.

**Key points**

- Therefore, HRV that can be easily obtained through low-cost equipment which are widely used in gyms and rehabilitation environment, may be considered a useful tool in practice to determine the intensity corresponding to LT1.
- The HRV method may have an impact on the prescription of exercise based on improvement of aerobic capacity and muscular endurance during resistance training program in CAD and healthy elderly men.
- The resistance exercise protocol applied demonstrated be safety in patients with CAD.

**AUTHOR BIOGRAPHY**



**Rodrigo P. SIMÕES**  
**Employment**  
 Postdoctoral Researcher at Federal University of Sao Carlos, Department of Physical Therapy.  
**Degree**  
 PhD  
**Research interests**  
 Exercise physiology, exercise prescription, exercise testing, physical therapy, cardiopulmonary disease.  
**E-mail:** rpssimoes@yahoo.com.br



**Renata G. MENDES**  
**Employment**  
 Professor at Federal University of Sao Carlos, Department of Physical Therapy.  
**Degree**  
 PhD  
**Research interests**  
 Exercise physiology, exercise prescription, exercise testing, physical therapy, cardiopulmonary disease.  
**E-mail:** mendesrg@hotmail.com



**Viviane CASTELLO-SIMÕES**  
**Employment**  
 Postdoctoral Researcher at Federal University of Sao Carlos, Department of Physical Therapy.  
**Degree**  
 PhD  
**Research interests**  
 Exercise physiology, exercise prescription, exercise testing, physical therapy, cardiopulmonary disease.  
**E-mail:** vivica\_castello@yahoo.com.br



**Aparecida M. CATAI**  
**Employment**  
 Full Professor at Federal University of Sao Carlos, Department of Physical Therapy.  
**Degree**  
 PhD  
**Research interests**  
 Exercise physiology, exercise prescription, exercise testing, physical therapy, cardiopulmonary disease.  
**E-mail:** mcatai@ufscar.br



**Ross ARENA**  
**Employment**  
 Professor at College of Applied Health Sciences – University of Illinois at Chicago, Department of Physical Therapy and Integrative Physiology Laboratory  
**Degree**  
 PhD  
**Research interests**  
 Exercise physiology, exercise prescription, exercise testing, physical therapy, cardiopulmonary disease.  
**E-mail:** rarena70@gmail.com



**Audrey BORGHI-SILVA**  
**Employment**  
 Associate Professor at Federal University of Sao Carlos, Department of Physical Therapy, Brazil.  
**Degree**  
 PhD  
**Research interests**  
 Exercise physiology, exercise prescription, exercise testing, physical therapy, cardiopulmonary disease.  
**E-mail:** audrey@ufscar.br

✉ **Rodrigo P. Simões**  
 Cardiopulmonary Physical Therapy Laboratory, Department of Physical Therapy, Federal University of Sao Carlos, Sao Carlos - SP, Brazil